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I_2-Catalyzed Oxidative N−S Bond Formation: Metal-Free Regiospecific Synthesis of N-Fused and 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles

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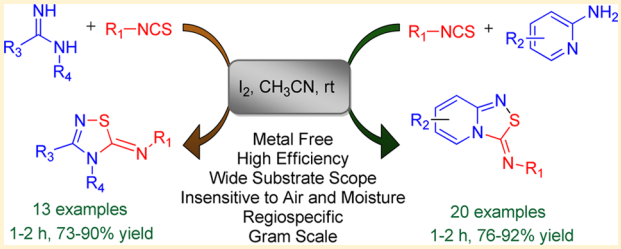
Supporting Information

ABSTRACT: A novel and expeditious approach for the synthesis of N-fused and 3,4-disubstituted 5-imino-1,2,4-thiadiazole derivatives has been achieved through the molecular iodine-catalyzed oxidative cyclization of 2-aminopyridine/amidine and isothiocyanate via N−S bond formation at ambient temperature. The present one-pot transition-metal-free protocol provides the facile and highly efficient regiospecific synthesis of various 1,2,4-thiadiazole derivatives in a scaled-up manner with good to excellent yields using inexpensive I_2 as a catalyst.



INTRODUCTION

Nitrogen-containing heterocyclic compounds are important structures found in natural and synthetic compounds. Development of new synthetic protocols for the synthesis of biologically active N-heterocyclic compounds through various N−N, N−O, and N−S bond formations is still in high demand. As a result, a plethora of methods were developed for heteroatom−heteroatom bond formation. Among these, metal-catalyzed protocols for N−N, N−O, and N−S bond construction have limitations, such as metal contamination, drastic reaction conditions, cost factors, air sensitivity, and scalability issues.[1] Earlier, metal-free protocols were developed for N−N, N−O, and N−S bond connections,[2] and of all of these, iodine-catalyzed reactions played a major role owing to its environmentally friendly nature, oxidizing ability, low cost, easy availability in solid form, and easy handling. Recently, iodine-catalyzed approaches were found during C−X (X = C, N, O, S) bond formation as well as in N−N and N−S bonds.[3] As a catalyst, iodine has been extensively used in organic transformations, such as esterification, acylation, and allylation as well as for Michael addition and aldol reaction.[4] It can also mediate domino, iodocyclization, and one-pot multicomponent reactions.[5a] However, it is very interesting to note that iodine could substitute for transition metal as a catalyst.[2a,5b]

1,2,4-Thiadiazoles are an important class of organic molecules for medicinal chemistry and are associated with a broad range of biological activity,[6a] including antibacterial,[6b] antiulcerative,[7] antidiabetic,[8] antirheumatic,[9] anti-inflammatory,[10] and antimicrobial agents.[11] A family of 1,2,4-thiadiazole derivatives also exhibits fungicidal[12] and herbicidal activity.[13] Despite their wide applications in pharmacology and organic synthesis, few methods were developed for the synthesis of 1,2,4-thiadiazoles. The general methods for the synthesis of 1,2,4-thiadiazoles mainly involve oxidative cyclization of primary thioamides with a variety of oxidizing reagents.[14] Recently, Wehn et al. invoked a palladium-catalyzed Suzuki−Miyaura coupling reaction for ready access to 3-amino-1,2,4-thiadiazoles.[15a] Independently, Khosropour and co-workers obtained 1,2,4-thiadiazoles from aryl nitriles in the presence of $(NH_4)_2S$ and TCT−DMSO.[15b] On the other hand, the 1,2,4-thiadiazole scaffold was also obtained from imidoyl thioureas.[16] Intramolecular oxidative S−N bond formation under copper catalysis was developed by Kim et al. for ready access to 3-substituted 5-amino-1,2,4-thiadiazoles.[17a] Muthusubramanian and co-workers developed a phenyliodine(III) bis-(trifluoroacetate)-catalyzed oxidative cyclization for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles.[17b]

However, some of these protocols suffer from limitations, such as prefunctionalization of starting materials, and require strong oxidative reaction conditions, tedious workup, and harsh reaction conditions. More importantly, these methods are mainly suitable for preparation of 3,5-disubstituted 1,2,4-thiadiazoles. Thus, it is desirable to develop an efficient protocol for the synthesis of fully substituted 1,2,4-thiadiazoles using readily available raw materials in one pot. However, there seems to be no reports in the literature on I_2-catalyzed N−S bond formation reactions for the synthesis of 1,2,4-thiadiazoles. Encouraged by our previous work on the development of efficient synthetic methods for various biologically active heterocycles,[18] in this paper, we envisioned for the first time the construction of the N−S bond by employing molecular

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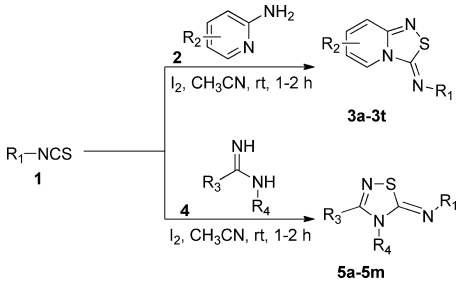
iodine as a catalyst to synthesize the biologically important N-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole scaffolds (Scheme 1).

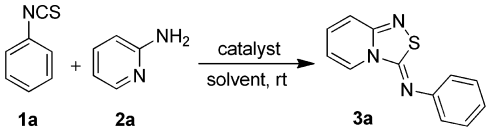
Scheme 1. Synthesis of N-Fused 1,2,4-Thiadiazoles and 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles



RESULTS AND DISCUSSION

Our initial study started with the reaction of isothiocyanate **1a** with 2-aminopyridine (**2a**) in the presence of iodine (0.2 equiv) with no solvent (neat) at room temperature. We were delighted to observe the formation of the expected 1,2,4-thiadiazole **3a**, although in low yields (Table 1, entry 1). The poor yield of **3a** might be due to the low solubility of the reactants. Next, we optimized the reaction conditions with various solvents, forward yield improvement, and the results are summarized in Table 1. Among all, acetonitrile proved to be a better solvent in terms of the reaction time and yield of the product (Table 1, entry 4). The replacement of iodine with other oxidizing catalysts, including KI, TBAI, and NIS resulted in a decrease yield of **3a** (Table 1, entries 8–10). Having established the suitable catalyst for synthesis of 1,2,4-thiadiazoles, we then focused on the quantity of iodine. Increasing the loading of iodine resulted in the desired product **3a** in high yields (Table 1, entries 11 and 12), and the use of 50 mol % of catalyst gave the best result (Table 1, entry 12). With further increasing of iodine from 0.5 to 1.0 equiv, the yield of **3a** was not augmented (Table 1, entry 13). Thus, the standardized conditions for this reaction are summarized as follows: **1a** (3 mmol, 1 equiv), **2a** (3 mmol, 1 equiv), and I_2 (50 mol %) at rt in CH_3CN in 1–2 h.

Table 1. Optimization of Reaction Conditions[a]

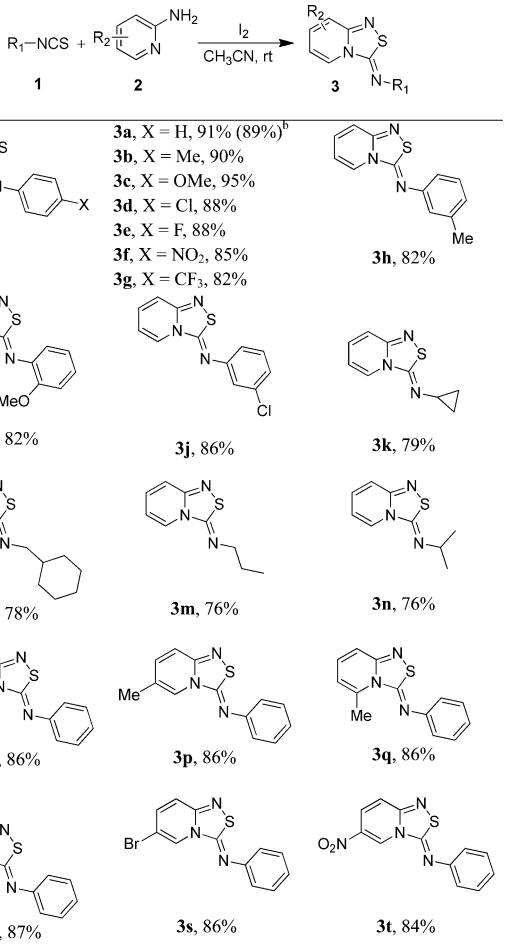


entry	catalyst (mol %)	solvent	yield (%)
1	I_2 (20)		19
2	I_2 (20)	DCE	32
3	I_2 (20)	1,4-dioxane	41
4	I_2 (20)	CH_3CN	58
5	I_2 (20)	DMF	29
6	I_2 (20)	EtOH	32
7	I_2 (20)	DMSO	30
8	KI (20)	CH_3CN	trace
9	TBAI (20)	CH_3CN	42
10	NIS (20)	CH_3CN	36
11	I_2 (30)	CH_3CN	72
12	I_2 (50)	CH_3CN	91
13	I_2 (100)	CH_3CN	91

[a]Reaction conditions: **1a** (3 mmol, 1 equiv), **2a** (3 mmol, 1 equiv), catalyst (*x* mol %), and solvent (1 mL) at rt for 1–2 h.

Next, we investigated the generality of the oxidative synthesis of N-fused 1,2,4-thiadiazoles (Scheme 2). A variety of isothiocyanates with different substituents were tested. As expected, all the isothiocyanates gave the corresponding N-fused 1,2,4-thiadiazoles in good to excellent yields. Phenyl isothiocyanate (**1a**) gave the desired product **3a** in 91% yield. Further structural confirmation of **3a** was ascertained by X-ray studies (see the Supporting Information). Arylisothiocyanates containing groups like methyl or methoxy at *para*-, *meta*-, and *ortho*-positions gave better reactivity and provided the corresponding products in good to excellent yields (**3b**, **3c**, **3h**, and **3i**). Conversely, arylisothiocyanates with electron-withdrawing groups such as chloro and fluoro at *para*- and *meta*-positions furnished corresponding products in moderate to good yields (**3d**, **3e** and **3j**). It should be noted that arylisothiocyanates with strong electron-withdrawing groups, including $-NO_2$ and $-CF_3$, were well tolerated under the reaction conditions, and the desired N-fused 1,2,4-thiadiazole products were obtained in good yields (**3f** and **3g**). It is worth mentioning that steric hindrance (**3b**, **3c**, and **3h**–**3j**) and electronic factors (**3a**–**3j**) of phenyl isothiocyanates seemingly

Scheme 2. Synthesis of N-Fused 1,2,4-Thiadiazoles[a]



[a]Reaction conditions: **1a** (3 mmol, 1 equiv), **2a** (3 mmol, 1 equiv), I_2 (50 mol %) and CH_3CN (1 mL) at rt for 1–2 h. [b]The reaction was conducted on gram scale.

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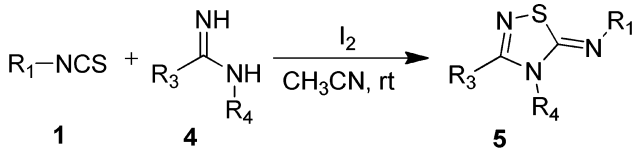
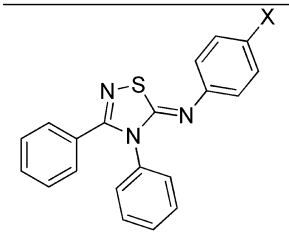
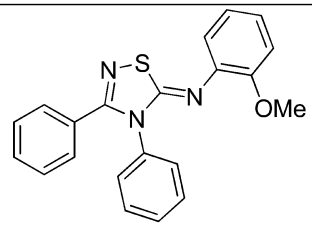
Scheme 3. Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles[a]

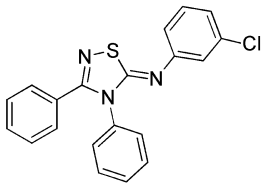




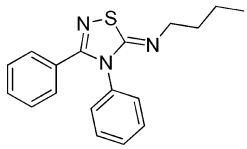
5a, X = H, 89%
5b, X = Me, 90%
5c, X = OMe, 90%
5d, X = Cl, 87%
5e, X = NO_2, 86%
5f, X = CF_3, 82%



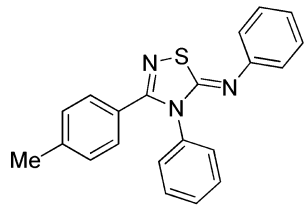
5g, 82%



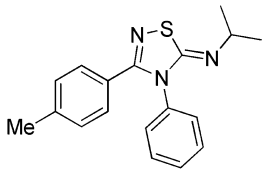
5h, 87%



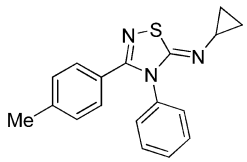
5i, 74%



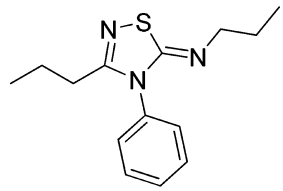
5j, 76%



5k, 75%



5l, 76%



5m, 73%

[a]Reaction conditions: **1a** (1.5 mmol, 1 equiv), **2a** (1.5 mmol, 1 equiv), I_2 (50 mol %) and CH_3CN (1 mL) at rt for 1−2 h.

exerted a negligible influence on the reaction rate or the yields of the products. An alicyclic isothiocyanate such as cyclopropyl isothiocyanate was also tolerated under these reaction conditions, and the corresponding product **3k** was isolated in 79% yield. Aliphatic isothiocyanates including cyclohexyl methyl, propyl, and isopropyl underwent the oxidative reaction to give the corresponding products in good yields (**3l**−**3n**). To further examine the scope and limitations of the reaction, we studied various 2-aminopyridines with phenyl isothiocyanate (Scheme 2). Methyl-substituted 2-aminopyridine was well tolerated, and the position of the methyl substituent at 4, 5, and 6 did not bear any significant effect on the reaction yield (**3o**−**3q**). Electron-withdrawing groups such as chloro and bromo were compatiable and gave the corresponding products **3r** and **3s** in 87 and 86% yields, respectively. When a strong electron-withdrawing nitro group was used, the desired product **3t** was obtained in 84% yield (**3t**). It should be noted that the catalytic transformation was successfully conducted in gram scale without any difficulty (Scheme 2, **3a**).

In light of a successful oxidative cyclization process for the synthesis of N-fused 1,2,4-thiadiazoles, we sought to further extend the scope of this practical approach by replacing 2-aminopyridine (**2**) with *N*-phenylbenzamidines (**4**) to prepare 3,4-disubstituted 5-imino-1,2,4-thiadiazoles under the optimal reaction conditions. Gratifyingly, following the above protocol, we were able to prepare 3,4-disubstituted 5-imino-1,2,4-thiadiazoles very efficiently. As shown in Scheme 3, this protocol tolerates a variety of arylisothiocyanates with different *N*-phenylbenzamidines. No significant substituent effect was observed, and excellent yields were obtained for arylisothiocyanates having both electron-donating and electron-withdrawing substituents with different *N*-phenylbenzamidines. This methodology worked equally well with alicyclic isothiocyanate such as cyclopropyl, and good yield was observed (**5l**). Fortunately, the reaction worked equally well with aliphatic isothiocyanates, including butaryl, isopropyl, and propyl, which gave corresponding 3,4-disubstituted 5-imino-1,2,4-thiadiazoles in good yields (**5i**, **5k**, and **5m**). Compound **5k** was fully characterized by X-ray analysis (please see Supporting Information).

To further probe the mechanism, we attempted control experiments, as shown in Scheme 4. Phenyl isothiocyanate (**1a**)

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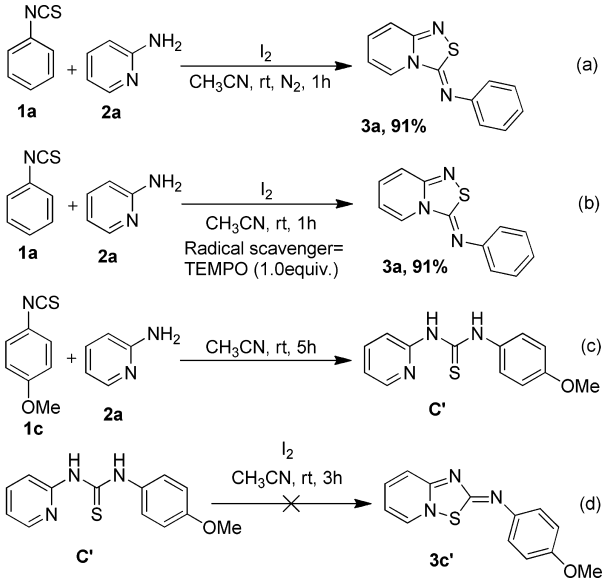
Scheme 4. Control Experiments



with 2-aminopyridine (**2a**) under optimized conditions in inert atmosphere gave the desired **3a** in 91% (Scheme 4a). It is highly likely that I_2 plays the role of oxidant. As expected, when 2,2,6,6-tetramethylpiperdine-1-oxide (TEMPO, a well-known radical inhibitor) was added to the reaction, no considerable effect was observed (Scheme 4b), demonstrating that a radical mechanism was ruled out. When the phenyl isothiocyanate (**1c**) was reacted with 2-aminopyridine (**2a**) in the absence of I_2, intermediate **C′** (Scheme 4c) was obtained, which was confirmed by ^{1}H, ^{13}C NMR, HRMS, and X-ray analysis (see the Supporting Information). However, **C′** did not produce **3c′** in the presence of I_2 (Scheme 4d). Thus, it maybe deduced that the present protocol is highly regiospecific and affords **3c** exclusively.

Based on the results presented above and previous reports,[19] a plausible mechanism was proposed and shown in Scheme 5. The first step for the formation of product **3a** involves a nucleophilic attack of activated 2-aminopyridine (**A**) on phenyl isothiocyanate (**1a**) to form intermediate **B**. Finally, the intermolecular nucleophilic attack of the NH group on the sulfur atom gave the corresponding derivative **3a**. However, when the same reaction was performed in the absence of I_2, nucleophilic addition of free amine on isothiocyanate gave stable thiourea derivative **C′**, which was isolated and characterized by its ^{1}H, ^{13}C NMR, HRMS, as well as X-ray analysis. Independently, **C′** upon treatment with I_2 did not afford the cyclized regioisomer **3c′** (Scheme 4d). Thus, it conclusively proves the intermediacy of **B** and its conversion into product **3a**.

CONCLUSION

In summary, a novel and convenient iodine-catalyzed oxidative protocol for N−S bond formation toward the regiospecific synthesis of N-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole derivatives was developed for the first time. This versatile and transition-metal-free one-pot protocol features a broad substrate scope with inexpensive and nontoxic molecular iodine as the catalyst, and no addition of any ligand, base, or additive is need and with an easy workup procedure. The developed synthetic approach can be easily scaled up to gram scale, thereby providing the possibility for the scaled production of diverse N-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole derivatives.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, common reagents and substrates were obtained from commercial suppliers and used without further purification. ^{1}H NMR was measured on a Bruker Avance-300, Varian Unity-400 MHz, and Avance New-500 MHz, and ^{13}C NMR was measured with a Varian Unity-400 MHz (100 MHz) and with Avance New-500 MHz (125 MHz), as specified and referred as the internal standard to TMS (tetramethylsilane). High-resolution mass spectra (HRMS) were performed on a high-resolution magnetic sector mass spectrometer. Melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. TLC analysis was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on silica gel (100−200 mesh) from Merck.

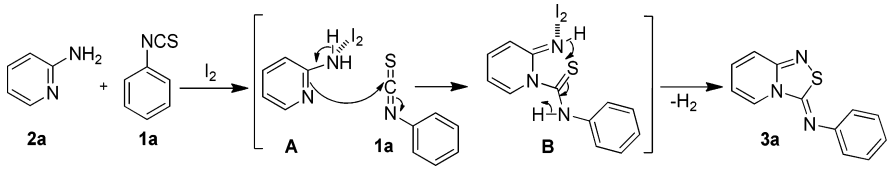
Typical Procedure for the Synthesis of N-Fused 1,2,4-Thiadiazoles 3a−3t. A mixture comprised isothiocyanate (**1**) (3 mmol), 2-aminopyridine (**2**) (3 mmol), and I_2 (50 mol %, 202 mg, 1.5 mmol) in CH_3CN (1 mL) at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography using EtOAc/hexane as eluents to afford corresponding product **3**.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)aniline (**3a**):*[20] Yield 91% (659 mg); pale yellow solid; mp 124−126 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.21 (d, J = 7.17 Hz, 1H), 7.42−7.37 (m, 2H), 7.22−7.10 (m, 4H), 7.06−7.03 (m, 1H), 6.46 (dd, J = 0.92 Hz, J = 5.34 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 159.2, 151.6, 148.5, 133.4, 129.5, 126.1, 124.3, 121.1, 119.4, 109.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{10}N_3S$ 228.0512; found 228.0520.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-methylaniline (**3b**):*[21] Yield 90% (692 mg); pale yellow solid; mp 104−106 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.20 (d, J = 7.17 Hz, 1H), 7.21−7.16 (m, 3H), 7.07−7.02 (m, 3H), 6.46−6.42 (m, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 158.5, 151.6, 145.9, 133.8, 133.3, 130.1, 126.1, 120.9, 119.4, 109.5, 21.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{12}N_3S$ 242.0745; found 242.0746.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-methoxyaniline (**3c**):*[22] Yield 95% (779 mg); pale yellow solid; mp 125−127 °C; eluent, hexane/ethyl acetate 94:6; ^{1}H NMR (400 MHz, $CDCl_3$) δ

Scheme 5. Plausible Mechanism for the Preparation of 3a



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= 8.20 (d, J = 7.21 Hz, 1H), 7.21−7.16 (m, 1H), 7.11−7.06 (m, 2H), 7.05−7.01 (m, 1H), 6.96−6.91 (m, 2H), 6.44 (dd, J = 5.38 Hz, J = 0.97 Hz, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 157.9, 156.3, 151.6, 141.6, 133.4, 126.1, 122.2, 119.4, 114.7, 109.5, 55.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3OS$ 258.0654; found 258.0663.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-chloroaniline (**3d**):*[22] Yield 88% (733 mg); pale yellow solid; mp 144−146 °C; eluent, hexane/ethyl acetate 95:5; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, J = 7.17 Hz, 1H), 7.36−7.32, (m, 2H), 7.24−7.20 (m, 1H), 7.09−7.06 (m, 3H), 6.49 (dd, J = 1.06 Hz, J = 5.34 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 159.7, 151.6, 147.1, 133.4, 129.6, 129.1, 125.9, 122.4, 119.4, 109.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9ClN_3S$ 262.0137; found 262.0142.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-fluoroaniline (**3e**):*[22] Yield 88% (688 mg); pale yellow solid; mp 148−150 °C; eluent, hexane/ethyl acetate 95:5; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, J = 7.17 Hz, 1H), 7.23−7.19 (m, 1H), 7.12−7.05 (m, 5H), 6.48 (dd, J = 1.06 Hz, J = 5.34 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 159.9 (d, J = 102 Hz), 158.5, 151.6, 144.7, 133.4, 125.9, 122.4 (d, J = 7 Hz), 119.4, 116.2 (d, J = 18 Hz), 109.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9FN_3S$ 246.0493; found 246.0495.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-nitroaniline (**3f**):*[22] Yield 85% (737 mg); orange solid; mp 189−191 °C; eluent, hexane/ethyl acetate 92:8; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.30−8.25 (m, 3H), 7.33−7.28 (m, 1H), 7.26−7.22 (m, 2H), 7.19−7.15 (m, 1H), 6.63−6.58 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 161.7, 154.3, 151.6, 143.5, 133.6, 125.8, 125.5, 121.5, 119.5, 110.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9N_4O_2S$ 273.0435; found 273.0441.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-4-(trifluoromethyl)aniline (**3g**):* Yield 82% (772 mg); pale yellow solid; mp 158−160 °C; eluent, hexane/ethyl acetate 93:7; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.24−8.20 (m, 1H), 7.64 (d, J = 8.55 Hz, 2H), 7.27−7.20 (m, 3H), 7.13−7.08 (m, 1H), 6.55−6.50 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 158.2, 149.1, 130.9, 125.0, 124.2 (d, J = 2 Hz), 123.4, 123.3 (q, J = 48.1 Hz), 121.8 (d, J = 216 Hz), 118.7, 116.9, 107.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_9F_3N_3S$ 296.0460; found 296.0464.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-3-methylaniline (**3h**):* Yield 82% (631 mg); pale yellow liquid; eluent, hexane/ethyl acetate 95:5; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.23−8.19 (m, 1H), 7.30−7.25 (m, 1H), 7.20 (dd, J = 1.37 Hz, J = 5.04 Hz, 1H), 7.07−7.03 (m, 1H), 6.98−6.92 (m, 3H), 6.49−6.44 (m, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 159.0, 151.6, 148.5, 139.5, 133.3, 129.4, 126.1, 125.1, 121.9, 119.4, 117.7, 109.6, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3S$ 242.0745; found 242.0746.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-2-methoxyaniline (**3i**):* Yield 82% (672 mg); pale yellow liquid; eluent, hexane/ethyl acetate 91:9; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.26−8.23 (m, 1H), 7.19 (dd, J = 1.37 Hz, J = 5.04 Hz, 1H), 7.14−7.09 (m, 2H), 7.03 (d, J = 9.46 Hz, 1H), 7.00−6.96 (m, 2H), 6.48−6.44 (m, 1H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 160.4, 151.6, 151.4, 138.1, 133.1, 126.2, 125.3, 121.3, 120.6, 119.4, 112.0, 109.6, 55.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3OS$ 258.0694; found 258.0695.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-3-chloroaniline (**3j**):* Yield 86% (716 mg); pale yellow solid; mp 107−109 °C; eluent, hexane/ethyl acetate 95:5; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.20−8.17 (m, 1H), 7.30 (t, J = 7.93 Hz, 1H), 7.22 (dd, J = 1.37 Hz, J = 5.04 Hz, 1H), 7.14 (t, J = 1.98 Hz, 1H), 7.11−7.05 (m, 2H), 7.02 (dd, J = 1.37 Hz, J = 8.08 Hz, 1H), 6.51−6.47 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 160.2, 151.5, 149.8, 135.0, 133.4, 130.5, 125.9, 124.2, 121.7, 119.4, 119.1, 110.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9ClN_3S$ 262.0154; found 262.0159.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-cyclopropanamine (**3k**):* Yield 79% (481 mg); pale yellow liquid; eluent, hexane/ethyl acetate 90:10; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90−7.86 (m, 1H), 7.15−7.10 (m, 1H), 6.99−6.95 (m, 1H), 6.35−6.31 (m, 1H), 2.49−2.42 (m, 1H), 0.86−0.83 (m, 2H), 0.69−0.65 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 161.4, 152.2, 133.2, 125.7, 119.3, 108.9, 36.0, 7.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{10}N_3S$ 192.0543; found 192.0551.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)-1-cyclohexylmethanamine (**3l**):* Yield 78% (614 mg); pale yellow liquid; eluent, hexane/ethyl acetate 90:10; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.95 (d, J = 7.17 Hz 1H), 7.13−7.09 (m, 1H), 6.94 (d, J = 9.46 Hz, 1H), 6.32 (t, J = 7.02 Hz, 1H), 2.96 (d, J = 6.56 Hz, 2H), 1.87−1.80 (m, 2H), 1.78−1.64 (m, 4H), 1.33−1.26 (m, 2H), 1.23−1.16 (m, 1H), 1.08−0.96 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 158.3, 152.3, 133.3, 126.1, 119.3, 108.6, 61.7, 39.4, 31.5, 26.6, 26.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{18}N_3S$ 248.1208; found 248.1215.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)propan-1-amine (**3m**):* Yield 76% (468 mg); pale yellow liquid; eluent, hexane/ethyl acetate 90:10; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.98−7.94 (m, 1H), 7.16−7.09 (m, 1H), 6.98−6.93 (m, 1H), 6.37−6.31 (m, 1H), 3.11 (t, J = 6.87 Hz, 2H), 1.82−1.68 (m, 2H), 1.01 (t, J = 7.43 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 158.6, 152.3, 133.3, 126.0, 119.3, 108.7, 56.7, 23.9, 12.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}N_3S$ 194.0756; found 194.0759.

*(Z)-N-(3H-[1,2,4]Thiadiazolo[4,3-a]pyridin-3-ylidene)propan-2-amine (**3n**):* Yield 76% (468 mg); pale yellow liquid; eluent, hexane/ethyl acetate 90:10; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, J = 7.32 Hz, 1H), 7.13−7.08 (m, 1H), 6.92 (d, J = 9.46 Hz, 1H), 6.31 (t, J = 7.02 Hz, 1H), 3.19−3.10 (m, 1H), 1.24 (d, J = 6.26 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 157.1, 152.3, 133.3, 126.2, 119.2, 108.6, 56.4, 22.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}N_3S$ 194.0745; found 194.0746.

*(Z)-N-(7-Methyl-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3o**):* Yield 86% (575 mg); pale yellow solid; mp 104−106 °C; eluent, hexane/ethyl acetate 93:7; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (d, J = 7.34 Hz, 1H), 7.41−7.36 (m, 2H), 7.16−7.08 (m, 3H), 6.82−6.79 (m, 1H), 6.30 (dd, J = 1.46 Hz, J = 7.34 Hz, 1H), 2.26 (d, J = 1.22 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 159.3, 151.8, 148.6, 144.8, 129.5, 124.9, 124.2, 121.1, 116.8, 112.8, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3S$ 242.0756; found 242.0759.

*(Z)-N-(6-Methyl-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3p**):* Yield 86% (575 mg); pale yellow solid; mp 147−149 °C; eluent, hexane/ethyl acetate 94:6; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.00 (s, 1H), 7.39 (t, J = 7.78 Hz, 2H), 7.18−7.05 (m, 4H), 7.01−6.97 (m, 1H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 159.5, 151.2, 148.7, 136.8, 129.5, 124.1, 122.7, 121.1, 119.4, 118.6, 17.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3S$ 242.0767; found 242.0773.

*(Z)-N-(5-Methyl-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3q**):* Yield 86% (575 mg); pale yellow solid; mp 98−100 °C; eluent, hexane/ethyl acetate 93:7; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.38 (t, J = 7.78 Hz, 2H), 7.11 (t, J = 7.47 Hz, 1H), 7.04 (d, J = 7.47 Hz, 2H), 6.90 (dd, J = 6.56 Hz, J = 9.46 Hz, 1H), 6.79 (d, J = 9.31 Hz, 1H), 5.99 (d, J = 6.56 Hz, 1H), 2.96 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 163.0, 154.0, 150.2, 141.9, 132.6, 129.7, 124.2, 120.3, 118.1, 110.7, 21.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3S$ 242.0753; found 242.0758.

*(Z)-N-(8-Chloro-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3r**):* Yield 87% (532 mg); pale yellow solid; mp 136−138 °C; eluent, hexane/ethyl acetate 95:5; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.20 (dd, J = 1.06 Hz, J = 7.17 Hz, 1H), 7.42−7.38 (m, 2H), 7.34 (dd, J = 1.06 Hz, J = 7.02 Hz, 1H), 7.16−7.11 (m, 3H), 6.43 (t, J = 7.02 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 158.9, 148.4, 147.9, 131.9, 129.6, 125.1, 124.8, 124.6, 121.0, 109.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9ClN_3S$ 262.0145; found 262.0149.

*(Z)-N-(6-Bromo-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3s**):* Yield 86% (456 mg); pale yellow solid; mp 147−149 °C; eluent, hexane/ethyl acetate 92:8; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.37 (dd, J = 0.85 Hz, J = 1.95 Hz, 1H), 7.43−7.37 (m, 2H), 7.21 (dd, J = 1.98 Hz, J = 9.76 Hz, 1H), 7.16−7.10 (m, 3H), 6.95 (dd, J = 0.76 Hz, J = 9.92 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 157.6, 149.6, 147.9, 136.7, 129.6, 125.8, 124.5, 121.0, 119.9, 104.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_9BrN_3S$ 305.9691; found 305.9695.

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*(Z)-N-(6-Nitro-3H-[1,2,4]thiadiazolo[4,3-a]pyridin-3-ylidene)-aniline (**3t**):* Yield 84% (493 mg); orange solid; mp 180−182 °C; eluent, hexane/ethyl acetate 91:9; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.38−9.35 (m, 1H), 7.91 (dd, J = 2.32 Hz, J = 10.27 Hz, 1H), 7.46−7.41 (m, 2H), 7.20 (t, J = 7.46 Hz, 1H), 7.16−7.13 (m, 2H), 7.08 (d, J = 10.27 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 155.8, 149.2, 146.7, 135.1, 129.7, 127.9, 126.9, 125.5, 121.1, 119.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_9N_4O_2S$ 273.0451; found 273.0458.

Typical Procedure for the Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles 5a−5m. A mixture comprised isothiocyanate (**1**) (1.5 mmol), *N*-phenylbenzamidines (**4**) (1.5 mmol), and I_2 (50 mol %, 97 mg, 0.75 mmol) in CH_3CN (1 mL) at room temperature for 1−2 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography using EtOAc/hexane as eluents to afford corresponding product **5**.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)aniline (**5a**):*[23] Yield 89% (448 mg); white solid; mp 196−198 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (500 MHz, $CDCl_3$) δ = ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10H), 7.26−7.19 (m, 2H), 7.10−6.99 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 164.5, 157.1, 150.6, 136.6, 130.3, 130.1, 129.53, 129.47, 128.8, 128.6, 128.3, 124.0, 121.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{16}N_3S$ 330.1034; found 330.1037.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-4-methylaniline (**5b**):* Yield 90% (472 mg); white solid; mp 192−194 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42−7.27 (m, 8H), 7.25−7.21 (m, 2H), 7.12 (d, J = 8.08 Hz, 2H), 6.91 (d, J = 8.24 Hz, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 164.1, 157.1, 148.2, 136.6, 133.4, 130.2, 130.15, 130.06, 129.4, 128.76, 128.72, 128.6, 128.3, 120.7, 20.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3S$ 344.1209; found 344.1215.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-4-methoxyaniline (**5c**):* Yield 90% (494 mg); white solid; mp 207−209 °C; eluent, hexane/ethyl acetate 94:6; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43−7.26 (m, 8H), 7.25−7.20 (m, 2H), 6.98−6.93 (m, 2H), 6.89−6.83 (m, 2H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 164.0, 157.1, 156.2, 144.1, 136.7, 130.3, 130.1, 129.4, 128.76, 128.72, 128.6, 128.3, 121.9, 114.6, 55.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3OS$ 360.1161; found 360.1165.

*(Z)-4-Chloro-N-(3,4-diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-aniline (**5d**):* Yield 87% (483 mg); white solid; mp 170−172 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.21 (m, 12H), 6.98−6.92 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 164.9, 157.2, 149.3, 136.5, 130.4, 129.9, 129.55, 129.48, 128.9, 128.7, 128.6, 128.3, 122.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClN_3S$ 364.0641; found 364.0645.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-4-nitroaniline (**5e**):* Yield 86% (492 mg); pale yellow solid; mp 180−182 °C; eluent, hexane/ethyl acetate 93:7; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20(d, J = 9.07 Hz, 2H), 7.48−7.23 (m, 10H), 7.12 (d, J = 9.07 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 166.2, 157.4, 156.4, 143.6, 136.2, 130.6, 129.6, 129.5, 129.3, 128.8, 128.5, 128.4, 125.5, 121.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}N_4O_2S$ 375.0838; found 375.0842.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-4-(trifluoromethyl)aniline (**5f**):* Yield 82% (528 mg); white solid; mp 227−229 °C; eluent, hexane/ethyl acetate 94:6; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.53 Hz, 2H), 7.47−7.22 (m, 10H), 7.10 (d, J = 8.53 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 165.5, 157.2, 153.7, 136.4, 130.5, 129.7, 129.5, 129.0, 128.7, 128.6, 128.3, 126.7 (d, J = 3 Hz), 125.7 (d, J = 26 Hz), 123.3, 121.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{15}F_3N_3S$ 398.0929; found 398.0933.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-2-methoxyaniline (**5g**):* Yield 82% (450 mg); white solid; mp 132−134 °C; eluent, hexane/ethyl acetate 94:6; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (m, 2H), 7.36−7.27 (m, 6H), 7.26−7.20 (m, 2H), 7.08−7.03 (m, 1H), 6.99−6.95 (m, 1H), 6.93−6.88 (m, 2H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 165.1, 156.9, 151.1, 140.1, 136.6, 130.2, 130.1, 129.4, 128.76, 128.70, 128.6, 128.2, 124.9, 121.5, 121.3, 112.4, 55.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3OS$ 360.1157; found 360.1162.

*(Z)-3-Chloro-N-(3,4-diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)-aniline (**5h**):* Yield 87% (483 mg); white solid; mp 164−166 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45−7.20 (m, 11H), 7.06−7.01 (m, 2H), 6.94−6.89 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 165.3, 157.2, 151.8, 136.4, 134.9, 130.5, 130.4, 129.8, 129.5, 128.9, 128.7, 128.6, 128.3, 123.9, 121.6, 119.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClN_3S$ 364.0669; found 364.0669.

*(Z)-N-(3,4-Diphenyl-1,2,4-thiadiazol-5(4H)-ylidene)butan-1-amine (**5i**):* Yield 74%(349 mg); white solid; mp 120−122 °C; eluent, hexane/ethyl acetate 92:8; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40−7.14 (m, 10H), 3.11 (t, J = 7.15 Hz, 2H), 1.66−1.54 (m, 2H), 1.44−1.30 (m, 2H), 0.92 (t, J = 7.43 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 162.4, 157.5, 136.7, 130.4, 130.1, 129.3, 128.7, 128.6, 128.5, 128.2, 55.6, 32.4, 20.6, 14.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{20}N_3S$ 310.1362; found 310.1367.

*(Z)-N-(4-Phenyl-3-(p-tolyl)-1,2,4-thiadiazol-5(4H)-ylidene)aniline (**5j**):* Yield 76% (372 mg); white solid; mp 175−177 °C; eluent, hexane/ethyl acetate 95:5; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45−7.27 (m, 7H), 7.21−7.16 (m, 2H), 7.09−6.99 (m, 5H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 164.5, 157.2, 150.7, 143.0, 140.6, 136.7, 129.5, 129.4, 128.9, 128.62, 128.67, 127.2, 123.9, 121.0, 21.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3S$ 344.1221; found 344.1224.

*(Z)-N-(4-Phenyl-3-(p-tolyl)-1,2,4-thiadiazol-5(4H)-ylidene)-propan-2-amine (**5k**):* Yield 75% (331 mg); white solid; mp 164−166 °C; eluent, hexane/ethyl acetate 92:8; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.26 (m, 3H), 7.18−7.10 (m, 4H), 7.00 (d, J = 8.06 Hz, 2H), 3.08−2.98 (m, 1H), 2.27 (s, 3H), 1.14 (d, J = 6.23 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 160.1, 157.5, 140.2, 137.1, 129.1, 128.8, 128.7, 128.6, 128.1, 127.7, 57.4, 23.2, 21.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{20}N_3S$ 310.1332; found 310.1336.

*(Z)-N-(4-Phenyl-3-(p-tolyl)-1,2,4-thiadiazol-5(4H)-ylidene)-cyclopropanamine (**5l**):* Yield 76% (333 mg); white solid; mp 166−168 °C; eluent, hexane/ethyl acetate 91:9; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.28 (m, 3H), 7.16−7.12 (m, 4H), 7.01 (d, J = 8.08 Hz, 2H), 2.45−2.39 (m, 1H), 2.28 (s, 3H), 0.75−0.70 (m, 2H), 0.57−0.53 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 166.4, 157.6, 140.4, 136.7, 129.3, 128.8, 128.62, 128.58, 128.4, 127.5, 36.3, 21.4, 7.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{18}N_3S$ 308.1124; found 308.1131.

*(Z)-N-(4-Phenyl-3-propyl-1,2,4-thiadiazol-5(4H)-ylidene)propan-1-amine (**5m**):* Yield 73% (352 mg); liquid; eluent, hexane/ethyl acetate 90:10; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54−7.48 (m, 2H), 7.47−7.41 (m, 1H), 7.28−7.23 (m, 2H), 3.00 (t, J = 7.02 Hz, 2H), 2.24 (t, J = 7.47 Hz, 2H), 1.65−1.53 (m, 4H), 0.89−0.85 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 163.1, 159.0, 136.3, 129.9, 129.1, 128.6, 57.8, 32.8, 23.5, 19.1, 13.6, 11.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{20}N_3S$ 262.1367; found 262.1372.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00646.

Copies of ^{1}H and ^{13}C NMR spectral data for all products (PDF)

X-ray crystallographic data for **3a** (CIF)

X-ray crystallographic data for **5k** (CIF)

X-ray crystallographic data for **C′** (CIF)

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The authors declare no competing financial interest.

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Advanced Synthesis & Catalysis

Hypervalent Iodine(III)-Mediated Solvent-Free, Regioselective Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles and 2-Aminobenzo[*d*]thiazoles

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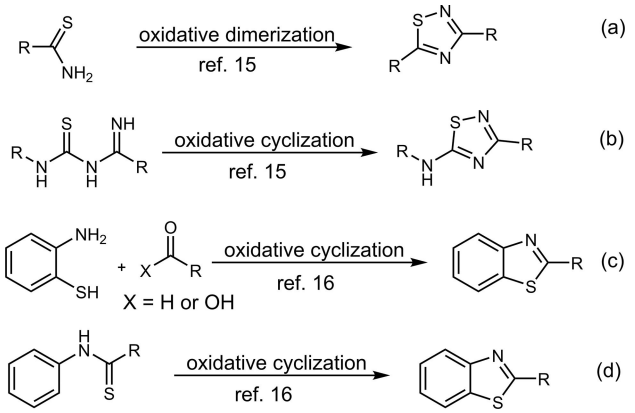
Abstract: A convenient approach for the synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles has been developed using phenyliodine diacetate (PIDA). This approach involves a metal-free oxidative C–N, N–S and C–S bond formations under neat conditions. High regioselectivity, solvent-free conditions, short reaction time and broad functional group compatibility are the notable features of this report.

Keywords: Hypervalent iodine; solvent-free; regioselectivity; 3,4-disubstituted 5-imino-1,2,4-thiadiazoles; 2-aminobenzo[*d*]thiazoles

Efficient transformations carried out under metal-free conditions have received great attention for synthesis of bioactive molecules and pharmaceuticals. In this context, carbon-hetero and hetero-hetero bond formations are an important process for the development of heterocyclic scaffolds.[1] Recently, hypervalent iodine reagents have found a wide range of applications in organic transformations due to their ready availability, easy handling, low toxicity and reactivity similar to heavy metals.[2] In particular, phenyliodine (III) diacetate (PIDA) has been successfully employed in the construction of C–C, C–N, C–O, C–S and also N–S bonds.[3] On the other hand, organic transformations under solvent-free conditions have gained significant attention in recent years.[4] This is because solvent-free reactions usually need shorter reaction times, lower costs with reduced pollution and simple workup procedures.[5]

1,2,4-Thiadiazoles and benzo[*d*]thiazoles are essential heterocyclic scaffolds because of their broad applications in the synthetic organic and pharmaceutical areas. These heterocycles show various biological activities such as antimicrobial,[6] antidiabetic,[7] antibacterial,[8] antifungal,[9] pesticides and corrosion inhibitors.[10] In addition, they are also found in important drugs such as cefozopran[11] (an antibiotic drug), zopolrestat[12] (used for the treatment of diabetic complications), calcimycin[13] (an ionophore antibiotic) and riluzole[14] (an anticonvulsant drug). Despite their wide applications, numerous protocols have been developed to construct the 1,2,4-thiadiazoles and benzo[*d*]thiazoles. Classical approaches for the synthesis of 1,2,4-thiadiazoles involves (a) the simple oxidative dimerization of primary thioamides using various oxidants, (b) oxidative cyclization of imidoyl thiourea using oxidants (Scheme 1a and 1b).[15] Whereas, (a) the simple condensation of *o*-aminothiophenols with either substituted aldehydes, carboxylic acids or esters followed by oxidative cyclizations, (b) oxidative cyclization of thiobenzamides with various oxidants are common protocols for the synthesis of benzo[*d*]thiazoles (Scheme 1c and 1d).[16]

Recently, some metal-free transformations including hypervalent iodine and iodide as catalysts for the synthesis of 1,2,4-thiadiazoles and benzo[*d*]thiazoles were also reported.[17] However, these approaches have one or more shortcomings such as metal catalysts, use of organic solvents, lack of substrate scope and harsh reaction conditions. Thus, more general and convenient synthetic methods for the preparation of 1,2,4-thiadiazoles and benzo[*d*]thiazoles are still in high demand. As part of our ongoing

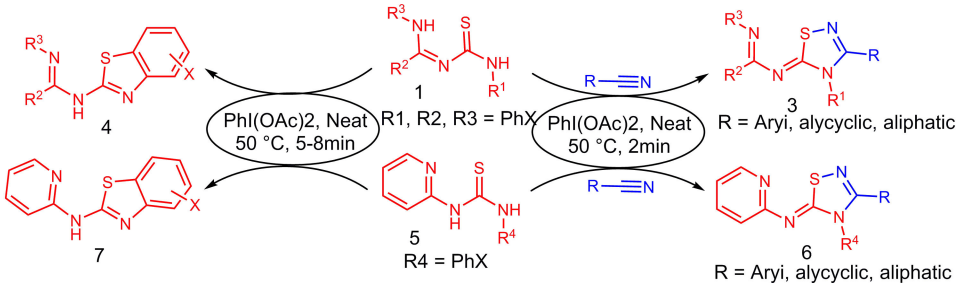


Scheme 1. Previous methods for 1,2,4-thiadiazoles and benzo[*d*]thiazoles.

project to investigate efficient synthetic methods for heterocycles[18] herein, we report a metal-free, solvent-free, regiospecific protocol for the construction of the C–N, N–S and C–S bond by employing PIDA under neat conditions for the synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles (Scheme 2).

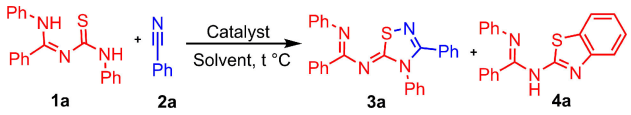
The required substrates imidoyl thioureas were readily prepared from the corresponding amidine and phenylisothiocynate. Initially imidoyl thiourea (**1a**) (1.0 equiv.) and benzonitrile (**2a**) (1.0 equiv.) and PIDA (1.0 equiv.) in DMSO at 50 °C was chosen as model reaction to explore and optimize the reaction conditions. Surprisingly, we observed the unexpected minor product benzo[*d*]thiazole (**4a**) along with the desired 1,2,4-thiadiazole (**3a**) under these conditions (Table 1, entry 1). Aiming to accomplish better yield of **3a** and suppress the formation of **4a**, the reaction was screened under diverse conditions and the results are summarized in Table 1. Performing the reaction in the presence of various solvents, such as DMF, DCE and THF, led to inferior results (Table 1, entries 2–4). The reaction also failed to improve the yield of **3a** with the protic solvents such as MeOH, IPA (Table 1, entries 5 and 6). Notably, in all cases **4a** was also observed in 21–34% yield. We examined the reaction in chlorobenzene and toluene which offered **3a** in 79% and 76% yields respectively in 1 h along with **4a** in minor amount (Table 1, entries 7 and 8). To our delight, when the reaction was carried out under neat reaction conditions we discovered that only **3a** in 88% yield was obtained (Table 1, entry 9). In addition, we investigated different oxidants including PIFA, PhIO, I_2 and CAN under neat condition. All these oxidants were not suitable for this transformation (Table 1, entries 10–13). Increasing the amount of PIDA did not affect the product yield but when the amount of PIDA was decreased, significantly lower yield was obtained (Table 1, entries 14 and 15). Next, reaction temperature affects were also studied. Poor yield was obtained when reaction was conducted at 35 °C and raising the temperature to 65 °C showed that no improvement can be achieved (Table 1, entries 16 and 17). Thus the optimal reaction conditions were set to be imidoyl thiourea (**1a**) (1.0 equiv.) and benzonitrile (**2a**) (1.2 equiv.) and PIDA (1.0 equiv.) at 50 °C under neat conditions.

With the optimized reaction conditions in hand, we then explored the scope and generality of synthetic protocol and the results are summarized in Table 2. As anticipated, all the benzonitriles gave the corresponding 3,4-disubstituted 5-imino-1,2,4-thiadiazoles in good to excellent yields. Benzonitriles with electron-donating groups like -methyl and -methoxy at ortho, para and meta positions gave the corresponding products **3b**, **3c**, **3h** and **3j** in good to high yields. It was noted that ortho-substituted benzonitriles gave a yield similar to that of para subsitituted benzonitrile. The reaction with halogen substituent on benzonitriles such as –F, –Cl and –Br afforded the products **3d**–**3f** in good yields. Benzonitriles with strong electron-withdrawing groups like *p*-CF_3 and *m*-NO_2 generated the corresponding thiadiazoles **3g** and **3i** in 78% and 80% yields respectively. In addition, the heteronitrile such as thiophene-2-carbonitrile gave **3o** in 79% yield. Interestingly, alicyclic and aliphatic nitriles like cyclohexyl, butaryl and methyl reacted smoothly to give the desired products **3p**–**3v** in reasonable good yields. The structure of compounds **3j** and **3s** was confirmed by single-crystal X-ray analysis (Figure 1).[19]



Scheme 2. Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles.

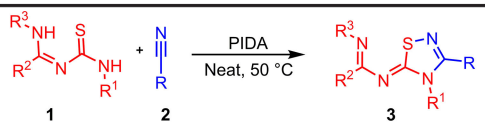
Table 1. Optimization of reaction conditions.

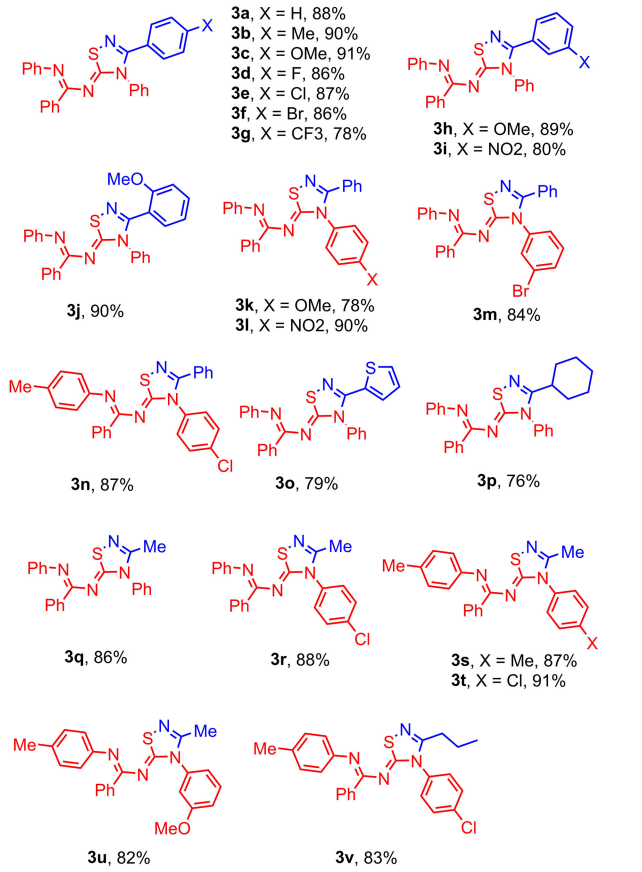


Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield **3a** (%)[c]	**4a** (%)[c]
1[a]	PIDA (100)	DMSO	50	55	21
2[a]	PIDA (100)	DMF	50	47	23
3[a]	PIDA (100)	DCE	50	45	30
4[a]	PIDA (100)	THF	50	49	34
5[a]	PIDA (100)	MeOH	50	30	22
6[a]	PIDA (100)	IPA	50	36	25
7[a]	PIDA (100)	PhCl	50	79	8
8[a]	PIDA (100)	Toluene	50	76	10
9[b]	PIDA (100)	neat	50	88	–
10[b]	PIFA (100)	neat	50	26	38
11[b]	PhIO (100)	neat	50	17	21
12[b]	I_2 (100)	neat	50	–	–
13[b]	CAN (100)	neat	50	Trace	–
14[b]	PIDA (150)	neat	50	88	–
15[b]	PIDA (50)	neat	50	72	–
16[b]	PIDA (100)	neat	35	79	–
17[b]	PIDA (100)	neat	65	88	–

[a] Reaction conditions: **1a** (0.6 mmol, 1.0 equiv.), **2a** (0.6 mmol, 1.0 equiv.) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.
[b] Reaction conditions: **1a** (0.6 mmol, 1.0 equiv.), **2a** (0.7 mmol, 1.2 equiv.) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.
[c] Isolated yield.

Table 2. Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles.[a,b]





[a] Reaction conditions: **1** (0.6 mmol), **2** (0.7 mmol) and PIDA (1.0 equiv.) under neat conditions at 50 °C for 2 min.
[b] Isolated yield.

Next, we investigated the scope of the protocol by varying the imidoyl thiourea, which proceeded successfully to afford the corresponding 3,4-disubstituted 5-imino-1,2,4-thiadiazoles in moderate to good yields. As described in Table 2, all imidoyl thiourea substrates bearing electron-rich substituents such as –Me and –OMe on the aryl ring and electron-deficient substrates like –Cl, –Br and $–NO_2$ on the aryl ring with different nitriles gave the desired products in moderate to good yields (Table 2, entries **3k–3n** and **3r–3v**). Imidoyl thioureas bearing aryl group with electron-withdrawing substituents gave considerably higher yields than those with electron-donating groups.

The design of molecules having potent polyheterocyclic scaffolds that emerge as novel drugs in discovery process is ever challange. In light of our above successive results and advances of polyheterocyclic compounds, we expand our methodology towards the synthesis of 3,4-disubstituted 2-pyridinyl 5-imino-1,2,4-thiadiazoles (**6**). We were glad to observe the formation of desired product **6a** in 90% yield. Next, we investigated the scope and generality of the reaction (Table 3). Benzonitriles bearing electron-donating groups like –Me and –OMe and electron-withdrawing groups such as –F, –Cl and $–CF_3$ were well tolerated and the desired products **6b–6f** were obtained in good to high yields. To our delight, alicyclic and aliphatic nitriles such as cyclohexly, pentyl and methyl were also good partners in this transformation (Table 3, entries **6j–6l**). Furthermore, various pyridinylthioureas with substitutents on aryl ring (R^4) such as methyl, chloro and nitro groups also were well tolerated to yield the desired products (Table 3, entries **6g–6i**). However, the substrates possessing phenyl and propyl group instead of pyridyl group in the pyridinylthiourea did not provide the desired product under the optimized conditions (Table 3, entries **6m** and **6n**). The structure of compound **6h** was further confirmed by X-ray analysis (Figure 1).[19]

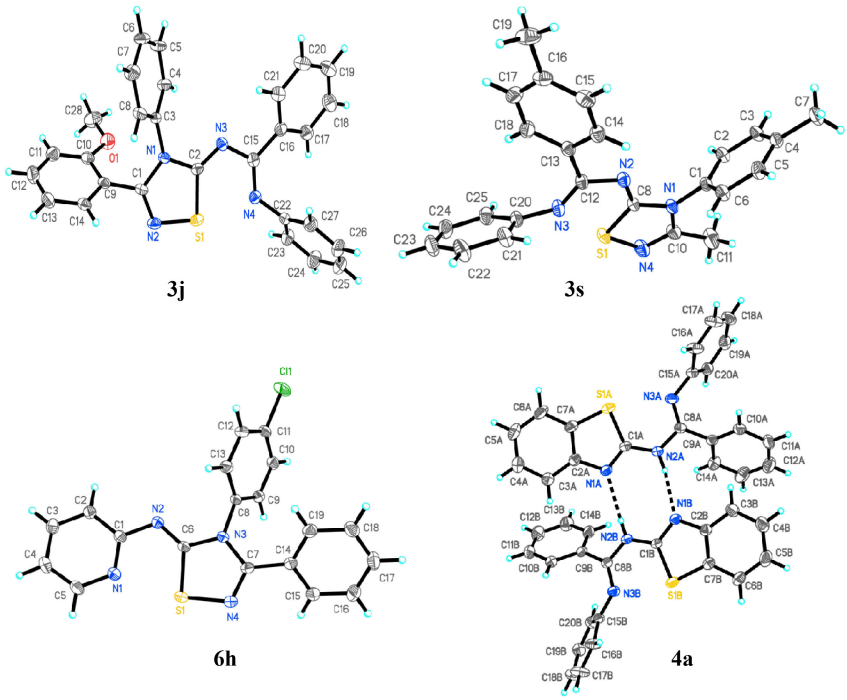
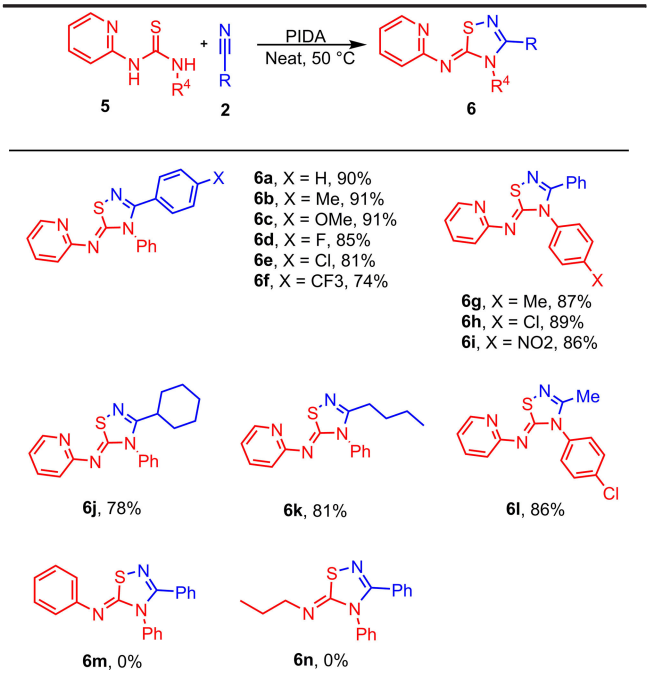


Figure 1. X-ray analysis.

Table 3. Synthesis of 3,4-disubstituted 2-pyridinyl 5-imino-1,2,4-thiadiazoles.[a,b]

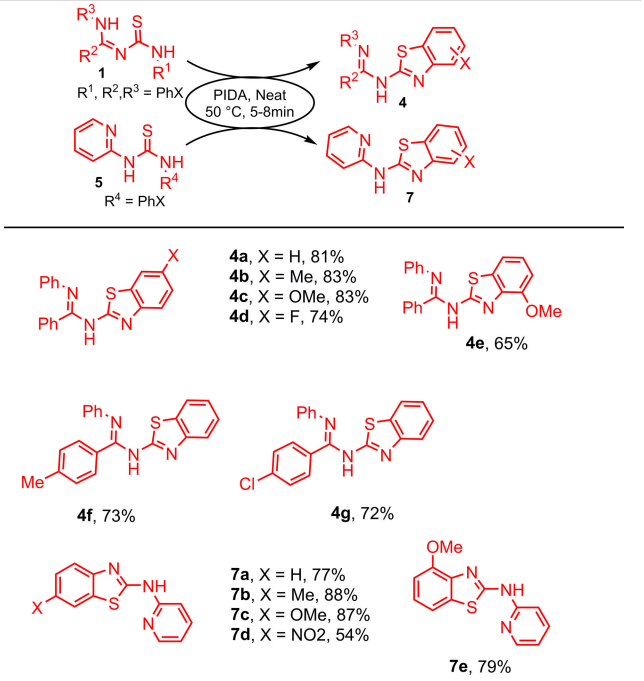


[a] Reaction conditions: **5** (0.8 mmol), **2** (1.0 mmol) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.
[b] Isolated yield.

After successful implementation of this protocol for the synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles, we focused on the byproduct 2-amino-benzo[*d*]thiazoles(**4**). In this context, an experiment was performed with **1a** in the absence of benzonitrile under the optimized reaction conditions which resulted in the corresponding 2-amino-benzo[*d*]thiazole (**4a**) in 81% yield. The structure of compound **4a** was confirmed by single-crystal X-ray analysis (Figure 1).[19] With these optimum reaction conditions in hand, we investigated the scope of the reaction with various substituted imidoyl thioureas (Table 4). Fortunately, imidoyl thiourea bearing both electron-rich and electron-deficient groups like –Me, –OMe, –F and –Cl on aryl ring (R^1 and R^2) reacted smoothly to give the corresponding product benzo[*d*]thiazoles in good yields (Table 4, entries **4b**–**4g**). Next, we turned to investigate the scope of the reaction with pyridinyl thiourea under the optimized reaction conditions. Interestingly, pyridinyl 2-aminobenzo[*d*]thiazoles was obtained in good yields, which was in agreement with the literature.[20] Moreover, the reaction of pyridinyl thiourea bearing electron donating and withdrawing groups on aryl ring (R^4) afforded the corresponding products **7b**–**7e** in good to fare yields.

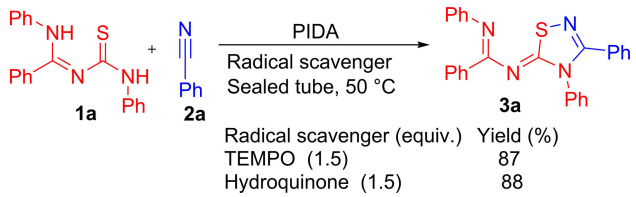
In order to explore the reaction mechanism, the radical trapping experiments were conducted in the presence of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone under the optimized conditions and no considerable effect was observed. These results indicated that the reaction proceeds through an ionic mechanism (Scheme 3). We performed a reaction between **1a** and **2a** in the

Table 4. Synthesis of 2-aminobenzo[*d*]thiazoles.[a,b]



[a] Reaction conditions: **1** (0.6 mmol) or **5** (0.8 mmol) and PIDA (1.0 equiv.) under neat condition at 50 °C for 5–8 min.
[b] Isolated yield.

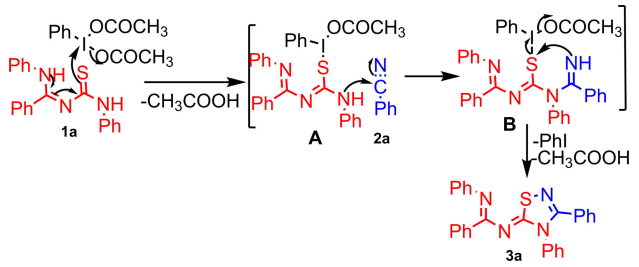
absence of PIDA but the reaction did not provide the desired product.



Scheme 3. Control experiments.

On the basis of these experimental results and previous reports,[21] a mechanism has been proposed for this regioselective synthesis, by taking the formation of **3a** as an example (Scheme 4). Initially, the imidoyl thiourea (**1a**) reacts with PIDA which provides intermediate **A** up on the removal of AcOH. Intermediate **A** reacts with benzonitrile (**2a**) to afford intermediate **B**, followed by intramolecular nucleophilic attack of NH group on the sulfur atom with the loss of iodobenzene and AcOH resulting in the desired product **3a**.

In conclusion, we have developed a novel and efficient method for the synthesis of 3,4-disubstituted



Scheme 4. Proposed reaction mechanism.

5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles. This method includes a PIDA-mediated regioselective oxidative C–N, N–S and C–S bond formation under neat conditions. This methodology proceeded with high efficiency and wide functional group tolerance, affording the corresponding products in good to excellent yields. The key features such as regioselectivity, solvent-free, metal-free, atom economy and short reaction time make it an attractive alternative for the preparation of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles.

Experimental Section

General Experimental Procedure for Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-Thiadiazoles 3a–3v:

To a screw cap reaction vial imidoyl thiourea (**1**) (0.6 mmol), benzonitrile (**2**) (0.7 mmol) and PIDA (1.0 equiv.) were added. The reaction mixture was heated to 50 °C and stirred until completion. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of Na_2CO_3. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding product **3a–3v.**

General Experimental Procedure for Synthesis of 3,4-Disubstituted 2-Pyridinyl 5-Imino-1,2,4-Thiadiazoles 6a–6l:

To a screw cap reaction vial pyridinyl thiourea (**5**) (0.8 mmol), benzonitrile (**2**) (1.0 mmol) and PIDA (1.0 equiv.) were added. The reaction mixture was heated to 50 °C and stirred until completion. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of Na_2CO_3. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding product **6a–6l.**

General Experimental Procedure for Synthesis of 2-Aminobenzo[*d*]Thiazoles 4a–4g and 7a–7e:

To a screw cap reaction vial imidoyl thiourea (**1**) (0.6 mmol) or pyridinyl thiourea (**5**) (0.8 mmol) and PIDA (1.0 equiv.) were added. The reaction mixture was heated to 50 °C and stirred until completion. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of Na_2CO_3. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding products **4a–4g** or **7a–7e.**

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Synthesis T. Nagaraju et al. Paper

$PhI(OAc)_2$-Mediated Regioselective Synthesis of 5-Guanidino-1,2,4-thiadiazoles and 1,2,4-Triazolo[1,5-*a*]pyridines via Oxidative N–S and N–N Bond Formation

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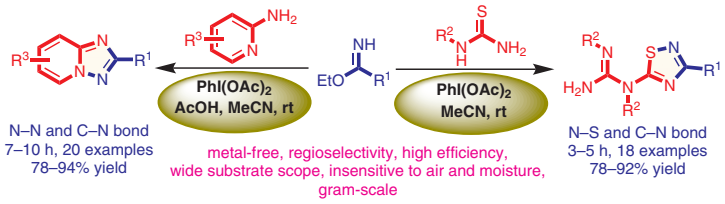

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Abstract An effective and expeditious approach for the construction of biologically important 5-guanidino-1,2,4-thiadiazole and 1,2,4-triazolo[1,5-*a*]pyridine derivatives has been developed. This new protocol involves the phenyliodine(III) diacetate [$PhI(OAc)_2$]-mediated oxidative cyclization of thioureas/2-aminopyridines and imidates via N–S and N–N bond formation at ambient temperature. This method furnishes the versatile 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines in a scalable manner with high efficiency and excellent regioselectivity.

Key words metal-free, regioselectivity, high efficiency, wide substrate scope, insensitivity to air and moisture, 5-guanidino-1,2,4-thiadiazoles, 1,2,4-triazolo[1,5-*a*]pyridines, gram scale

Heterocyclic chemistry is the most demanding and amply rewarding field, and by far heterocyclic scaffolds are the largest class in organic chemistry. Synthetic organic chemists made significant progresses in discovering and developing wide range of heterocyclic compounds for the benefit of mankind. Among these, nitrogen-rich heterocycles are the most important class of compounds with wide applications and biological activities.[1] Due to their importance and success, *N*-containing heterocycles are key targets for the synthesis, and there is a demand for the construction of new approaches that provide access to novel and underdeveloped nitrogen-rich compounds.

1,2,4-Thiadiazoles and 1,2,4-triazoles are considered as very significant nitrogen-based heterocyclic scaffolds due to their important biological activities which can be used as key skeletons in many pharmaceuticals with anticancer,[2] antifungal,[3] antibacterial,[4] and anti-inflammatory activities.[5] In addition, they are also available in biologically active drugs such as Cefozopran,[6] Sitagliptin,[7] Ravuconazole,[8] and Anastrozole[9] (Figure 1).

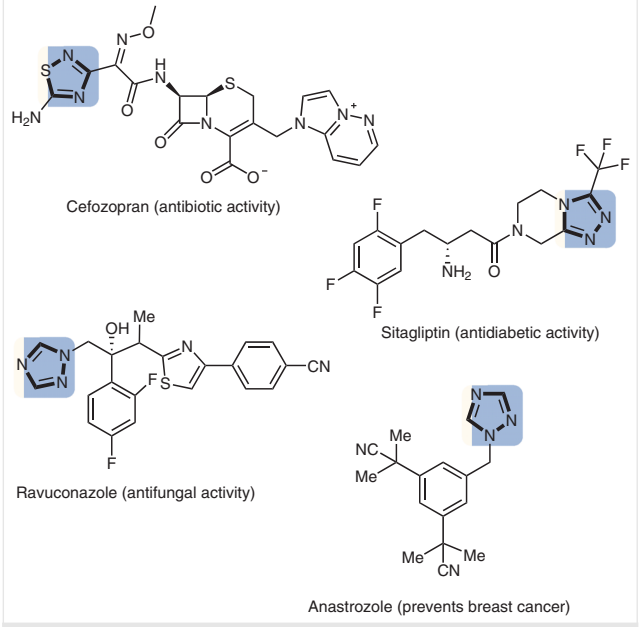
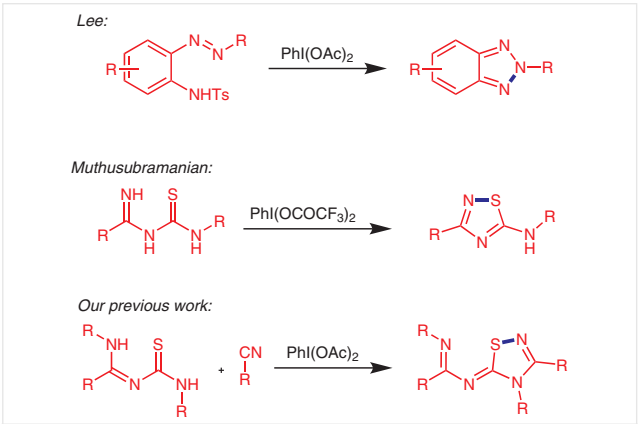


Figure 1 Selected biologically active 1,2,4-thiadiazole and 1,2,4-triazole derivatives

Due to their broad applications in medicinal and pharmaceutical areas, the syntheses of 1,2,4-thiadiazoles and 1,2,4-triazoles have attracted great attention. The most common pathways for the synthesis of 1,2,4-thiadiazoles and 1,2,4-triazoles mainly involves the simple oxidative dimerization of primary thioamides using various oxidants[10] and coupling of carboxylic acids or their derivatives with amidrazones, followed by cyclodehydration,[11] respectively.

On the other hand, hypervalent iodine(III) reagents are highly dominant non-metal oxidants due to their low toxicity, easy accessibility, high reactivity, and environmentally benign nature.[12] In particular, hypervalent iodine(III) re-

agents of phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have been employed in the construction of C–C, C–X, and N–X (X = N,O,S) bond formation protocols.[13–15] Among these methods, carbon–carbon and carbon–heteroatom bond constructions have been intensively explored. A careful literature survey reveals that there are only a few reports providing the formation of heterocyclic compounds through the heteroatom–heteroatom bond formation approach. In particular, the construction of heterocycles through the hypervalent iodine(III)-mediated N–N and N–S bond forming reactions were very limited, as shown in Scheme 1.[16]

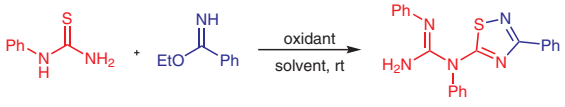


Scheme 1 Previous methods for the construction of heterocycles through iodine(III)-mediated N–S and N–N bond formation

In a continuation of our previous efforts for the construction of biologically important heterocyclic compounds,[17] we present here efficient and regioselective N–S and N–N bond formations from imidates[18] for the synthesis of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines using $PhI(OAc)_2$.

Initially the phenylimidate, ethyl benzenecarboximidate (**1a**; 1.0 equiv), *N*-phenylthiourea (**2a**; 2.0 equiv), and $PhI(OAc)_2$ (1.0 equiv) in CH_2Cl_2 at room temperature were selected as a model reaction to explore and screening the reaction conditions. At first, the desired product 5-guanidino-1,2,4-thiadiazole **3a** was formed in very low yield (Table 1, entry 1). To enhance the yield of the product, we have studied several solvents such as $CHCl_3$, DMF, DMSO, MeCN, and PhCl and the results revealed that MeCN was superior to other solvents (entries 2–6). Next, we extended our investigation by studying various oxidants like $PhI(OCOCF_3)_2$, PhIO, I_2, and TBAI (entries 7–10). The stronger oxidant $PhI(OCOCF_3)_2$ could not provide a better yield of the product **3a** (entry 7) and PhIO was found to be less potent under the studied conditions (entry 8). Oxidants like I_2 and TBAI were also inefficient to provide the desired product (entries 9, 10). Having acceptable oxidant for the synthesis of guanidino thiadiazoles, we further focused on the quantity of $PhI(OAc)_2$. Raising the equivalance of $PhI(OAc)_2$ resulted in improved yields of product **3a** (entries 11, 12), and the use of 2 equivalents of oxidant gave the best result (entry 12). However, with a further increase of $PhI(OAc)_2$ from 2 to 2.5 equivalents, the yield of **3a** did not increase (entry 13). Thus, the established conditions are: 1 equivalent of **1a** and 2 equivalents of **2a** with 2 equivalents of $PhI(OAc)_2$ in the presence of acetonitrile (entry 12).

Table 1 Optimization of Reaction Conditions[a]



2a **1a** **3a**

Entry	Oxidant (equiv)	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$ (1)	CH_2Cl_2	18
2	$PhI(OAc)_2$ (1)	$CHCl_3$	10
3	$PhI(OAc)_2$ (1)	DMF	15
4	$PhI(OAc)_2$ (1)	DMSO	28
5	$PhI(OAc)_2$ (1)	MeCN	40
6	$PhI(OAc)_2$ (1)	PhCl	trace
7	$PhI(OCOCF_3)_2$ (1)	MeCN	25
8	PhIO (1)	MeCN	20
9	I_2 (1)	MeCN	15
10	TBAI (1)	MeCN	NR
11	$PhI(OAc)_2$ (1.5)	MeCN	72
12	**$PhI(OAc)_2$ (2)**	**MeCN**	**90**
13	$PhI(OAc)_2$ (2.5)	MeCN	90

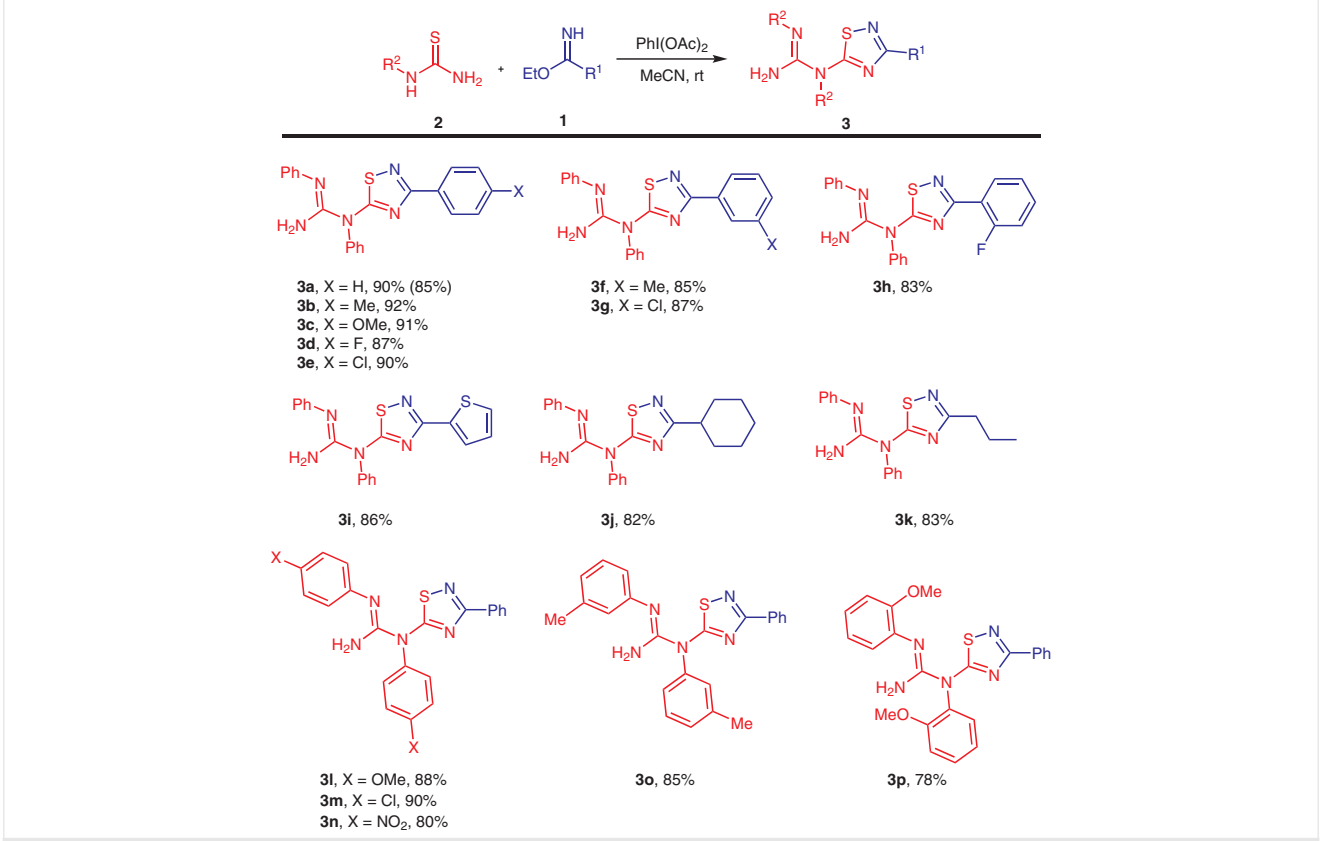
[a] Reaction conditions: **1a** (2 mmol, 1 equiv), **2a** (4 mmol, 2 equiv), catalyst (1–2.5 equiv), and solvent (1 mL) at rt for 3 to 5 h.
[b] Isolated yield. NR: No reaction.

Under the optimal reaction conditions (Table 1, entry 12), we explored the generality and functional group compatibility of this transformation for the synthesis of 5-guanidino-1,2,4-thiadiazoles and the results are summarized in Scheme 2. A wide variety of imidates with various substituents were explored. As anticipated, all the imidates gave the corresponding 5-guanidino-1,2,4-thiadiazoles in good to high yields. Phenylimidates with electron-donating groups like methyl and methoxy at *para*- and *meta*-positions afforded the corresponding products **3b**, **3c**, and **3f** in good to excellent isolated yields. Conversely, the reaction progress with halogen substituent on phenylimidates such as F and Cl at *para*, *meta*, and *ortho* positions afforded the products **3d**, **3e**, **3g**, and **3h** in moderate to good yields. The structure of product **3e** was unambiguously secured by the X-ray diffraction analysis (Figure 2). Gratifyingly, *ortho*-substituted electron-withdrawing phenylimidate afforded the yield similar to that of *para*-subsitituted phenylimidate. In addition, the heteroimidate like thiophene-2-carbimidate gave **3i** in 86% yield. Notably, an alicyclic imidate such as cyclo-

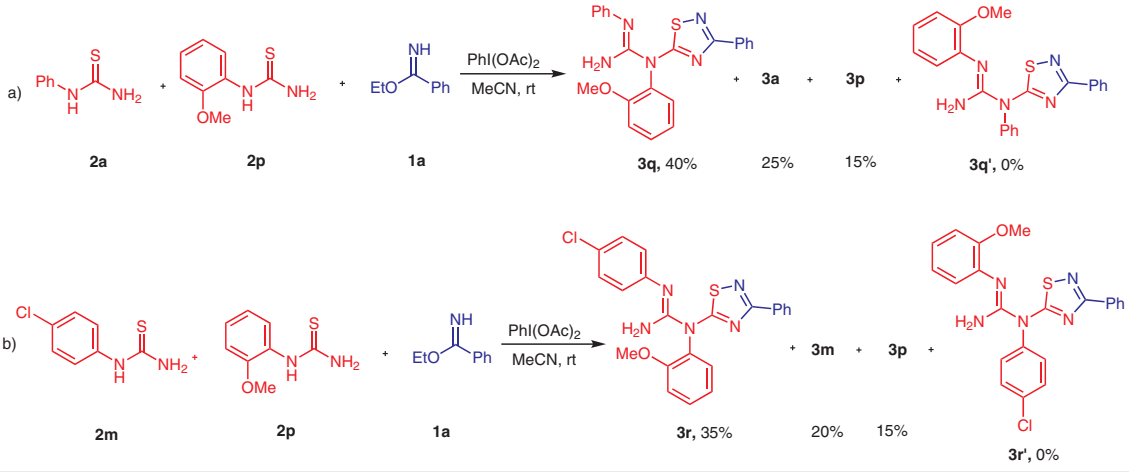
hexyl imidate could also be compatible with the reaction to deliver the corresponding product **3j** in 82% yield. In the case of aliphatic propylimidate, the corresponding product **3k** was obtained in moderate yield. To extend the scope of the substrates and limitations of the reaction, we further studied various *N*-phenylthioureas with phenylimidate, which proceeded proficiently to afford the corresponding 5-guanidino-1,2,4-thiadiazoles in good to excellent yields. As mentioned in Scheme 2, all *N*-phenylthiourea substrates bearing electron-donating substituents such as Me and OMe at *para*, *meta*, and *ortho* positions of the phenyl ring gave the corresponding products **3l**, **3o**, and **3p** in good to high yields. Electron-withdrawing substrate like Cl on the aryl ring gave the desired product in very good yield (Scheme 2, → **3m**). *N*-Phenylthiourea with strong electron-withdrawing group like NO_2 generated the corresponding thiadiazole **3n** in 80% yield. It should be observed that the oxidative cyclization was satisfyingly conducted in gram scale without any complication (Scheme 2, → **3a**).

Further, we wanted to check if this protocol works equally well when a mixture of thioureas were used. Thus, when the reaction was conducted between 1 equivalent of **2a** and 1 equivalent of **2p** with 1 equivalent of phenylimidate **1a** under the established reaction conditions, a mixture of products **3q** in 40% yield along with **3a** and **3p** in 25% and 15% yield, respectively, were obtained. This indicates that a cross-dimerization of *N*-phenylthioureas takes place to furnish the corresponding product **3q** (confirmed by X-ray crystal structure analysis, Figure 2) along with homo-dimerized products **3a** and **3p** (Scheme 3a). The regioisomeric **3q**, namely **3q′** was not observed mainly due the electronic factors of electron-donating *ortho*-methoxy group on the phenyl, which prefers to stay substituted to nitrogen atom of the 1,2,4-thiadiazole ring as it facilitates its formation, which is not the case with **3q′**. To substantiate this, another experiment was conducted with a substrate possessing an electron-withdrawing substrate like **2m** (1 equiv) and **2p** (1 equiv) with **1a** (1 equiv) under the same reaction conditions (Scheme 3b). We isolated similar set of products, **3r** in 35% yield along with **3m** and **3p** in 20%

Figure 2 X-ray crystal structures of **3e**, **3q**, and **5b** (see Supporting Information for details)



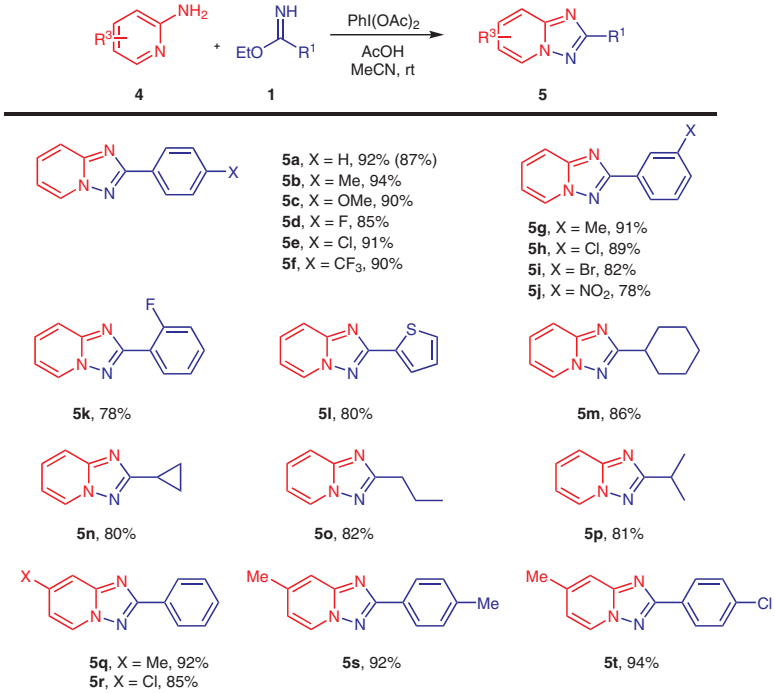
Scheme 2 Synthesis of 5-guanidino-1,2,4-thiadiazoles. *Reagents and conditions*: **1** (2 mmol, 1 equiv), **2** (4 mmol, 2 equiv), PIDA (2 equiv), and MeCN (1 mL) at rt for 3 to 5 h. Isolated yields are shown. The yield shown in parentheses for **3a** is for the reaction conducted on a gram scale.



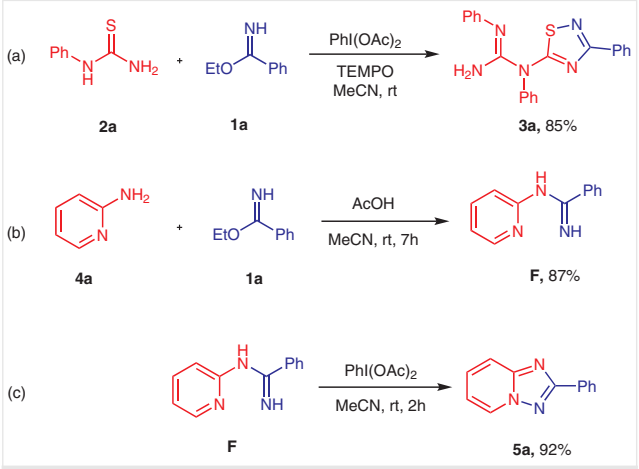
Scheme 3 Synthesis of cross-dimerization products of 5-guanidino-1,2,4-thiadiazoles

and 15%, respectively. This clearly states that the donating-group containing aryl moiety prefers to remain as *N*-substituent of 1,2,4-thiadiazole ring, while the withdrawing-group-bearing aryl group decorates the guanidino nitrogen.

The aforementioned results prompted us to further extend the scope of this practical approach by replacing *N*-phenylthioureas **2** with 2-aminopyridines **4** under the standard conditions to prepare 1,2,4-triazolo[1,5-*a*]pyridines. For this the equivalents of $PhI(OAc)_2$ used were varied and AcOH was used as an additive to enhance the reaction rate. Finally, we arrived at the optimum reaction conditions as: 1 equivalent of **1**, 1 equivalent of **4** with 1 equivalent of $PhI(OAc)_2$ in the presence of 1 equivalent of the additive AcOH in acetonitrile at room temperature. As shown in Scheme 4, this protocol tolerates a variety of phenylimidates with 2-aminopyridines. No significant substituent effect was observed, and excellent yields were obtained for phenylimidates having both electron-donating and elec-



Scheme 4 Synthesis of 1,2,4-triazolo[1,5-*a*]pyridines. *Reagents and conditions*: **1** (2 mmol, 1 equiv), **4** (2 mmol, 1 equiv), PIDA (1 equiv), AcOH (1 equiv), and MeCN (1 mL) at rt for 7 to 10 h. Isolated yields are shown. The yield shown in parentheses for **5a** is for the reaction conducted on a gram scale.

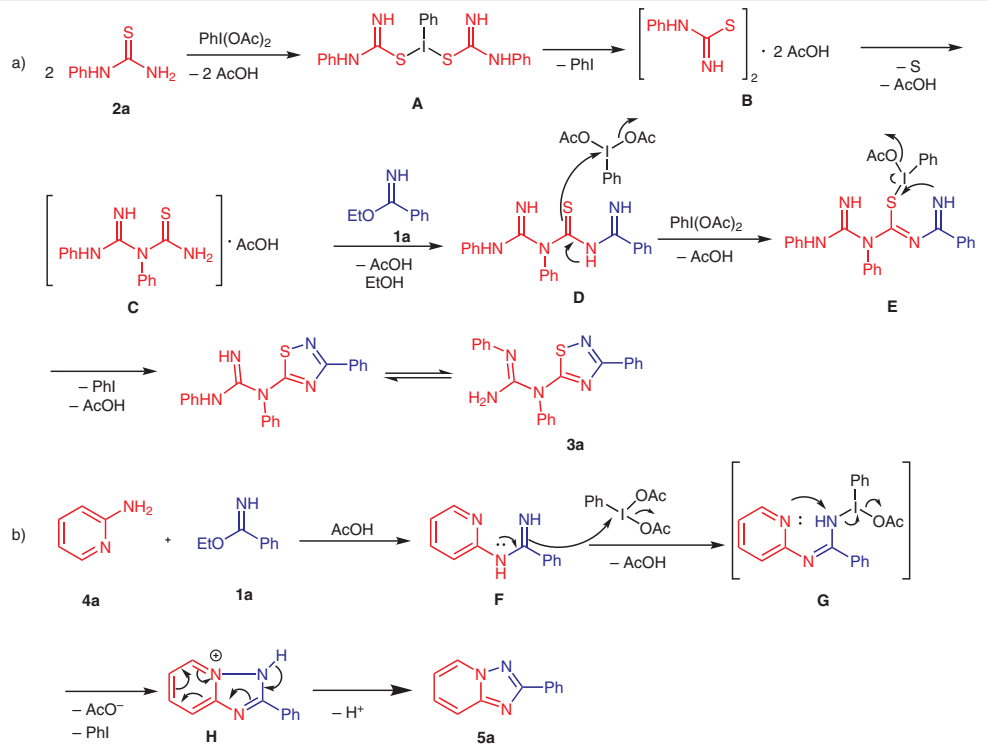


Scheme 5 Control experiments

tron-withdrawing substituents with 2-aminopyridines. It is worth noting that heterocyclic substituent such as thienyl ring (→ **5l**) could also well survive the process with 80% yield. This methodology worked equally well with alicyclic imidates such as cyclohexyl and cyclopropyl, and good yields were observed (→ **5m** and **5n**). Fortunately, the reaction worked equally well with aliphatic imidates, including propyl and isopropyl, which gave corresponding 1,2,4-triazolo[1,5-*a*]pyridines in good yields (→ **5o** and **5p**). The heterocyclic ring of 2-aminopyridine was found to be tolerant of both electron-donating group such as methyl (→ **5q**) and electron-withdrawing group such as halogen (→ **5r**). Reactions of halogen-containing substrates negatively affected the reaction yields compared to the methyl-containing substrate, which was due to the relatively low nucleophilicity of the pyridines affected by the halogens (→ **5q–t**). Here also we synthesized compound **5a** in gram scale successfully. Compound **5b** has been unambiguously determined by X-ray diffraction analysis (Figure 2).

To gain a better understanding of the reaction mechanism, a series of control experiments were carried out under the standard reaction conditions (Scheme 5). When the control experiment was carried out with a radical scavenger such as TEMPO (2,2,6,6-tetramethylpiperdine-1-oxide), it did not influence the reaction rate and outcome of the product yield, which suggests a favoring of ionic mechanism (Scheme 5a). When the phenylimidate **1a** and 2-aminopyridine **4a** undergo reaction in the presence of acetic acid in the absence of $PhI(OAc)_2$, the intermediate *N*-(pyridin-2-yl)imidamide (**F**) (Scheme 5b) was obtained. This intermediate **F** reacts with $PhI(OAc)_2$ to give our desired product **5a** in 92% yield (Scheme 5c).

On the basis of existing literature reports[19,20] and our experimental results, a plausible reaction mechanism for the formation of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines is proposed (Scheme 6). Initially, **2a** undergoes reaction with $PhI(OAc)_2$ to afford polyvalent iodine intermediate **A**, which undergoes iodobenzene elim-



Scheme 6 Proposed reaction mechanism

ination and dimerizes to form 1,6-diphenyldithioformamidine **B**. Then the intermediate **B** eliminates sulfur and forms amidinothiourea **C**. Next, intermediate **C** reacts with **1a** to give the thiourea intermediate **D**, which undergoes reaction with second equivalent of $PhI(OAc)_2$ to form the intermediate **E**, which on intramolecular nucleophilic attack of the NH group on sulfur followed by isomerization affords the desired guanidinothiadiazole **3a** (Scheme 6a). Whereas **1a** condensed with **4a** to afford the intermediate *N*-(pyridin-2-yl)imidamide **F** in the presence of acetic acid, the intermediate **F** reacts with $PhI(OAc)_2$ to generate the intermediate **G** with the release of acetic acid and then intramolecular nucleophilic attack of the nitrogen atom of the pyridine ring takes place to give ammonium ion **H**, which affords the required product **5a** after rearomatization through the elimination of a proton (Scheme 6b).

In summary, we could develop a novel and convenient approach for the construction of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines under mild conditions through oxidative N–S and N–N bond formation from thioureas/2-aminopyridines and imidates for the first time. The use of environmentally benign $PhI(OAc)_2$ reagent makes this protocol green and highly practical. Moreover, the metal-free nature of the protocol, its regioselectivity and high functional group tolerance, the mild reaction conditions, and the scalability are all attractive features of this method.

Chemicals and all solvents were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were measured on Bruker Avance-300, Varian Unity-400 MHz and Avance New-500 MHz and ^{13}C NMR spectra were measured with Varian Unity-300 MHz (75 MHz), Varian Unity-400 MHz (100 MHz) and Avance New-500 MHz (125 MHz), as specified and referred to TMS as the internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in hertz (Hz). High-resolution mass spectra (HRMS) were performed on a high-resolution magnetic sector mass spectrometer. TLC analysis was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on silica gel (100–200 mesh) from Merck. Melting points were measured using melting point apparatus and are uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

5-Guanidino-1,2,4-thiadiazoles 3a–r; General Procedure

A mixture of imidate **1** (2 mmol), *N*-phenylthiourea **2** (4 mmol), and $PhI(OAc)_2$ (4 mmol) in MeCN (1 mL) was stirred at rt. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with sat. aq $NaHCO_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford the corresponding product **3a–r**.

(*E*)-1,2-Diphenyl-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3a)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 672 mg (90%); mp 198–200 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04–8.03 (m, 2 H), 7.63–7.51 (m, 5 H), 7.41–7.32 (m, 5 H), 7.14–7.10 (m, 3 H), 4.41 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 166.2, 145.7, 137.9, 133.7, 130.2, 129.7, 129.6, 129.4, 129.3, 128.3, 127.7, 123.7, 122.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}N_5S$: 372.1277; found: 372.1281.

Scale-Up Reaction for 3a

A mixture of ethyl benzenecarboximidate (**1a**; 0.894 g, 6 mmol), *N*-phenylthiourea (**2a**; 1.98 g, 13 mmol), and $PhI(OAc)_2$ (4.18 g, 13 mmol) in MeCN (1 mL) was stirred at rt. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with sat. aq $NaHCO_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford **3a**; yield: 1.8921g (85%).

(*E*)-1,2-Diphenyl-1-[3-(*p*-tolyl)-1,2,4-thiadiazol-5-yl]guanidine (3b)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 651 mg (92%); mp 205–207 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.1 Hz, 2 H), 7.63–7.51 (m, 5 H), 7.41–7.37 (m, 2 H), 7.14–7.09 (m, 5 H), 4.41 (s, 2 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 166.3, 145.8, 145.7, 139.4, 137.9, 131.1, 130.2, 129.7, 129.6, 129.3, 128.9, 127.6, 123.7, 122.8, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_5S$: 386.1433; found: 386.1440.

(*E*)-1-[3-(4-Methoxyphenyl)-1,2,4-thiadiazol-5-yl]-1,2-diphenylguanidine (3c)

Eluent: Hexane/EtOAc (90:10); white solid; yield: 611 mg (91%); mp 202–204 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.7 Hz, 2 H), 7.63–7.49 (m, 5 H), 7.41–7.37 (m, 2 H), 7.13–7.09 (m, 3 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.41 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 166.0, 160.6, 145.8, 145.6, 137.9, 130.2, 129.7, 129.6, 129.3, 129.2, 126.8, 123.6, 122.8, 113.5, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_5OS$: 402.1383; found: 402.1384.

(*E*)-1-[3-(4-Fluorophenyl)-1,2,4-thiadiazol-5-yl]-1,2-diphenylguanidine (3d)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 607 mg (87%); mp 199–201 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.99 (m, 2 H), 7.64–7.50 (m, 5 H), 7.41–7.37 (m, 2 H), 7.14–7.09 (m, 3 H), 7.03–6.97 (m, 2 H), 4.42 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 165.2, 164.8, 162.4, 145.6, 137.8, 130.3, 130.0, 129.7, 129.6, 129.3, 123.8, 122.8, 115.2 (d, *J* = 21.6 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}FN_5S$: 390.1183; found: 390.1187.

(*E*)-1-[3-(4-Chlorophenyl)-1,2,4-thiadiazol-5-yl]-1,2-diphenylguanidine (3e)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 597 mg (90%); mp 220–222 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.5 Hz, 2 H), 7.64–7.51 (m, 5 H), 7.42–7.38 (m, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.15–7.09 (m, 3 H), 4.42 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 165.1, 145.6, 137.8, 135.3, 132.2, 130.3, 129.7, 129.2, 129.0, 128.4, 123.8, 122.8;

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}ClN_5S$: 406.0887; found: 406.0892.

(*E*)-1,2-Diphenyl-1-[3-(*m*-tolyl)-1,2,4-thiadiazol-5-yl]guanidine (3f)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 602 mg (85%); mp 181–183 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.81 (d, *J* = 7.7 Hz, 1 H), 7.64–7.52 (m, 5 H), 7.42–7.38 (m, 2 H), 7.23–7.19 (m, 1 H), 7.15–7.10 (m, 4 H), 4.42 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 166.4, 145.7, 137.9, 133.6, 130.2, 129.7, 129.6, 129.3, 128.2, 128.1, 125.0, 123.7, 122.8, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_5S$: 386.1433; found: 386.1440.

(*E*)-1-[3-(3-Chlorophenyl)-1,2,4-thiadiazol-5-yl]-1,2-diphenylguanidine (3g)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 576 mg (87%); mp 209–211 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.92 (d, *J* = 7.5 Hz, 1 H), 7.64–7.51 (m, 5 H), 7.41–7.38 (m, 2 H), 7.30–7.24 (m, 2 H), 7.15–7.10 (m, 3 H), 4.42 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 164.8, 145.7, 137.7, 135.4, 134.2, 130.3, 129.8, 129.7, 129.5, 129.4, 129.2, 127.7, 125.8, 123.8, 122.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}ClN_5S$: 406.0887; found: 406.0901.

(*E*)-1-[3-(2-Fluorophenyl)-1,2,4-thiadiazol-5-yl]-1,2-diphenylguanidine (3h)

Eluent: Hexane/EtOAc (92:8); white solid; yield: 579 mg (83%); mp 207–209 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88–7.85 (m, 1 H), 7.62–7.59 (m, 2 H), 7.55–7.51 (m, 3 H), 7.41–7.38 (m, 2 H), 7.14–7.06 (m, 6 H), 4.43 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 162.5, 162.0, 159.5, 145.6, 137.8, 131.5, 130.8, 130.7, 130.3, 129.76, 129.72, 129.2, 123.7, 122.8, 118.9, 116.5 (d, *J* = 22.1 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}FN_5S$: 390.1183; found: 390.1187.

(*E*)-1,2-Diphenyl-1-[3-(thiophen-2-yl)-1,2,4-thiadiazol-5-yl]guanidine (3i)

Eluent: Hexane/EtOAc (90:10); white solid; yield: 627 mg (86%); mp 230–232 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.65–7.54 (m, 6 H), 7.40–7.35 (m, 3 H), 7.10–7.03 (m, 4 H), 5.85 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 176.6, 160.4, 146.4, 145.4, 137.5, 137.4, 129.9, 129.3, 128.2, 127.7, 127.1, 122.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}N_5S_2$: 378.0841; found: 378.0851.

(*E*)-1-(3-Cyclohexyl-1,2,4-thiadiazol-5-yl)-1,2-diphenylguanidine (3j)

Eluent: Hexane/EtOAc (90:10); white solid; yield: 597 mg (82%); mp 175–177 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 2 H), 7.54–7.51 (m, 1 H), 7.47–7.44 (m, 2 H), 7.38–7.35 (m, 2 H), 7.11–7.08 (m, 1 H), 7.06–7.04 (m, 2 H), 4.38 (s, 2 H), 2.67 (tt, *J* = 11.6, 3.5 Hz, 1 H), 1.94–1.91 (m, 2 H), 1.74–1.71 (m, 2 H), 1.64–1.61 (m, 2 H), 1.49–1.41 (m, 2 H), 1.32–1.26 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 174.4, 146.0, 145.8, 138.1, 130.2, 129.6, 129.5, 129.3, 123.5, 122.7, 41.9, 31.5, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}N_5S$: 378.1746; found: 378.1751.

(*E*)-1,2-Diphenyl-1-(3-propyl-1,2,4-thiadiazol-5-yl)guanidine (3k)

Eluent: Hexane/EtOAc (90:10); white solid; yield: 729 mg (83%); mp 186–188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.49 (m, 3 H), 7.46–7.43 (m, 2 H), 7.39–7.34 (m, 2 H), 7.12–7.05 (m, 3 H), 4.37 (s, 2 H), 2.65–2.62 (m, 2 H), 1.72–1.62 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 170.5, 145.7, 137.9, 130.3, 129.7, 129.2, 123.6, 122.8, 35.2, 21.4, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_5S$: 338.1433; found: 338.1436.

(*E*)-1,2-Bis(4-methoxyphenyl)-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3l)

Eluent: Hexane/EtOAc (88:12); white solid; yield: 763 mg (88%); mp 202–204 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 2 H), 7.43–7.40 (m, 2 H), 7.34–7.33 (m, 3 H), 7.10–7.02 (m, 4 H), 6.95–6.93 (m, 2 H), 4.42 (s, 2 H), 3.91 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.3, 166.1, 160.1, 156.1, 146.2, 138.8, 133.8, 130.4, 129.4, 128.2, 127.7, 123.6, 115.3, 115.0, 55.64, 55.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_5O_2S$: 432.1488; found: 432.1484.

(*E*)-1,2-Bis(4-chlorophenyl)-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3m)

Eluent: Hexane/EtOAc (88:12); white solid; yield: 797 mg (90%); mp 237–239 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.91–7.89 (m, 2 H), 7.67 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 8.7 Hz, 2 H), 7.40–7.37 (m, 5 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 6.19 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 176.8, 164.7, 147.0, 144.7, 136.5, 133.7, 133.1, 131.3, 129.9, 129.6, 129.0, 128.5, 127.0, 126.6, 124.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}Cl_2N_5S$: 440.0498; found: 440.0509.

(*E*)-1,2-Bis(4-nitrophenyl)-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3n)

Eluent: Hexane/EtOAc (85:15); yellow solid; yield: 742 mg (80%); mp 248–250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.48 (d, *J* = 8.7 Hz, 2 H), 8.25 (d, *J* = 8.8 Hz, 2 H), 7.95–7.90 (m, 4 H), 7.45–7.37 (m, 3 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 6.74 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.2, 165.5, 153.6, 148.2, 148.0, 143.6, 142.6, 133.3, 131.8, 130.3, 129.1, 127.6, 125.6, 124.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_7O_4S$: 462.0979; found: 462.0987.

(*E*)-1-(3-Phenyl-1,2,4-thiadiazol-5-yl)-1,2-di-(*m*-tolyl)guanidine (3o)

Eluent: Hexane/EtOAc (85:15); white solid; yield: 682 mg (85%); mp 181–183 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.02 (m, 2 H), 7.50–7.46 (m, 1 H), 7.38–7.24 (m, 7 H), 6.94–6.88 (m, 3 H), 4.41 (s, 2 H), 2.45 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 166.1, 145.7, 140.4, 139.6, 137.8, 133.8, 130.4, 129.9, 129.6, 129.5, 129.4, 128.3, 127.7, 126.2, 124.5, 123.5, 119.7, 21.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_5S$: 400.1590; found: 400.1593.

(*E*)-1,2-Bis(2-methoxyphenyl)-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3p)

Eluent: Hexane/EtOAc (85:15); white solid; yield: 676 mg (78%); mp 195–197 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.52–7.47 (m, 2 H), 7.34–7.30 (m, 3 H), 7.16–7.07 (m, 4 H), 7.02–6.97 (m, 2 H), 4.39 (s, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 161.3, 151.2, 146.8, 141.2, 130.2, 129.3, 126.4, 126.1, 124.5, 123.4, 123.0, 121.9, 120.2, 119.7, 117.1, 116.7, 108.4, 108.3, 51.6, 51.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_5O_2S$: 432.1488; found: 432.1481.

(*E*)-1-(2-Methoxyphenyl)-2-phenyl-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3q)

Eluent: Hexane/EtOAc (85:15); white solid; yield: 322 mg (40%); mp 190–191 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05–8.02 (m, 2 H), 7.55–7.51 (m, 1 H), 7.47 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.40–7.37 (m, 2 H), 7.34–7.31 (m, 3 H), 7.17–7.10 (m, 5 H), 4.42 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 166.2, 155.9, 145.9, 133.9, 131.3, 130.8, 130.1, 129.6, 129.3, 128.2, 127.7, 126.4, 123.5, 122.9, 121.5, 113.0, 56.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_5OS$: 402.1383; found: 402.1396.

(*E*)-2-(4-Chlorophenyl)-1-(2-methoxyphenyl)-1-(3-phenyl-1,2,4-thiadiazol-5-yl)guanidine (3r)

Eluent: Hexane/EtOAc (85:15); white solid; yield: 306 mg (35%); mp 213–215 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.56–7.52 (m, 1 H), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.36–7.31 (m, 5 H), 7.18–7.13 (m, 2 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 4.43 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 166.3, 155.9, 146.2, 144.6, 133.8, 131.4, 130.8, 129.6, 129.3, 128.7, 128.2, 127.7, 126.3, 124.2, 121.5, 113.0, 56.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}ClN_5OS$: 436.0993; found: 436.1002.

1,2,4-Triazolo[1,5-*a*]pyridines 5a–t; General Procedure

A mixture of imidate **1** (2 mmol), 2-aminopyridine **4** (2 mmol), $PhI(OAc)_2$ (2 mmol), and AcOH (2 mmol) in MeCN (1 mL) was stirred at rt. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with sat. aq $NaHCO_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford the corresponding product **5a–t**.

***N*-(Pyridin-2-yl)benzimidamide (F)**[20]

Eluent: hexane/EtOAc (70:30); white solid; yield: 345 mg (87%); mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 4.9, 1.4 Hz, 1 H), 7.92–7.91 (m, 2 H), 7.67–7.63 (m, 1 H), 7.49–7.43 (m, 3 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 6.95–6.92 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7, 159.2, 145.9, 137.5, 137.3, 130.6, 128.6, 126.9, 122.3, 117.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3$: 198.1025; found: 198.1031.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyridine (5a)[20]

Eluent: Hexane/EtOAc (86:14); white solid; yield: 361 mg (92%); mp 136–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 6.8 Hz, 1 H), 8.31–8.27 (m, 2 H), 7.76 (d, *J* = 8.9 Hz, 1 H), 7.53–7.46 (m, 4 H), 7.02–6.98 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 151.7, 130.8, 130.1, 129.5, 128.7, 128.3, 127.3, 116.4, 113.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}N_3$: 196.0869; found: 196.0865.

Scale-Up Reaction for 5a

A mixture of ethyl benzenecarboximidate (**1a**; 0.894 g, 6 mmol), 2-aminopyridine **4a** (0.56 g, 6 mmol), $PhI(OAc)_2$ (1.93 g, 6 mmol), and AcOH (0.36 g, 6 mmol) in MeCN (1 mL) was stirred at rt. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with sat. aq $NaHCO_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford corresponding product **5a**; yield: 1.0106g (87%).

2-(*p*-Tolyl)[1,2,4]triazolo[1,5-*a*]pyridine (5b)[20]

Eluent: Hexane/EtOAc (85:15); white solid; yield: 395 mg (94%); mp 170–172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 6.8 Hz, 1 H), 8.18 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.9 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 6.96–6.92 (m, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 151.6, 140.2, 129.45, 129.42, 128.2, 127.9, 127.2, 116.2, 113.4, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_3$: 210.1025; found: 210.1022.

2-(4-Methoxyphenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5c)[20]

Eluent: Hexane/EtOAc (80:20); white solid; yield: 339 mg (90%); mp 140–142 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 6.8 Hz, 1 H), 8.24–8.21 (m, 2 H), 7.72 (d, *J* = 8.9 Hz, 1 H), 7.50–7.47 (m, 1 H), 7.03–7.00 (m, 2 H), 6.99–6.96 (m, 1 H), 3.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1, 161.2, 151.7, 129.4, 128.8, 128.2, 123.4, 116.1, 114.1, 113.3, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_3O$: 226.0974; found: 226.0970.

2-(4-Fluorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5d)[20]

Eluent: Hexane/EtOAc (86:14); white solid; yield: 325 mg (85%); mp 177–179 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 6.8 Hz, 1 H), 8.30–8.26 (m, 2 H), 7.75 (d, *J* = 8.9 Hz, 1 H), 7.53–7.49 (m, 1 H), 7.20–7.16 (m, 2 H), 7.02–6.99 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2 (d, *J* = 213.5 Hz), 163.1, 151.7, 129.5 (d, *J* = 39.3 Hz), 129.2, 128.3, 127.0 (d, *J* = 2.7 Hz), 116.4, 115.7 (d, *J* = 21.8 Hz), 113.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9FN_3$: 214.0775; found: 214.0771.

2-(4-Chlorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5e)[20]

Eluent: Hexane/EtOAc (87:13); white solid; yield: 341 mg (91%); mp 227–229 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 6.8 Hz, 1 H), 8.24–8.21 (m, 2 H), 7.75 (d, *J* = 8.9 Hz, 1 H), 7.54–7.46 (m, 3 H), 7.04–7.01 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 151.7, 136.1, 129.7, 129.3, 129.0, 128.6, 128.3, 116.4, 113.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9ClN_3$: 230.0479; found: 230.0477.

2-[4-(Trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*a*]pyridine (5f)[20]

Eluent: Hexane/EtOAc (87:13); white solid; yield: 327 mg (90%); mp 234–236 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 6.8 Hz, 1 H), 8.41 (d, *J* = 8.0 Hz, 2 H), 7.80–7.74 (m, 3 H), 7.57–7.52 (m, 1 H), 7.07–7.03 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 151.7, 134.2, 131.7 (q, *J* = 32.4 Hz), 129.8, 128.4, 127.5, 125.6 (d, *J* = 3.4 Hz), 124.1 (d, *J* = 272.1 Hz), 116.6, 114.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_9F_3N_3$: 264.0743; found: 264.0738.

2-(*m*-Tolyl)[1,2,4]triazolo[1,5-*a*]pyridine (5g)[20]

Eluent: Hexane/EtOAc (84:16); white solid; yield: 382 mg (91%); mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 6.8 Hz, 1 H), 8.13–8.08 (m, 2 H), 7.75 (d, *J* = 8.9 Hz, 1 H), 7.51–7.47 (m, 1 H), 7.41–7.37 (m, 1 H), 7.29 (s, 1 H), 7.00–6.97 (m, 1 H), 2.45 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 151.6, 138.4, 130.9, 130.6, 129.5, 128.6, 128.3, 127.9, 124.4, 116.3, 113.6, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_3$: 210.1025; found: 210.1027.

2-(3-Chlorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5h)[20]

Eluent: Hexane/EtOAc (84:16); white solid; yield: 333 mg (89%); mp 186–188 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58–8.56 (m, 1 H), 8.29–8.28 (m, 1 H), 8.17–8.15 (m, 1 H), 7.75–7.72 (m, 1 H), 7.52–7.47 (m, 1 H), 7.42–7.38 (m, 2 H), 7.02–6.98 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 151.6, 134.7, 132.6, 130.0, 129.9, 129.7, 128.3, 127.4, 125.3, 116.5, 113.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9ClN_3$: 230.0479; found: 230.0481.

2-(3-Bromophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5i)

Eluent: Hexane/EtOAc (83:17); white solid; yield: 295 mg (82%); mp 201–203 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 6.8 Hz, 1 H), 8.47–8.46 (m, 1 H), 8.22 (d, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 9.0 Hz, 1 H), 7.61–7.52 (m, 2 H), 7.39–7.35 (m, 1 H), 7.06–7.02 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 151.7, 133.0, 132.8, 130.3, 130.2, 129.8, 128.4, 125.8, 122.9, 116.6, 113.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9BrN_3$: 273.9974; found: 273.9971.

2-(3-Nitrophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5j)

Eluent: Hexane/EtOAc (80:20); white solid; yield: 289 mg (78%); mp 280–282 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16–9.15 (m, 1 H), 8.65–8.61 (m, 2 H), 8.33–8.31 (m, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 7.70–7.66 (m, 1 H), 7.60–7.56 (m, 1 H), 7.11–7.07 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1, 151.8, 132.9, 132.7, 130.1, 129.7, 128.5, 124.6, 122.3, 116.7, 114.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_4O_2$: 241.0720; found: 241.0716.

2-(2-Fluorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (5k)[20]

Eluent: Hexane/EtOAc (85:15); white solid; yield: 297 mg (78%); mp 169–171 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 6.8 Hz, 1 H), 8.28–8.24 (m, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 7.57–7.53 (m, 1 H), 7.49–7.43 (m, 1 H), 7.31–7.23 (m, 2 H), 7.07–7.03 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 160.3 (d, *J* = 129.0 Hz), 151.1, 131.5 (d, *J* = 8.6 Hz), 130.9, 129.7, 128.5, 124.3, 118.8, 116.8, 116.6, 113.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9FN_3$: 214.0775; found: 214.0776.

2-(Thiophen-2-yl)[1,2,4]triazolo[1,5-*a*]pyridine (5l)[20]

Eluent: Hexane/EtOAc (85:15); white solid; yield: 311 mg (80%); mp 168–170 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 6.8 Hz, 1 H), 7.89 (dd, *J* = 3.6, 1.2 Hz, 1 H), 7.73 (d, *J* = 8.9 Hz, 1 H), 7.53–7.49 (m, 1 H), 7.45 (dd, *J* = 5.0, 1.2 Hz, 1 H), 7.17 (dd, *J* = 5.0, 3.6 Hz, 1 H), 7.02–6.99 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 151.5, 133.6, 129.8, 128.2, 128.0, 127.9, 127.7, 116.2, 113.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8N_3S$: 202.0433; found: 202.0436.

2-Cyclohexyl[1,2,4]triazolo[1,5-*a*]pyridine (5m)

Eluent: Hexane/EtOAc (82:18); white solid; yield: 334 mg (86%); mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 6.8 Hz, 1 H), 7.67 (d, *J* = 8.9 Hz, 1 H), 7.47–7.43 (m, 1 H), 6.96–6.92 (m, 1 H), 3.00–2.92 (m, 1 H), 2.15–2.12 (m, 2 H), 1.89–1.85 (m, 2 H), 1.76–1.66 (m, 2 H), 1.50–1.26 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 150.9, 129.0, 128.0, 115.9, 112.9, 38.1, 31.9, 26.1, 25.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}N_3$: 202.1338; found: 202.1336.

2-Cyclopropyl[1,2,4]triazolo[1,5-*a*]pyridine (5n)

Eluent: Hexane/EtOAc (82:18); pale yellow liquid; yield: 337 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 6.8 Hz, 1 H), 7.59 (d, *J* = 8.9 Hz, 1 H), 7.45–7.41 (m, 1 H), 6.93–6.90 (m, 1 H), 2.25–2.19 (m, 1 H), 1.17–1.06 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 151.1, 129.1, 127.7, 115.5, 112.7, 9.2, 8.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{10}N_3$: 160.0869; found: 160.0866.

2-Propyl[1,2,4]triazolo[1,5-*a*]pyridine (5o)

Eluent: Hexane/EtOAc (82:18); pale yellow liquid; yield: 344 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.52 (m, 1 H), 7.69–7.67 (m, 1 H), 7.47–7.44 (m, 1 H), 6.96–6.93 (m, 1 H), 2.93–2.90 (m, 2 H), 1.94–1.88 (m, 2 H), 1.06–1.02 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 151.0, 129.2, 127.9, 115.8, 113.0, 30.6, 21.6, 13.8;

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}N_3$: 162.1025; found: 162.1023.

2-Isopropyl[1,2,4]triazolo[1,5-*a*]pyridine (5p)

Eluent: Hexane/EtOAc (82:18); pale yellow liquid; yield: 340 mg (81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 6.8 Hz, 1 H), 7.68 (d, *J* = 8.9 Hz, 1 H), 7.48–7.45 (m, 1 H), 6.96–6.93 (m, 1 H), 3.32–3.24 (m, 1 H), 1.45 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 151.1, 129.1, 128.1, 116.0, 113.0, 28.7, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}N_3$: 162.1025; found: 162.1027.

7-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (5q)[20]

Eluent: Hexane/EtOAc (84:16); white solid; yield: 387 mg (92%); mp 142–144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 6.9 Hz, 1 H), 8.27 (dd, *J* = 8.0, 1.6 Hz, 2 H), 7.51–7.45 (m, 4 H), 6.80 (dd, *J* = 6.9, 1.6 Hz, 1 H), 2.47 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2, 151.9, 141.0, 130.9, 129.9, 128.6, 127.2, 116.1, 115.0, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_3$: 210.1025; found: 210.1028.

7-Chloro-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (5r)[20]

Eluent: Hexane/EtOAc (84:16); white solid; yield: 391 mg (85%); mp 198–200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 7.2, 0.7 Hz, 1 H), 8.27–8.24 (m, 2 H), 7.74 (dd, *J* = 2.2, 0.7 Hz, 1 H), 7.53–7.47 (m, 3 H), 6.99 (dd, *J* = 7.2, 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 151.8, 136.2, 130.4, 130.3, 128.8, 128.4, 127.4, 115.5, 115.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9ClN_3$: 230.0479; found: 230.0481.

7-Methyl-2-(*p*-tolyl)[1,2,4]triazolo[1,5-*a*]pyridine (5s)

Eluent: Hexane/EtOAc (84:16); white solid; yield: 377 mg (92%); mp 194–196 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 6.9 Hz, 1 H), 8.15 (d, *J* = 8.1 Hz, 2 H), 7.47 (s, 1 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 6.76 (d, *J* = 6.9 Hz, 1 H), 2.44 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2, 151.8, 140.8, 140.0, 129.4, 128.1, 127.2, 127.1, 115.9, 114.8, 21.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3$: 224.1182; found: 224.1177.

2-(4-Chlorophenyl)-7-methyl[1,2,4]triazolo[1,5-*a*]pyridine (5t)

Eluent: Hexane/EtOAc (84:16); white solid; yield: 374 mg (94%); mp 202–204 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 7.0 Hz, 1 H), 8.21–8.18 (m, 2 H), 7.48–7.43 (m, 3 H), 6.82 (dd, *J* = 7.0, 1.7 Hz, 1 H), 2.48 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 151.9, 141.2, 135.9, 129.5, 128.9, 128.5, 127.2, 116.2, 114.9, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}ClN_3$: 244.0636; found: 244.0631.

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Transition-metal-free PhI(OAc)$_2$-mediated oxidative S—S and C—N bond formation: Regioselective synthesis of 3*H*-1,2,4-dithiazol-3-imines

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ABSTRACT

An effective and new approach is proposed for the synthesis of regioselective 3*H*-1,2,4-dithiazol-3-imines through S—S and C—N bond formation for the first time from benzothioamides and isothiocyanates under transition-metal-free conditions. This protocol proceeds by using hypervalent iodine(III) compound of phenyliodine diacetate (PhI(OAc)$_2$) having additive cesium carbonate in acetonitrile solution at room temperature to provide facile access to 3*H*-1,2,4-dithiazol-3-imine derivatives from readily available starting materials with broad substrate scope, insensitive to air and moisture, regioselectivity and affluent up to gram scale.

Chemistry of heterocyclic compounds is most interesting and challenging branch in organic chemistry, in which the heterocycles containing both sulphur and nitrogen atoms could furnish development of new synthetic strategies and important biological activities [1]. Among the divergent heterocyclic scaffolds, dithiazoles (both 1,2,3- and 1,2,4-) and their derivatives provided with various interesting biological activities, particularly, antimicrobial activity [2]. Some of the important derivatives of dithiazoles having antifungal and antibacterial activities are shown in Fig. 1. *N*-3-(1,2,4-dithiazole-5-thione)-*β*-resorcylcarbothioamide, 5,6-dihydro-3*H*-imidazo[2,*l*-*c*]-l,2,4-dithiazole-3-thione and *N*-arylimino-l,2,3-dithiazoles were found to exhibit antifungal activity [3–5], whereas, 5-(4-chloro-[1,2,3] dithiazol-5-ylideneamino)-naphthalen-1-ol possesses notable antifungal as well as antibacterial activities [6]. These dithiazole compounds are reported to having various modes of action and their targets comprise enzymes such as leucine arylamidase, α-glucosidase, esterases, lipases, *N*-acetyl-β-glucosaminidase, and alkaline phosphatase [3].

Phenyliodine(III) diacetate (PhI(OAc)$_2$) commonly known as PIDA is the most important and commercially available representative of hypervalent iodine(III) carboxylates. Recently, important bioactive molecules of heterocyclic compounds were successfully synthesized by using hypervalent iodine(III) compounds. In particularly, PhI(OAc)$_2$ has been successfully employed in the C—C, C—N, C—O, C—S and N—S bond formation reactions [7]. Hence, the construction of efficient and sustainable heterocyclic ring formations employing PhI(OAc)$_2$ is still highly desirable. Herein, we report a strategy for heteroatom–heteroatom bond formation of S—S for the first time using PhI(OAc)$_2$ successfully.

Due to having various pharmaceutical applications [8] of 1,2,4-dithiazoles few methods were developed as shown in Scheme 1. Singh group reported an open pot strategy of dimerization/deaminative cyclization cascade process from *β*-ketothioamides using eosin Y as a photoinitiator for the synthesis of 1,2,4-dithiazolidine derivatives in presence of visible-light at ambient temperature (Scheme 1a) [9]. Pan and his group developed a strategy using visible light for the synthesis of 1,2,4-dithiazoles from thioamides with *p*-quinone methides and $(NH_4)_2S$ in presence of acridinium salt (Scheme 1b) [10]. Kuhle group reported a strategy for the synthesis of 1,2,4-dithiazolidine-3,5-diones from *O*-alkyl esters of *N*-monosubstituted thiocarbamic acids and chlorocarbonylsulfenylchloride (Scheme 1c) [11]. However, majority of shortcomings of these protocols occurred due to the general requirement of special structural features in substrates, use of metal catalysts and harsh reaction conditions. To the best of our knowledge, there is no transformation method available for the synthesis of 1,2,4-dithiazoles using PhI(OAc)$_2$. In continuation of our previous achievements for the synthesis of biologically important heterocyclic scaffolds [12], herein, we propose an efficient regioselective synthesis of 3*H*-1,2,4-dithiazol-3-imines employing PhI(OAc)$_2$ from readily available benzothioamides and isothiocyanates for the first time at ambient temperature (Scheme 1d). This protocol consti-

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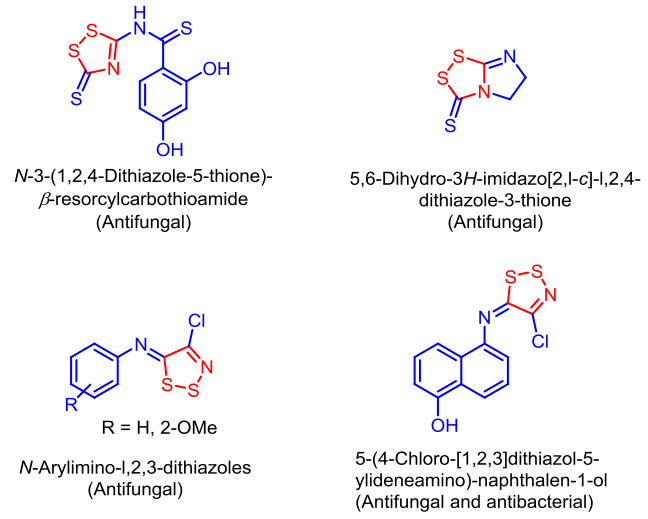
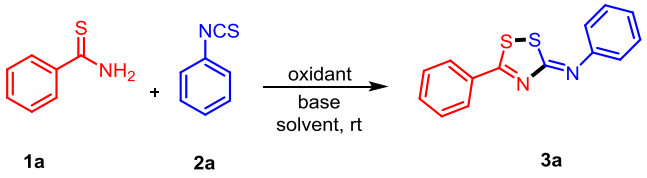


Fig. 1. Selective important antifungal and antibacterial derivatives of dithiazoles.

tutes an efficient and novel access for the 3*H*-1,2,4-dithiazol-3-imine derivatives and which to far has not been reported in the literature.

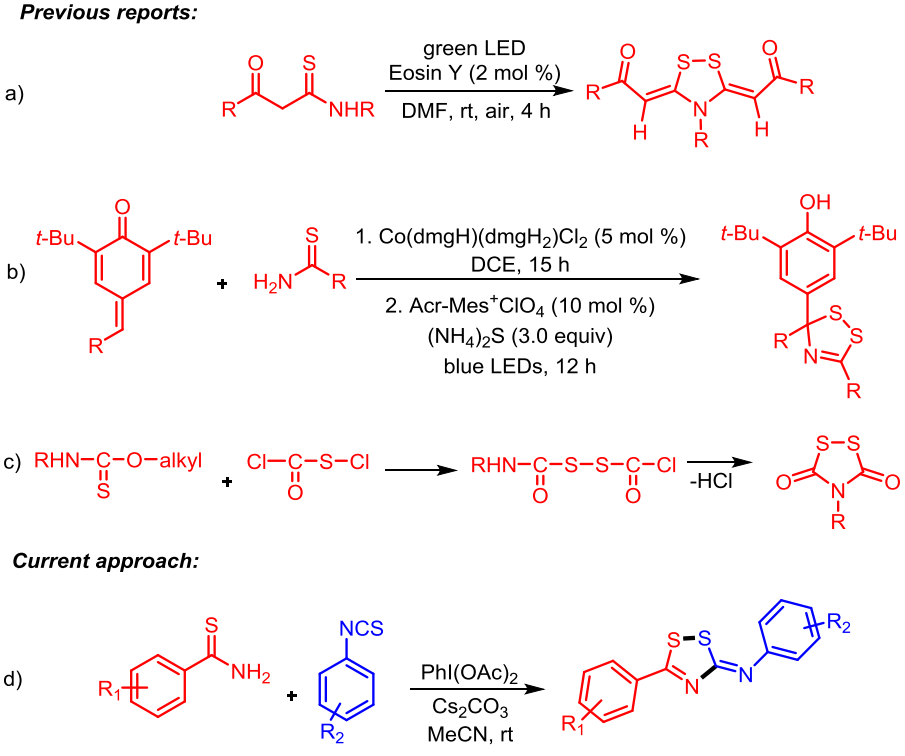
We started our analysis by following the reaction of benzothioamides **1a** and isothiocyanates **2a** using $PhI(OAc)_2$ as an oxidant (Table 1). As useful starting materials, thioamides behave both as nucleophiles and electrophiles and widely used in the synthesis of many heterocyclic compounds comprising thiophene, thiazole, and pyrrole [13]. When a mixture of **1a** (1.0 equiv) and **2a** (1.0 equiv) in $CHCl_3$ using $PhI(OAc)_2$ (1.0 equiv) at room temperature, satisfyingly, oxidative-cyclization proceeded smoothly and affording desired product 1,2,4-dithiazole (**3a**) through S—S and C—N bond formation in only 15% yield (Table 1, entry 1). To increase the yield of the product, we have monitored with several solvents such as DMSO, MeOH, MeCN, and toluene and it was found that MeCN was worked better than other solvents (entries 2–5). Next, to improve the yield of the product screening of various

Table 1
Optimization of reaction conditions.[a]



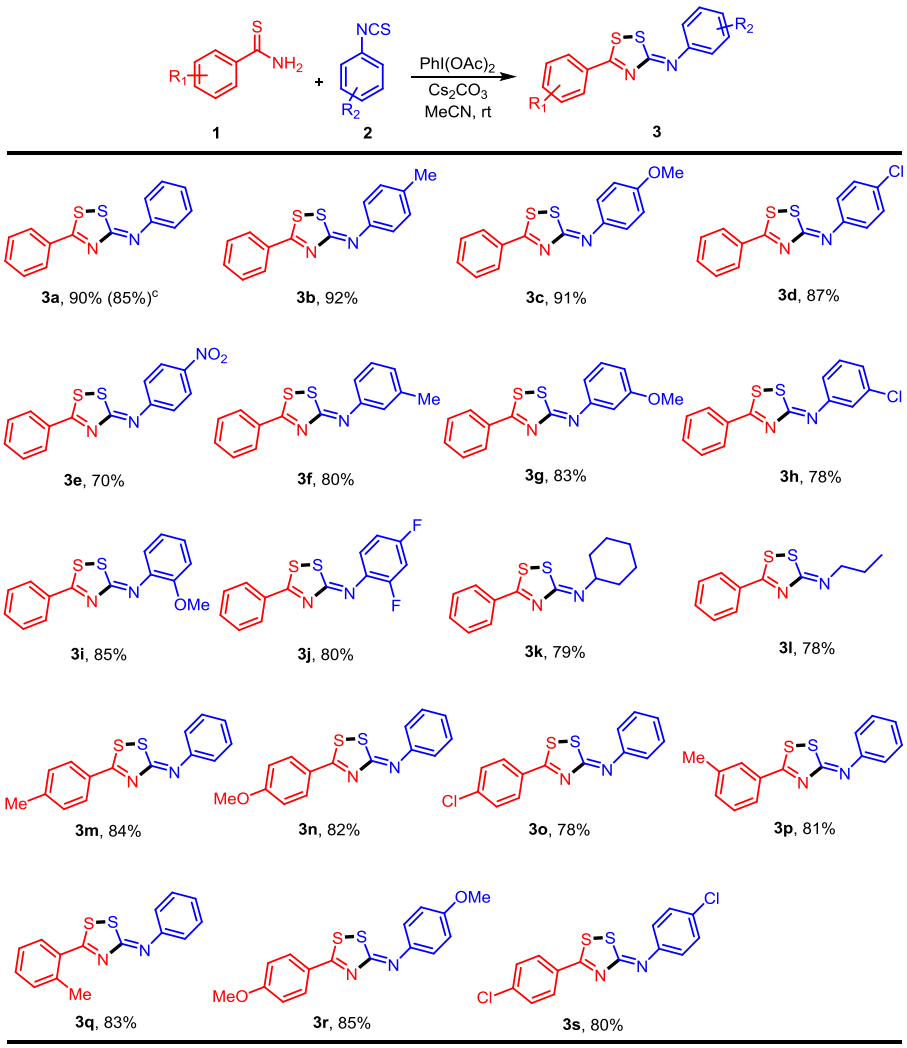
Entry	Oxidant (x equiv)	Base (1 equiv)	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$ (1)	–	$CHCl_3$	15
2	$PhI(OAc)_2$ (1)	–	DMSO	20
3	$PhI(OAc)_2$ (1)	–	MeOH	10
4	$PhI(OAc)_2$ (1)	–	MeCN	30
5	$PhI(OAc)_2$ (1)	–	toluene	5
6	$PhI(OAc)_2$ (1)	KOH	MeCN	70
7	$PhI(OAc)_2$ (1)	NaOH	MeCN	75
8	**$PhI(OAc)_2$ (1)**	**Cs_2CO_3**	**MeCN**	**90**
9	$PhI(OAc)_2$ (1)	LiOH	MeCN	60
10	$PhI(OCOCF_3)_2$ (1)	Cs_2CO_3	MeCN	20
11	I_2 (1)	Cs_2CO_3	MeCN	Trace
12	PhIO (1)	Cs_2CO_3	MeCN	10
13	$PhI(OAc)_2$ (1.5)	Cs_2CO_3	MeCN	90
14	$PhI(OAc)_2$ (0.5)	Cs_2CO_3	MeCN	44

[a] Reaction conditions: **1a** (1 mmol, 1 equiv), **2a** (1 mmol, 1 equiv), catalyst (x equiv), base (1 equiv) and solvent (2 mL) at rt for 1–2 h.
[b] Isolated yield.



Scheme 1. Previous reports and current approach for the synthesis of 1,2,4-dithiazoles.

Table 2
Substrate scope of the 3*H*-1,2,4-dithiazol-3-imines.[a,b,c]



[a] Reaction conditions: **1** (1 mmol, 1 equiv), **2** (1 mmol, 1 equiv), $PhI(OAc)_2$ (1 equiv), Cs_2CO_3 (1 equiv) and MeCN (2 mL) at rt for 1–2 h.
[b] Isolated yield.
[c] The reaction was conducted on gram scale.

bases as additive revealed Cs_2CO_3 (1 equiv) as the base of choice (Table 1, entry 8) [14]. KOH, NaOH and LiOH gave lower yields (Table 1, entries 6, 7 and 9). With these control experiments, all of the starting materials with $PhI(OAc)_2$ oxidant and base were essential for this reaction. Several other oxidants $PhI(OCOCF_3)_2$, I_2, and PhIO were screened, but only lower yields of **3a** could be observed in all the cases (Table 1, entries 10–12). Further screening the equivalence of oxidant, no affect of yield was observed when increasing the amount of $PhI(OAc)_2$ but the yield of the product significantly decreased with decreasing amount of $PhI(OAc)_2$ observed (Table 1, entries 13 and 14). Thus, the most efficient conditions were identified to be exploration of this protocol as follows: 1 equiv of **1a** and 1 equiv of **2a** with 1 equiv of PIDA in the presence of 1 equiv of the additive base Cs_2CO_3 in acetonitrile at room temperature (Table 1, entry 8).

With the help of optimized reaction conditions, we explored the applicability of this regioselective oxidative cyclization strategy, and the results are summarized in Table 2. The high efficiency shown by the model reaction was efficiently translated to a wide variety of substituted 3*H*-1,2,4-dithiazol-3-imine derivatives (**3**) with different benzothioamides (**1**) and isothiocyanates (**2**) using $PhI(OAc)_2$ oxidative system provided good to excellent yields in all cases. Isothiocyanates having electron-donating groups like methyl and methoxy at *para*-, *meta*- and *ortho*-positions afforded the corresponding 3*H*-1,2,4-dithiazol-3-imines (**3b**, **3c**, **3f**, **3g** and **3i**) in high yields (80–92%). Conversely, electron-deficient halogen substituents like –Cl and –F at *para*-, *meta*- and *ortho*-positions delivered respective 3*H*-1,2,4-dithiazol-3-imines (**3d**, **3h** and **3j**) in good yields (78–87%). Moreover, strong electron-withdrawing $–NO_2$ group provides good yield of the product **3e** (70%). Interestingly, electron-deficient disubstituted fluoro phenylisothiocyanate underwent oxidative cyclization smoothly provided the dithiazole product **3j** in good isolated yield (80%). In addition, an alicyclic isothiocyanate such as cyclohexyl isothiocyanate could also be examined with the reaction conditions and furnished the corresponding product **3k** in 79% yield. It is worthy to mention that an aliphatic propyl isothiocyanate also delivered the desired product **3l** in moderate yield. Further to extend the substrate scope

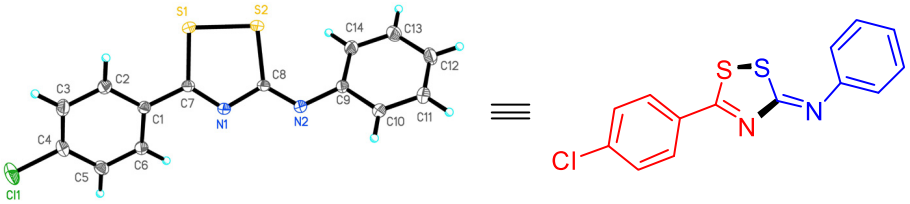
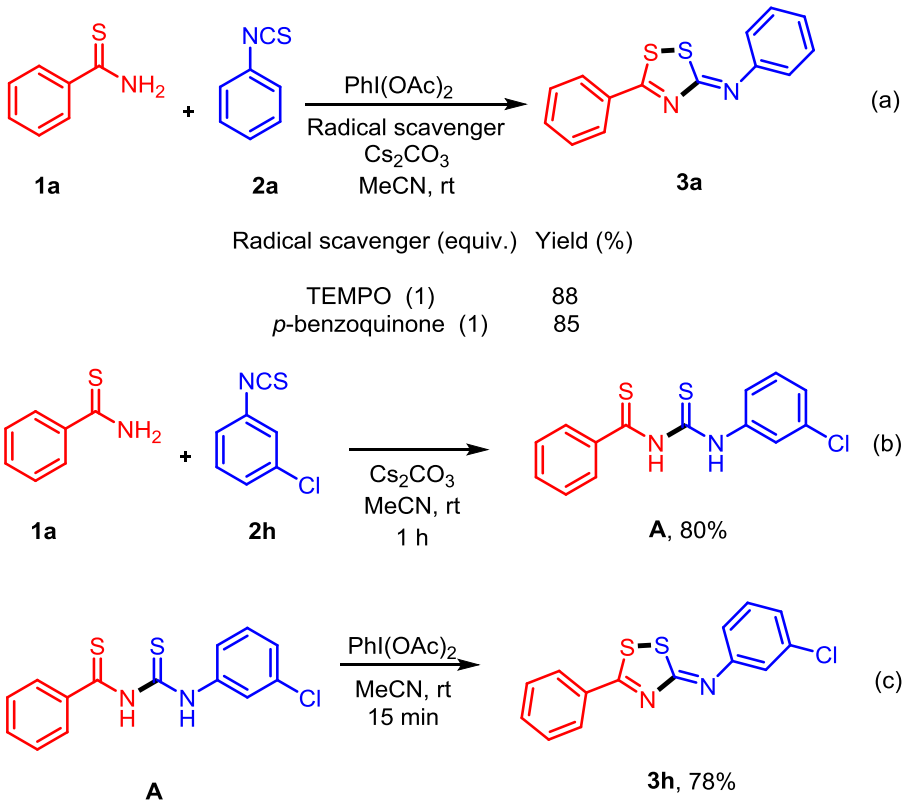
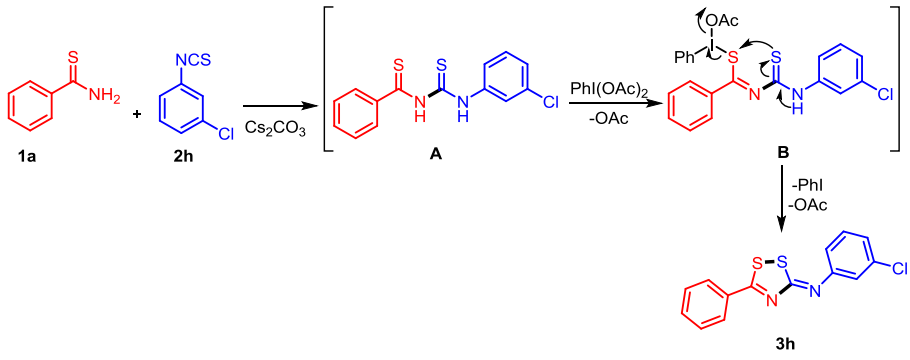


Fig. 2. Crystallographic representation of compound **3o**.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction mechanism.

and limitations of the reaction, we studied effect of different substituents present at the benzothioamide ring with phenyl isothiocyanates, which proceeded proficiently to afford the corresponding 3*H*-1,2,4-dithiazol-3-imines in good to excellent yields. As shown in Table 2, benzothioamide bearing electron-donating groups such as methyl and methoxy at *para*-, *meta*- and *ortho*-positions of the phenyl ring afforded corresponding products **3m**, **3n**, **3p** and **3q** in good to excellent yields. Additionally, benzothioamide substituted with electron-withdrawing group like –Cl at *para*-position afforded the desired product in good yield

(**3o**). It is notable that the reaction successfully afforded the expected product **3r** when electron-donating group (–OMe) presenting on the both benzothioamide and phenyl isothiocyanate substrates. Conversely, good yield of the product **3s** obtained when electron-withdrawing group (–Cl) presenting on the both substrates. Further structural confirmation of compound **3o** was unambigiously studied by X-ray diffraction analysis (Fig. 2). It should be observed that the practical applicability of this oxidative cyclization strategy was confirmed successfully by the gram-scale synthesis under optimized reaction conditions (Table 2, **3a**).

Next we turned to explain the possible reaction pathway, few control experiments were performed (Scheme 2). The experiments were conducted in the presence of free radical trapping reagents like 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and *p*-benzoquinone (BQ) under the optimized reaction conditions and no significant effect was noticed (Scheme 2a). These results summarized that an ionic mechanism was probably involved in this transformation. When the benzothioamide **1a** and 3-chloro phenyl isothiocyanate **2h** undergo reaction in the presence of Cs_2CO_3 with the absence of $PhI(OAc)_2$, the intermediate **A** (Scheme 2b) was obtained, which was confirmed by its characteristic free NH protons observed in ^1H NMR data (see Supporting Information). [16] This intermediate **A** reacts with $PhI(OAc)_2$ to give our desired product **3h** in 78% yield (Scheme 2c).

Based on above experimental results and previous reports [12b,15], a possible mechanism has been proposed for the formation of **3h** as an example for this oxidative regioselective approach (Scheme 3). Initially, the benzothioamide (**1a**) reacts with 3-chloro phenyl isothiocyanate (**2h**) in presence of Cs_2CO_3 to generate the intermediate **A**. The intermediate **A** reacts with $PhI(OAc)_2$ to form the thiourea intermediate **B**, followed by intramolecular nucleophilic attack on the sulfur atom by the another sulfur atom, the removal of iodobenzene and acetic acid takes place to afford the desired product **3h**.

In summary, we have developed the first regioselective oxidative cyclization of transition-metal-free strategy for the synthesis of 3*H*-1,2,4-dithiazol-3-imines [16] by using an efficient oxidative reagent $PhI(OAc)_2$ from benzothioamides and isothiocyanates through C—N and S—S bond formation. These compounds are the novel dithiazole heterocyclic scaffolds.

Declaration of Competing Interest

This work interests the organic chemist fraternity in general and the heterocyclic chemists in particular. This report describes the synthetic methodology for the facile preparation of fully substituted 1,2,4-dithiazoles using readily available raw materials in one pot using hypervalent Iodine as catalyst.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151424.

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I_2-Mediated Oxidative C−N and N−S Bond Formation in Water: A Metal-Free Synthesis of 4,5-Disubstituted/N-Fused 3-Amino-1,2,4-triazoles and 3-Substituted 5-Amino-1,2,4-thiadiazoles

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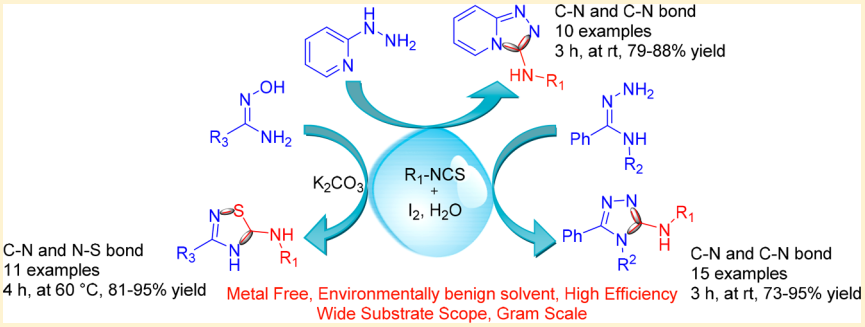
Supporting Information



ABSTRACT: An environmentally benign and convenient strategy for the synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles from isothiocyanates has been developed. This metal-free method involves I_2-mediated oxidative C−N and N−S bond formations in water. Furthermore, this facile protocol exhibited excellent substrate tolerance in good to high yields and scalable fashion.

INTRODUCTION

N-Containing heterocyclic molecules constitute an important class of compounds in the fields of material and pharmaceutical chemistry due to their many fold applications. Among them, 1,2,4-triazoles and 1,2,4-thiadiazoles have emerged as an important structural motif present in a large number of functionalized molecules with a broad range of biological activities, such as antibacterial,[1] anti-inflammatory,[2] antifungal,[3] and antiviral.[4] Moreover, they are also found in valuable pharmaceuticals, including sitagliptin,[5] maraviroc,[6] trizaolam,[7] deferasirox,[8] and cefozopran.[9] Owing to its broad spectrum of functions, the efficient methods for the synthesis of 1,2,4-triazoles and 1,2,4-thiadiazoles hasve attracted much attention. The most generally explored synthetic pathways for 1,2,4-triazoles involve cyclodehydration of *N*-acylamidrazone obtained from hydrazines and carboxylic acid derivatives,[10] whereas the simple oxidative dimerization of thioamides using various oxidants is a very common protocol for the synthesis of 1,2,4-thiadiazoles.[11] Apart from these, some other synthetic methods to access 1,2,4-triazoles or 1,2,4-thiadiazoles were also disclosed.[12] These protocols suffer from one or more drawbacks, such as use of transition metals, harsh reaction conditions with high temperatures or strong acids, or use of organic solvent. Thus, more general and practical synthetic methods for the preparation of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles are still in high demand.

On the other hand, molecular iodine has attracted considerable attention because of its low toxicity, ready availability, and low cost in contrast to transition-metal catalysts. As a potent catalyst, iodine is widely used in various organic reactions.[13] Recently, our group developed an efficient and regiospecific protocol by using molecular iodine as a catalyst for the synthesis of N-fused 1,2,4-thiadiazoles and 3,4-disubstituted 5-imino-1,2,4-thiadiazoles via N−S bond formations.[14a] In addition, the development of reactions in the presence of water has become highly advantageous to meet environmentally friendly processes in life sciences. Inspired by these advances, in connection with previous work and continuation of our studies on the construction of valuable synthetic methodologies for diverse biologically active heterocyclic scaffolds[14b,c] herein, we report a novel and environmentally benign protocol for the formation of C−N and N−S bonds using molecular iodine as an oxidant in water for the synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles (Scheme 1).

RESULTS AND DISCUSSION

We began our study by examining the reaction of phenyl isothiocyanate (**1a**), *N*-phenylbenzamidrazone (**2a**), and iodine (0.5 equiv) in DMSO at rt for 3 h, which provided the desired product **3a** in 38% yield (Table 1, entry 1). To improve the

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Scheme 1. Synthesis of 4,5-Disubstituted/N-Fused 3-Amino-1,2,4-triazoles and 3-Substituted 5-Amino-1,2,4-thiadiazoles

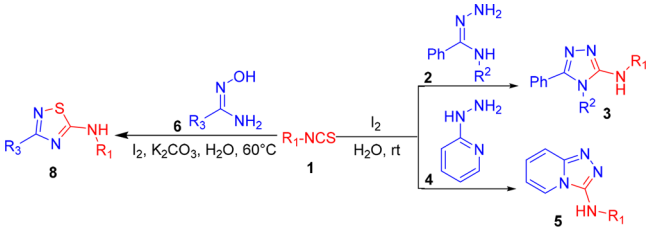
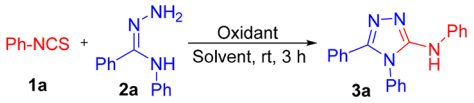


Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (mol %)	solvent	yield (%)
1	I_2 (50)	DMSO	38
2	I_2 (50)	DMF	31
3	I_2 (50)	MeOH	43
4	I_2 (50)	MeCN	18
5	I_2 (50)	DCM	22
6	I_2 (50)	EtOAc	
7	I_2 (50)	H_2O	52
8	TBAI (50)	H_2O	30
9	KI (50)	H_2O	26
10	NIS (50)	H_2O	35
11	PIDA (50)	H_2O	trace
12	I_2 (100)	H_2O	92
13	I_2 (150)	H_2O	92

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and oxidant (*x* mol %) in solvent (2 mL) at room temperature for 3 h.

reaction yield, we have screened various solvents under the same conditions. Polar solvents such as DMF and MeOH provided moderate yields (Table 1, entries 2 and 3). Moderate conversions were observed using MeCN and DCM, whereas no reaction took place in EtOAc (Table 1, entries 4–6). The reaction efficiency was observed in a protic solvent; considering the requirements of green chemistry, we attempted the water as solvent. The reaction was significantly accelerated in water to give **3a** in 52% yield (Table 1, entry 7). Subsequently, other iodine containing catalysts were also studied, such as TBAI, KI, NIS, and PIDA which showed a lower yield of **3a** (Table 1, entries 8–11). Next, we studied the amount of iodine, raising the quantity of iodine from 0.5 equiv to 1 equiv, which provided the product **3a** in 92% yield (Table 1, entry 12). However, further increase of iodine did not improve the yield (Table 1, entry 13). Thus, the optimized reaction conditions of isothiocyanate (1.0 mmol), *N*-phenylbenzamidrazone (1.0 mmol), and iodine (1.0 equiv) in water at room temperature were chosen as the optimum reaction conditions for the synthesis of 4,5-disubstituted 3-amino-1,2,4-triazoles.

With this promising result in hand, the scope and generality of the reaction was investigated and the results are summarized in Scheme 2. The reaction is applicable to a wide variety of isothiocyanates under the established reaction conditions, giving the corresponding 4,5-disubstituted 3-amino-1,2,4-triazoles in good to high yields. Simple phenyl isothiocyanate (**1a**) with *N*-phenylbenzamidrazone (**2a**) gave the corresponding 3-amino-1,2,4-triazole (**3a**) in 92% yield (entry **3a**). Electron-donating groups, such as *o*-methoxy, *m*-methoxy, *p*-methoxy, *m*-methyl, and *p*-methyl on the phenyl ring of isothiocyanates underwent the reaction efficiently in excellent yields (entries **3b**, **3c**, and **3g–3i**). Meanwhile, the steric hindrance is not obvious for the *o*-methoxy group on the phenyl isothiocyanate in this protocol (entry **3i**). On the other hand, phenyl isothiocyanates with electron-deficient groups, like chloro, nitro, and trifluoro methyl on the para position, generated the corresponding 3-amino-substituted 1,2,4-triazoles in good yields (entries **3d–3f and 3j**). These results demonstrate that substitutents on phenyl isothiocyanates have no bearing on the reaction yield. To our delight, alkyl isothiocyanates such as *tert*-butyl, butyl, and alicyclic isothiocyanate like cyclohexyl also reacted smoothly to afford the desired products **3l–3o** in 73–76% yield. Furthermore, we investigated the scope of the method by varying the *N*-phenylbenzamidrazones, which proceeded successfully to afford the corresponding 3-amino-1,2,4-triazoles in good yields (entries **3j**, **3k**, **3m**, and **3o**). After the successful study of substrate scope, we evaluated this green methodology toward the gram scale level. Importantly, the methodology can be carried out in gram scale without any complications, and **3a** was isolated in 89% yield, demonstrating the efficiency and practicality of this methodology.

Encouraged by these successful results, the utility of this iodine mediated protocol was further investigated for the synthesis of N-fused 3-amino-substituted 1,2,4-triazoles. For this purpose, amidrazone (**2**) was replaced with 2-hydrazinopyridine (**4**) under the established optimized reaction conditions (Scheme 3). Gratifyingly, we were able to prepare the desired product *N*-phenyl-[1,2,4]triazolo[4,3-*a*]pyridin-3-amine (**5a**) in 87% yield. Furthermore, the substrate scope of phenyl isothiocyanate was examined, and both electron-donating and electron-withdrawing groups at different positions of the phenyl ring gave the desired products **5b–5i** in 82–88% yields. Replacing the 2-hydrazinopyridine with 2-hydrazineylquinoline was also compatible with the reaction conditions to deliver **5j** in 79% yield. However, the alkyl isothiocyanates did not provide the desired product under the optimal reaction conditions; only the uncyclized products were observed (Scheme 3, **5k** and **5l**).

In light of our above consecutive results, we attempted to synthesize 1,2,4-oxadiazoles (**7**) by replacing amidrazones (**2**) with amidoximes (**6**). Surprisingly, we observed the unexpected product 3-substituted 5-amino-1,2,4-thiadiazoles (**8**) in the presence of I_2 (0.5 equiv) and K_2CO_3 (1 equiv) at room temperature within 5 h in 74% yield (Table 2, entry 2), while the other bases Na_2CO_3 and Cs_2CO_3 gave the product in 20 and 26% yields, respectively (Table 2, entries 3 and 4). However, the unexpected product yield could be improved to 90% by raising the temperature to 60 °C in 4 h (Table 2, entry 5). Raising the amount of iodine from 0.5 to 1.0 equiv, the yield of **8a** did not improve (Table 2, entry 6). With the results in hand, we proceeded to investigate the substrate scope on the outcome of the reaction. It was observed that benzamidoxime reacts with different isothiocyanites to furnish the respective products in good to high yields. The phenyl isothiocyanates containing electron-donating groups like methyl and methoxy at ortho, para, and meta positions provided the corresponding products in 86–95% yield (Scheme 4, entries **8b**, **8c**, **8f**, and **8g**). Phenyl isothiocyanites with electron-withdrawing groups on the para-positions like –F and $-NO_2$ generated the corresponding products in 88 and 87% yields, respectively (Scheme 4, entries **8d** and **8e**). Interestingly, the reaction also

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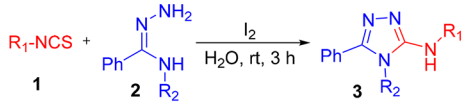
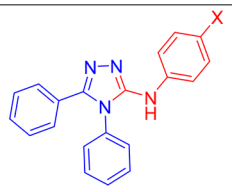
Scheme 2. Synthesis of 4,5-Disubstituted 3-Amino-Substituted 1,2,4-Triazoles[a]





3a, X = H, 92% (89%)[b]

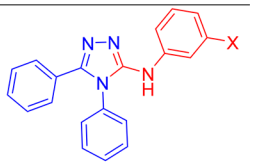
3b, X = Me, 91%

3c, X = OMe, 95%

3d, X = Cl, 87%

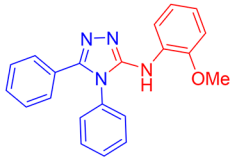
3e, X = NO_2, 82%

3f, X = CF_3, 82%

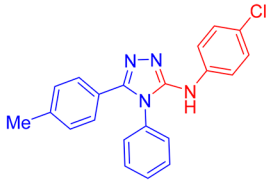


3g, X = Me, 89%

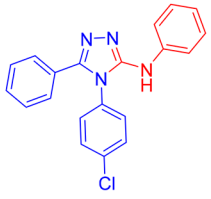
3h, X = OMe, 92%



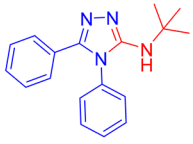
3i, 81%



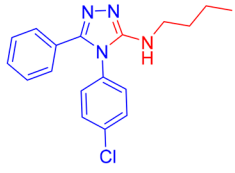
3j, 90%



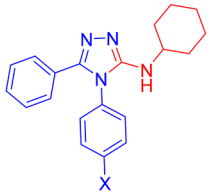
3k, 79%



3l, 76%



3m, 75%



3n, X = H, 76%

3o, X = Cl, 73%

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), and iodine (1.0 equiv) in water at rt for 3 h. [b]Gram scale reaction.

proceeded with propyl and cyclohexyl isothiocyanates to afford the desired compounds **8h** and **8i** in good yields. Furthermore, we investigated the scope of the method with various amidoximes, such as *p*-methy and *p*-chloro benzamidoximes, which proceeded successfully to afford the corresponding products in 91 and 89% yields, respectively (Scheme 4, entries **8j** and **8k**).

In order to gain more insights into the mechanism of this I_2-catalyzed reaction, a series of control experiments were performed, as shown in Scheme 3. The radical inhibition studies under the standard reaction conditions with TEMPO, benzoquinone, and BHT gave the corresponding compound **3a** in 92, 91, and 91% yields, respectively (Scheme 5, eq 1). These results amply proved a radical mechanism can be ruled out. Next, the reaction of **1a** with (*Z*)-*N*-(4-chlorophenyl)-benzohydrazonamide (**2k**) was carried out in the absence of I_2 in water for 1.5 h and gave the intermediate **A**, whose structure was assigned by ^{1}H, ^{13}C NMR, and HRMS (Scheme 5, eq 2). Furthermore, the intermediate **A** under the standard conditions produces **3k**, indicating that **A** might be an intermediate for this transformation (Scheme 5, eq 3).

On the basis of these experimental results and previous reports,[15] a plausible reaction mechanism for the formation of 4,5-disubstituted 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles is proposed, as shown in Scheme 6. Initially, **1a** condensed with **2a** in water to afford intermediate **A**. Next, an intramolecular attack on the carbon atom by the NH group gave the intermediate **B** through the formation of the S−I bond, which on cleavage of HI and S gave the desired product **3a**. Whereas **1a** condensed with **6a** to afford intermediate **C**, the intermediate **C** reacts with iodine under basic conditions and generates the plausible iodo species **D**. Then, the S−I bond cleaved in intermediate **D** and gave the desired **8a** with formation of a new N−S bond.

CONCLUSION

In conclusion, we have developed a metal-free and ecofriendly strategy for the oxidative C−N and N−S bond formation for the synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 4,5-disubstituted 5-amino-1,2,4-thiadiazoles from isothiocyanates for the first time. Furthermore, this efficient and operationally simple protocol features nontoxic and inexpensive molecular iodine as the catalyst and water as an environmentally friendly solvent. Moreover, the wide variety of substrate tolerance in good to excellent yields and amenable to gram-scale synthesis of our method allowed the construction of a library of compounds.

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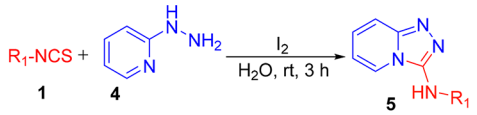
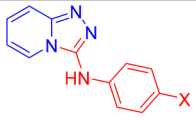
Scheme 3. Synthesis of N-Fused 3-Amino-1,2,4-triazoles[a]





5a, X = H, 87% (83%)[b]

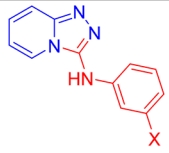
5b, X = Me, 87%

5c, X = OMe, 88%

5d, X = Cl, 85%

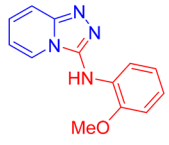
5e, X = F, 83%

5f, X = CF_3, 83%

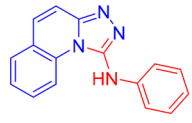


5g, X = Me, 87%

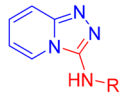
5h, X = OMe, 88%



5i, 82%



5j, 79%

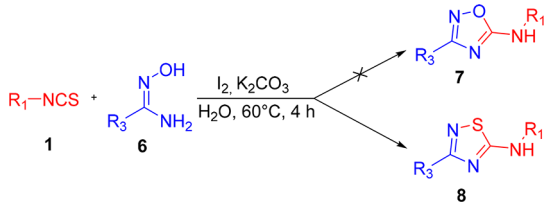


5k, R = propyl, 0%

5l, R = butyl, 0%

[a]Reaction conditions: **1** (1.0 mmol), **4** (1.0 mmol), and iodine (1.0 equiv) in water at rt for 3 h. [b]Gram scale reaction.

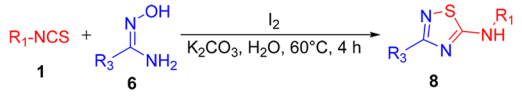
Table 2. Optimization of Reaction Conditions for the Synthesis 3-Substituted 5-Amino-1,2,4-thiadiazoles[a]

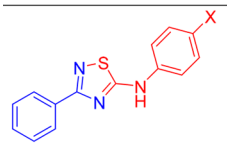


entry	iodine (mol %)	base	temp	yield (%)
1	I_2 (50)		rt	NR
2	I_2 (50)	K_2CO_3	rt	74
3	I_2 (50)	Na_2CO_3	rt	20
4	I_2 (50)	Cs_2CO_3	rt	26
5	I_2 (50)	K_2CO_3	60	90
6	I_2 (100)	K_2CO_3	60	90

[a]Reaction conditions: **1a** (1.0 mmol), **6a** (1.0 mmol), base (1.0 mmol), and iodine (*x* mol %) in water for 4–5 h.

Scheme 4. Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles[a]





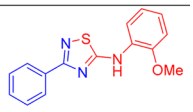
8a, X = H, 90% (88%)[b]

8b, X = Me, 92%

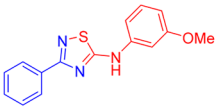
8c, X = OMe, 95%

8d, X = F, 88%

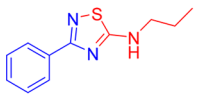
8e, X = NO_2, 87%



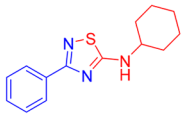
8f, 86%



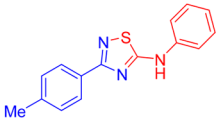
8g, 89%



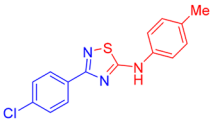
8h, 84%



8i, 81%



8j, 91%



8k, 89%

[a]Reaction conditions: **1** (1.0 mmol), **6** (1.0 mmol), iodine (0.5 equiv), and K_2CO_3 (1.09 mmol) in water at 60 °C for 4 h. [b]Gram scale reaction.

EXPERIMENTAL SECTION

General Information and Reagents. The glassware to be used in reactions was thoroughly washed and dried in an oven, and the experiments were carried out with required precautions. Chemicals and all solvents were obtained from commercial suppliers and used without further purification. ^{1}H NMR was measured on Bruker Avance-300, Varian Unity-400 MHz, and Avance New-500 MHz instruments, and ^{13}C NMR was measured with Varian Unity-400 MHz (100 MHz) and Avance New-500 MHz (125 MHz) instruments, as specified and referred as the internal standard to TMS (tetramethylsilane). Chemical shifts (δ) are given in ppm, and *J* values are given in Hz. High resolution mass spectra (HRMS) were measured on a high resolution magnetic sector mass spectrometer. TLC analysis was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on silica gel (100–200 mesh) from Merck. Melting points were measured using a melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

The Scale-up Reaction. The mixture of isothiocyanate (**1a**) (7.4 mmol), *N*-phenylbenzamidrazone (**2a**) (7.4 mmol)/2-hydrazinopyridine (**4a**) (7.4 mmol), and I_2 (100 mol %, 933 mg, 7.4 mmol) in water (15 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture

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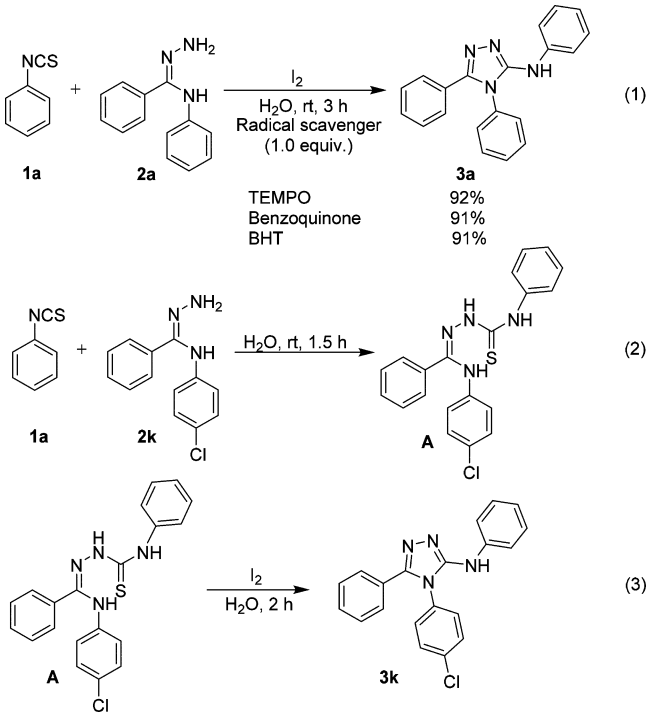
Scheme 5. Control Experiments



was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford the corresponding product **3a**/**5a.**

Typical Procedure for the Synthesis of Intermediate A. The mixture of phenyl isothiocyanate (**1a**) (1.0 mmol, 135 mg) and *N*-phenylbenzamidrazone (**2k**) (1.0 mmol, 245 mg) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was treated with $NaHCO_3$ and extracted with EtOAc. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding product **A**.

***(Z)*-2-(((4-Chlorophenyl)amino)(phenyl)methylene)-*N*-phenylhydrazinecarbothioamide (A).** White solid; Mp 165−167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (s, 1H), 9.91 (s, 1H), 9.12 (s, 1H), 7.62 (t, J = 8.5 Hz, 4H), 7.37 (dd, J = 14.9, 7.8 Hz, 5H), 7.19 (d, J = 8.4 Hz, 3H), 6.65 (d, J = 8.6 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 175.4, 142.2, 140.1, 139.0, 132.9, 129.7, 128.8, 128.5, 128.2, 128.0, 125.1, 125.0, 120.9; HRMS (ESI): [M + H]$^+$ calcd for $C_{20}H_{17}N_4ClS$, 381.0935; found, 381.0962.

Typical Procedure for the Synthesis of 4,5-Disubstituted 3-Amino-1,2,4-triazoles 3a−3o. The mixture of isothiocyanate (**1**) (1.0 mmol), *N*-phenylbenzamidrazone (**2**) (1.0 mmol), and I_2 (100 mol %, 126 mg, 1.0 mmol) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding products **3a−3o**.

*N,4,5-Triphenyl-4H-1,2,4-triazol-3-amine (**3a**).*[16] White solid; yield: 92% (287 mg); Mp 210−211 °C; eluent: hexane/ethyl acetate 70:30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.55−7.50 (m, 5H), 7.43−7.40 (m, 2H), 7.35−7.31 (m, 5H), 7.23 (t, J = 7.9 Hz, 2H), 6.87 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.9, 150.0, 141.6, 133.3, 129.9, 129.6, 129.1, 128.5, 128.4, 128.3, 127.7, 127.4, 120.4, 117.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{17}N_4$, 313.1447; found, 313.1437.

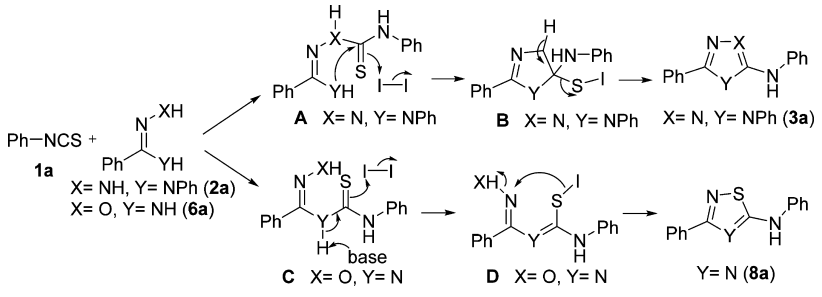
*4,5-Diphenyl-N-(p-tolyl)-4H-1,2,4-triazol-3-amine (**3b**).* White solid; yield: 91% (299 mg); Mp 198−200 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.54−7.53 (m, 3H), 7.42−7.40 (m, 4H), 7.34−7.30 (m, 5H), 7.04 (d, J = 8.3 Hz, 2H), 2.22 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 152.2, 149.8, 138.9, 133.3, 129.9, 129.6, 129.2, 129.0, 128.9, 128.4, 128.3, 127.6, 127.4, 117.2, 20.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}N_4$, 327.1604; found, 327.1593.

*N-(4-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3c**).* White solid; yield: 95% (324 mg); Mp 178−180 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.55−7.53 (m, 3H), 7.49 (d, J = 9.0 Hz, 2H), 7.42 (dd, J = 6.4, 3.1 Hz, 2H), 7.35−7.29 (m, 5H), 6.84 (d, J = 9.0 Hz, 2H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 153.6, 152.6, 149.5, 134.6, 133.3, 129.9, 129.6, 129.0, 128.4, 128.3, 127.6, 127.5, 119.0, 113.7, 55.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}N_4O$, 343.1553; found, 343.1544.

*N-(4-Chlorophenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3d**).* White solid; yield: 87% (301 mg); Mp 178−180 °C; eluent: hexane/ethyl acetate 74:26; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.59−7.54 (m, 5H), 7.44−7.41 (m, 2H), 7.38−7.27 (m, 7H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.7, 150.0, 140.5, 133.1, 129.9, 129.7, 129.2, 128.4, 128.3, 127.7, 127.3, 123.8, 118.5; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}ClN_4$, 347.1058; found, 347.1049.

*N-(4-Nitrophenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3e**).* Yellow solid; yield: 82% (292 mg); Mp 270−272 °C; eluent: hexane/ethyl acetate 67:33; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.15 (d, J = 9.3 Hz, 2H), 7.64 (d, J = 9.2 Hz, 2H), 7.55−7.54 (m, 3H), 7.45 (dd, J = 6.4, 3.1 Hz, 2H), 7.44−7.34 (m, 5H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 151.5, 150.9, 148.9, 140.3, 133.4, 130.4, 129.9, 128.9, 128.8, 128.4, 127.5, 125.7, 116.4; HRMS

Scheme 6. Proposed Reaction Mechanism



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(ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}N_5O_2$, 358.1298; found, 358.1288.

*4,5-Diphenyl-N-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-amine (**3f**).* White solid; yield: 82% (311 mg); Mp 230−232 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.59−7.54 (m, 5H), 7.44 (dd, J = 6.7, 2.9 Hz, 2H), 7.39−7.31 (m, 5H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.1, 150.5, 145.3, 133.1, 129.9, 129.8, 129.3, 128.3, 127.8, 127.2, 125.9 (d, J = 3 Hz), 122.9, 120.4 (d, J = 32 Hz), 116.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{16}F_3N_4$, 381.1321; found, 381.1314.

*4,5-Diphenyl-N-(m-tolyl)-4H-1,2,4-triazol-3-amine (**3g**).* White solid; yield: 89% (290 mg); Mp 196−198 °C; eluent: hexane/ethyl acetate 73:27; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.54 (s, 3H), 7.37 (d, J = 29.2 Hz, 9H), 7.10 (t, J = 7.7 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 2.24 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.9, 149.9, 141.5, 137.6, 133.3, 129.9, 129.6, 129.1, 128.4, 128.3, 127.7, 127.4, 121.16, 117.4, 114.1, 21.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_4$, 327.1604; found, 327.1594.

*N-(3-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3h**).* White solid; yield: 92% (314 mg); Mp 203−205 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.55−7.54 (m, 3H), 7.42−7.40 (m, 2H), 7.32−7.31 (m, 5H), 7.18 (t, J = 2.1 Hz, 1H), 7.13−7.10 (m, 2H), 6.47−6.44 (m, 1H), 3.71 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 160.2, 152.3, 150.5, 143.2, 133.7, 130.4, 130.2, 129.8, 129.6, 128.9, 128.8, 128.2, 127.8, 110.0, 106.6, 103.2, 55.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_4O$, 343.1553; found, 343.1542.

*N-(2-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3i**).* White solid; yield: 81% (277 mg); Mp 203−205 °C; eluent: hexane/ethyl acetate 69:31; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (d, J = 8.0 Hz, 1H), 7.62−7.60 (m, 3H), 7.53−7.49 (m, 2H), 7.37−7.35 (m, 5H), 6.97−6.89 (m, 4H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 151.7, 150.1, 147.2, 133.7, 130.9, 130.6, 130.0, 129.7, 129.0, 128.4, 128.0, 127.6, 121.5, 121.3, 116.5, 111.1, 56.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_4O$, 343.1553; found, 343.1541.

*N-(4-Chlorophenyl)-4-phenyl-5-(p-tolyl)-4H-1,2,4-triazol-3-amine (**3j**).* White solid; yield: 90% (324 mg); Mp 210−212 °C; eluent: hexane/ethyl acetate 75:25; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.58−7.53 (m, 5H), 7.40 (dd, J = 6.3, 2.7 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.26 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.5, 150.1, 140.6, 138.8, 133.2, 129.9, 129.7, 128.9, 128.4, 128.3, 127.6, 124.4, 123.8, 118.5, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}N_4Cl$, 361.1214; found, 361.1206.

*4-(4-Chlorophenyl)-N,5-diphenyl-4H-1,2,4-triazol-3-amine (**3k**).* White solid; yield: 79% (273 mg); Mp 259−260 °C; eluent: hexane/ethyl acetate 75:25; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.37−7.34 (m, 5H); 7.24 (t, J = 7.9 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.9, 149.7, 141.3, 134.3, 132.2, 130.4, 130.0, 129.2, 128.5, 128.4, 127.8, 127.2, 120.5, 117.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}N_4Cl$, 347.1058; found, 347.1049.

*N-(tert-Butyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3l**).* White solid; yield: 76% (221 mg); Mp 198−200 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.51 (m, 3H), 7.33−7.23 (m, 7H), 4.60 (s, 1H), 1.36 (s, 9H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 154.0, 148.6, 133.78, 130.0, 129.3, 128.7, 128.2, 128.0, 127.6, 127.3, 51.5, 28.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{21}N_4$, 293.1760; found, 293.1749.

*N-Butyl-4-(4-chlorophenyl)-5-phenyl-4H-1,2,4-triazol-3-amine (**3m**).* White solid; yield: 75% (244 mg); Mp 162−164 °C; eluent: hexane/ethyl acetate 70:30; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (d, J = 8.6 Hz, 2H), 7.39−7.25 (m, 7H), 5.89 (t, J = 5.6 Hz, 1H), 3.22 (dd, J = 13.1, 6.7 Hz, 2H), 1.53 (dd, J = 14.5, 7.5 Hz, 2H), 1.36−1.24 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 160.8, 153.9, 139.2, 137.7, 135.3, 134.1, 133.6, 132.6, 47.7, 36.1, 24.7, 19.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}N_4Cl$, 327.1371; found, 327.1363.

*N-Cyclohexyl-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3n**).* White solid; yield: 76% (241 mg); Mp 202−204 °C; eluent: hexane/ethyl acetate 71:29; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52−7.51 (m, 3H), 7.39−7.24 (m, 7H), 5.23 (d, J = 7.8 Hz, 1H), 3.39 (s, 1H), 1.95 (s, 2H), 1.67−1.56 (m, 3H), 1.17 (d, J = 49.1 Hz, 5H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 155.19, 148.87, 133.75, 130.00, 129.29, 128.62, 128.27, 128.04, 127.78, 127.26, 52.03, 32.34, 25.37, 24.93; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}N_4$, 319.1917; found, 319.1905.

*4-(4-Chlorophenyl)-N-cyclohexyl-5-phenyl-4H-1,2,4-triazol-3-amine (**3o**).* White solid; yield: 73% (256 mg); Mp 203−204 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 8.2 Hz, 2H), 7.36−7.26 (m, 7H), 5.45 (d, J = 7.6 Hz, 1H), 3.50 (s, 1H), 1.93 (d, J = 15.2 Hz, 2H), 1.68 (s, 2H), 1.58 (d, J = 12.5 Hz, 1H), 1.25 (dd, J = 19.5, 10.2 Hz, 4H), 1.07 (d, J = 10.7 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 171.9, 155.1, 148.7, 133.8, 132.6, 130.0, 130.0, 128.7, 128.3, 127.6, 127.4, 52.0, 32.3, 25.4, 24.9, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N_4Cl$, 353.1527; found, 353.1518.

*Typical Procedure for the Synthesis of N-Fused 3-Amino-1,2,4-triazoles **5a**−**5j**.* The mixture of phenyl isothiocyanate (**1**) (1.0 mmol), 2-hydrazinopyridine (**4**) (1.0 mmol), and I_2 (100 mol %, 126 mg, 1.0 mmol) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding products **5a**−**5j**.

*N-Phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5a**).*[17] Pale yellow solid; yield: 87% (182 mg); Mp 229−230 °C; eluent: hexane/ethyl acetate 61:39; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.35 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.26 (dd, J = 9.0, 6.7 Hz, 1H), 6.95−6.90 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 146.7, 144.7, 141.8, 129.4, 127.0, 123.1, 120.9, 116.6, 115.9, 112.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}N_4$, 211.0978; found, 211.0972.

*N-(p-Tolyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5b**).*[17] White solid; yield: 87% (194 mg); Mp 265−267 °C; eluent: hexane/ethyl acetate 60:40; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.32 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 8.6, 6.5 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.88 (t, J = 6.6 Hz, 1H), 2.26 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 146.6, 145.0, 139.3, 129.8, 129.6, 126.8, 123.0, 116.8, 116.0, 112.6, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_4$, 225.1134; found, 225.1129.

*N-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5c**).*[18] White solid; yield: 88% (211 mg); Mp 240 °C; eluent: hexane/ethyl acetate 58:42; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.31 (d, J = 7.0 Hz, 1H), 7.56 (dd, J = 19.6, 9.1 Hz, 3H), 7.21 (dd, J = 8.8, 6.4 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.87 (t, J = 6.5 Hz, 1H), 3.73 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 154.0, 146.5, 145.4, 135.0, 126.8, 122.9, 118.4, 115.9, 114.7, 112.5, 55.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_4O$, 241.1083; found, 241.1077.

*N-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5d**).* White solid; yield: 85% (207 mg); Mp 220−221 °C; eluent: hexane/ethyl acetate 61:39; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.35 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 8.7 Hz, 3H), 7.36 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.9, 6.7 Hz, 1H), 6.92 (t, J = 6.6 Hz, 1H); ^{13}C{^{1}H}NMR (125 MHz, DMSO-d_6) δ 146.7, 144.5, 140.7, 129.2, 127.1, 124.3, 123.0, 118.2, 115.9, 112.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}N_4Cl$, 245.0588; found, 245.0582.

*N-(4-Fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5e**).*[17] White solid; yield: 83% (189 mg); Mp 246−248 °C; eluent: hexane/ethyl acetate 62:38; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28

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(s, 1H), 8.34 (d, J = 7.1 Hz, 1H), 7.63−7.60 (m, 3H), 7.26−7.22 (m, 1H), 7.19−7.15 (m, 2H), 6.92−6.89 (m, 1H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 158.2, 155.8, 146.6, 144.9, 138.2, 127.0, 123.0, 118.2 (d, J = 7 Hz), 116.0, 115.9 (d, J = 5 Hz), 112.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}FN_4$, 229.0884; found, 229.0877.

*N-(4-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5f**).*[17] White solid; yield: 83% (230 mg); Mp 240−241 °C; eluent: hexane/ethyl acetate 60:40; ^1H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.37 (d, J = 6.9 Hz, 1H), 7.73−7.66 (m, 5H), 7.32−7.30 (m, 1H), 6.95 (t, J = 6.6 Hz, 1H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 146.5, 144.9, 143.4, 126.8, 126.3 (d, J = 3 Hz), 122.7 (d, J = 32 Hz), 120.5, 120.1, 115.7 (d, J = 217 Hz), 115.5, 112.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}F_3N_4$, 279.0852; found, 279.0842.

*N-(m-Tolyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5g**).* White solid; yield: 87% (194 mg); Mp 216−218 °C; eluent: hexane/ethyl acetate 62:38; ^1H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.33 (d, J = 6.7 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.40 (s, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.19−7.17 (m, 2H), 6.90 (t, J = 6.4 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 2.30 (s, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 146.2, 144.2, 141.3, 138.1, 128.8, 126.4, 122.5, 121.2, 116.6, 115.4, 113.4, 112.2, 21.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_4$, 225.1134; found, 225.1128.

*N-(3-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5h**).* White solid; yield: 88% (211 mg); Mp 205−207 °C; eluent: hexane/ethyl acetate 60:40; ^1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.34 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.26−7.19 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 6.6 Hz, 1H), 6.51 (dd, J = 8.0, 2.0 Hz, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 159.9, 146.1, 144.1, 142.5, 129.7, 126.6, 122.6, 115.4, 112.3, 108.7, 105.9, 102.1, 54.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_4O$, 241.1083; found, 241.1078.

*N-(2-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5i**).* White solid; yield: 82% (196 mg); Mp 106−108 °C; eluent: hexane/ethyl acetate 60:40; ^1H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.23 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.44 (dd, J = 7.6, 1.8 Hz, 1H), 7.30−7.26 (m, 1H), 7.05 (dd, J = 7.8, 1.5 Hz, 1H), 6.93−6.85 (m, 3H), 3.89 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 148.3, 147.5, 144.7, 131.7, 127.3, 123.6, 121.4, 121.1, 116.4, 115.7, 112.6, 111.6, 56.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_4O$, 241.1083; found, 241.1077.

*N-Phenyl-[1,2,4]triazolo[4,3-a]quinolin-1-amine (**5j**).* White solid; yield: 79% (205 mg); Mp 259−260 °C; eluent: hexane/ethyl acetate 64:36; ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.62 (t, J = 8.7 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.7 Hz, 2H), 6.87 (d, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 147.8, 146.7, 143.9, 131.3, 129.3, 129.2, 128.9, 126.0, 124.0, 120.2, 116.2, 115.4, 114.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_4$, 261.1134; found, 261.11264.

*Typical Procedure for the Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles **8a**−**8k**.* The mixture of phenyl isothiocyanate (**1**) (1.0 mmol), amidoximes (**6**) (1.0 mmol), I_2 (50 mol %, 63 mg, 0.5 mmol), and K_2CO_3 (1.0 mmol) in water (2 mL) was stirred magnetically at 60 °C. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc:hexane as eluents to afford corresponding products **8a**−**8k**.

*N,3-Diphenyl-1,2,4-thiadiazol-5-amine (**8a**).*[19] White solid; yield: 90% (227 mg); Mp 174−176 °C; eluent: hexane/ethyl acetate 90:10; ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.20−8.18 (m, 2H), 7.65 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 6.4 Hz, 3H), 7.44 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 179.1, 168.5, 139.8, 132.7, 130.1, 129.3, 128.7, 127.5, 122.9, 117.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_3S$, 254.0746; found, 254.0740.

*3-Phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8b**).*[19] White solid; yield: 92% (245 mg); Mp 153−155 °C; eluent: hexane/ethyl acetate 92:8; ^1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.19−8.17 (m, 2H), 7.55−7.48 (m, 5H), 7.24 (d, J = 8.3 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 179.2, 168.5, 137.4, 132.7, 132.0, 130.0, 129.7, 128.7, 127.5, 117.8, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_3S$, 268.0902; found, 268.0895.

*N-(4-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8c**).*[20] White solid; yield: 95% (268 mg); Mp 144−145 °C; eluent: hexane/ethyl acetate 90:10; ^1H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.19−8.16 (m, 2H), 7.58−7.50 (m, 5H), 7.02 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 179.6, 168.5, 155.3, 133.2, 132.8, 130.0, 128.6, 127.5, 119.7,114.5, 55.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_3OS$, 284.0852; found, 284.0844.

*N-(4-Fluorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8d**).*[19] White solid; yield: 88% (238 mg); Mp 170−173 °C; eluent: hexane/ethyl acetate 90:10; ^1H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.19 (d, J = 5.9 Hz, 2H), 7.71 (dd, J = 8.6, 4.6 Hz, 2H), 7.52 (d, J = 6.6 Hz, 3H), 7.28 (t, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 179.1, 168.5, 159.3, 156.2, 136.3, 132.7, 130.1, 128.7, 127.5, 119.5 (d, J = 7 Hz), 115.9 (d, J = 226 Hz); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_3FS$, 272.0652; found, 272.0644.

*N-(4-Nitrophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8e**).*[21] Yellow solid; yield: 87% (259 mg); Mp 216−218 °C; eluent: hexane/ethyl acetate 85:15; ^1H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.33 (d, J = 9.1 Hz, 2H), 8.25−8.24 (m, 2H), 7.95 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 5.3 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 178.4, 168.6, 145.2, 141.5, 132.4, 130.4, 128.8, 127.6, 125.6, 117.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_4O_2S$, 299.0597; found, 299.0589.

*N-(2-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8f**).*[21] White solid; yield: 86% (243 mg); Mp 96−98 °C; eluent: hexane/ethyl acetate 88:12; ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.49 (d, J = 6.9 Hz, 1H), 8.19−8.17 (m, 2H), 7.54−7.49 (m, 3H), 7.11−7.05 (m, 3H), 3.90 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 179.97, 168.4, 148.9, 133.4, 130.4, 129.4, 129.2, 127.9, 124.0, 121.2, 119.4, 111.7, 56.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_3OS$ 284.0852; found, 284.0866

*N-(3-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8g**).* White solid; yield: 89% (251 mg); Mp 123−125 °C; eluent: hexane/ethyl acetate 90:10; ^1H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.19 (d, J = 3.3 Hz, 2H), 7.52 (s, 3H), 7.37 (d, J = 14.1 Hz, 2H), 7.16 (s, 1H), 6.70 (d, J = 6.4 Hz, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 179.5, 168.9,160.5, 141.4, 133.2, 130.7, 130.6, 129.2, 127.9, 110.4, 108.7, 104.1, 55.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_2OS$, 284.0852; found, 284.0846.

*3-Phenyl-N-propyl-1,2,4-thiadiazol-5-amine (**8h**).* White solid; yield: 84% (183 mg); Mp 82−84 °C; eluent: hexane/ethyl acetate 95:5; ^1H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.11−8.07 (m, 2H), 7.50−7.43 (m, 3H), 3.30 (d, J = 5.9 Hz, 2H), 1.64 (dd, J = 14.3, 7.2 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 183.1, 168.5, 133.1, 129.7, 128.4, 127.4, 47.0, 21.8, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}N_3S$, 220.0902; found, 220.0895.

*N-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine (**8i**).*[19] White powder; yield: 81% (209 mg); mp 126−127 °C; eluent: hexane/ethyl acetate 94:6; ^1H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.10 (s, 2H), 7.45 (s, 3H), 3.52 (s, 1H), 2.00 (s, 2H), 1.72 (s, 2H), 1.57 (s, 1H), 1.30 (t, J = 32.6 Hz, 5H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 182.0, 168.4, 133.2, 129.6, 128.4, 127.4, 54.4, 31.9, 25.1, 24.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}N_3S$, 260.1215; found, 260.1210.

*N-Phenyl-3-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8j**).* White solid; Yield; 91% (242 mg); Mp 187−188 °C; eluent: hexane/ethyl acetate 94:6; ^1H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.07 (d, J = 8.1

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Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.44 (t, J = 7.9 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.38 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6) δ 179.4, 169.0, 140.3, 140.3, 130.6, 129.9, 129.8, 128.0, 123.3, 118.1, 21.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_3S$, 268.0902; found, 268.0896.

*3-(4-Chlorophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8k**).* White solid; yield: 89% (267 mg); Mp 220−222 °C; eluent: hexane/ethyl acetate 95:5; ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.18−8.15 (m, 2H), 7.59−7.57 (m, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6) δ 179.4, 167.3, 137.3, 134.7, 132.2, 131.5, 129.7, 129.2, 128.8, 117.9, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}ClN_3S$, 302.0513; found, 302.0505.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00753.

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Notes

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Synthesis G. Manikanta et al. Paper

Total Synthesis of the Proposed Structures of the Novel Antimalarial Pyranone Cryptorigidifoliol E

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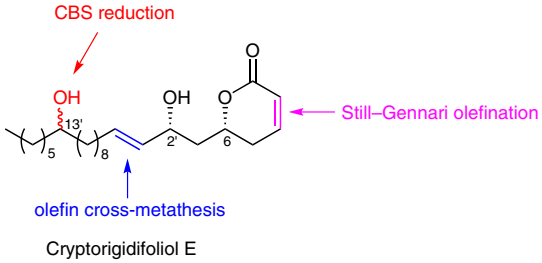

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Abstract The total syntheses of the proposed structures of the antimalarial lactone cryptorigidifoliol E are described. The synthetic sequence notably features a Bartlett–Smith halocyclization to give a chiral epoxide, followed by its regioselective ring-opening reaction, Still–Gennari olefination, Corey–Bakshi–Shibata (CBS) ynone reduction, and olefin cross-metathesis.

Key words total synthesis, cryptorigidifoliol E, lactones, Bartlett–Smith halocyclization, Corey–Bakshi–Shibata reduction, cross-metathesis

The δ-lactone moiety is a privileged scaffold, widely distributed among natural products. In particular, pyranones are extremely important because of their bioactivities, which include antifungal, antibacterial, antitumor, and antimalarial activities.[1] Five new antimalarial α,β-unsaturated δ-lactones were recently isolated from the root wood of *Cryptocarya rigidifolia* and were named cryptorigidifoliols A–E (Figure 1).[2] Inspired by the biological activity of these compounds and by the synthetic challenges offered by their structures, and because of our interest in this class of natural products,[3] we set out to synthesize cryptorigidifoliol E. As the absolute stereochemistry at C13′ had not been determined, we attempted to synthesize both epimers of the target molecule.

Our retrosynthetic analysis of compound **5** is shown in Scheme 1. Compounds **5a** and **5b** might be obtained from the two pairs of intermediates **6** and **7a** (for **5a**) and **6** and **7b** (for **5b**) by Grubbs catalyst assisted olefin cross-metathesis. The key lactone fragment **6** might in turn be obtained from enoate **8** by an acid-catalyzed one-pot acetonide deprotection, followed by lactonization. Enoate **8** might be prepared by Still–Gennari olefination and regioselective epoxide ring cleavage of epoxide **9**, which might in turn be prepared from the known homoallylic alcohol **10**.[4] Because the configuration of the C13′ stereogenic carbon had not been assigned, we proposed to synthesize both epimers of the target molecule. Accordingly, the pivotal enantiomeric olefins **7a** and **7b**, the other olefinic partners, might be synthesized from ynone **11**, and the lone stereogenic center might be generated by Corey–Bakshi–Shibata (CBS) reduction. Advantageously, both enantiomers might be obtainable merely by changing the catalyst. The silyl-protected ynone **11** might be prepared from commercially available octane-1,8-diol.

To begin our synthesis, we prepared the known optically active homoallylic alcohol **10**[4] from commercially available propane-1,3-diol (Scheme 2). Next, alcohol **10** was

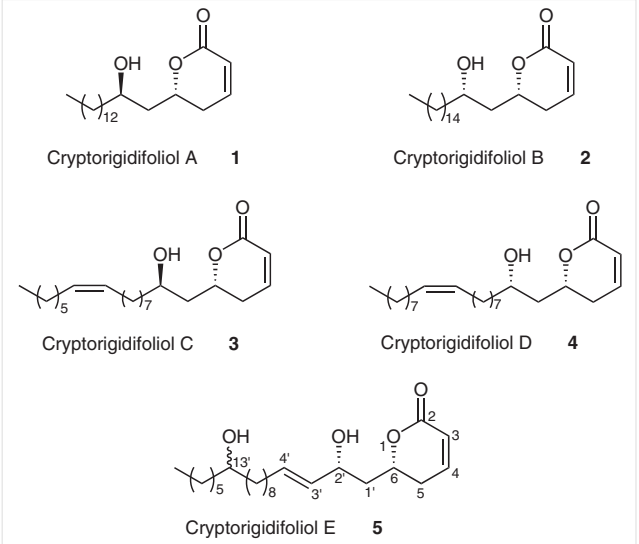
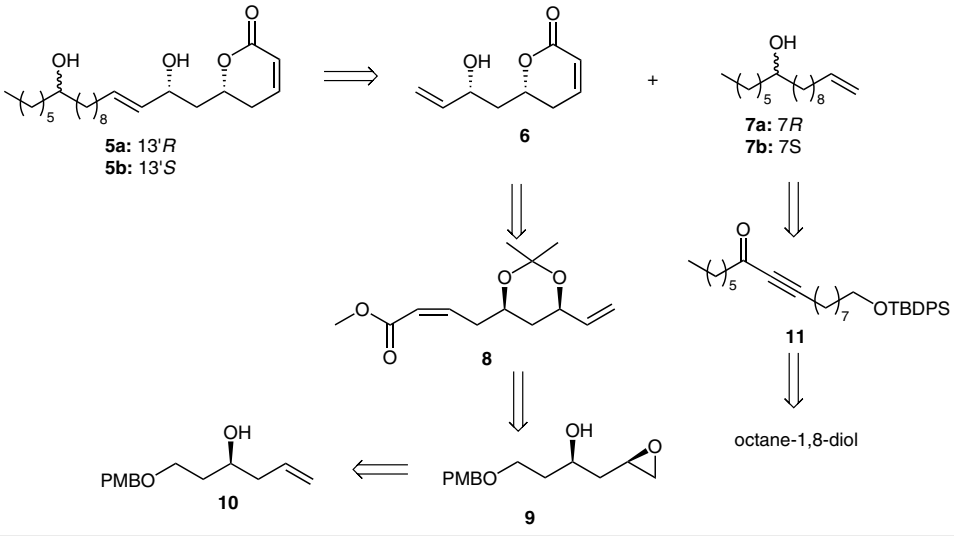


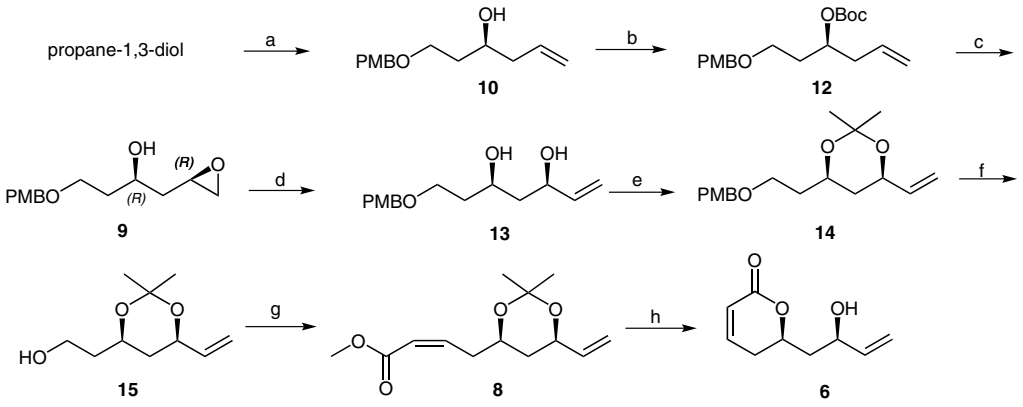
Figure 1 Structures of cryptorigidifoliols A–E



Scheme 1 Retrosynthetic analysis of cryptorigidifoliol E

treated with di-*tert*-butyl dicarbonate in the presence of DMAP to give the homoallylic *tert*-butyl carbonate **12** in 90% yield. Bartlett–Smith halocyclization[5] of carbonate **12** with *N*-iodosuccinimide (NIS) or iodine in MeCN at 0 °C, followed by treatment of the crude mixture with K_2CO_3 in methanol, delivered the epoxy alcohol **9**[6] in 66% yield. All the spectral data for this compound agreed with reference data, but the optical rotation had the opposite sign. Consequently, the stereochemistry of the epoxide-bearing carbon was initially assigned as *R*, on the basis of chemical correlation. Next, regioselective ring-opening of **9** with trimethylsulfonium iodide and BuLi in THF at –10 °C to 0 °C gave the corresponding diol **13** in 75% yield. The stereochemistry of the newly created stereogenic center in **13** was assigned by examination of the ^{13}C NMR spectra of the acetonide **14**, obtained from **13** by treatment with 2,2-dimethoxypropane in the presence of PPTS in CH_2Cl_2 at room temperature (90% yield). The ^{13}C NMR of **14** showed signals assigned to the acetonide methyl group at δ = 19.8 and 30.1 ppm, in accordance with Rychnovsky's model for a 1,3-*syn* relationship between the acetonide-attached carbons.[7] Thus the relative stereochemistry of the newly created stereogenic center was unequivocally assigned as *syn* to the existing one, and its absolute stereochemistry was confirmed as *R*.

In the next stage, deprotection of the PMB group in **14** with DDQ in CH_2Cl_2/H_2O (9:1) gave enol **15** in 87% yield. Further oxidation of the resulting alcohol **15** with Dess–Martin periodinane in CH_2Cl_2 at 0 °C gave the corresponding aldehyde, which was directly subjected to a Still–Gennari reaction[8] with methyl [bis(2,2,2-trifluoroeth-



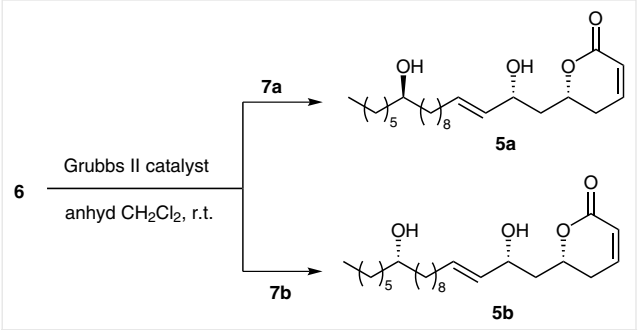
Scheme 2 *Reagents and conditions*: (a) Ref. 3; (b) $(Boc)_2O$, DMAP, CH_2Cl_2, r.t., 5 h, 90%; (c) NIS, MeCN, –40 to 0 °C, 20 h, then K_2CO_3, MeOH, 0 °C to r.t., 2 h, 66 % (two steps); (d) TMSI, BuLi, THF, –20 °C, 75%; (e) $Me_2C(OMe)_2$, PPTS, 0 °C to r.t., 6 h, 90%; (f) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to r.t., 1 h, 87%; (g) Dess–Martin periodinane, anhyd CH_2Cl_2, 0 °C, then $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, –78 °C, 1 h, 75% (two steps); (h) 3 N HCl, THF, r.t., 12 h, 79%.

oxy)phosphoryl]acetate in THF at –78 °C for one hour to afford the chromatographically separable α,β-unsaturated ester **8** as the major *Z*-isomer (*Z*/*E* = 92:8) in 75% yield. Subsequent acetonide deprotection and cyclization of ester **8** with 3 N HCl gave the required fragment **6** in 79% yield.

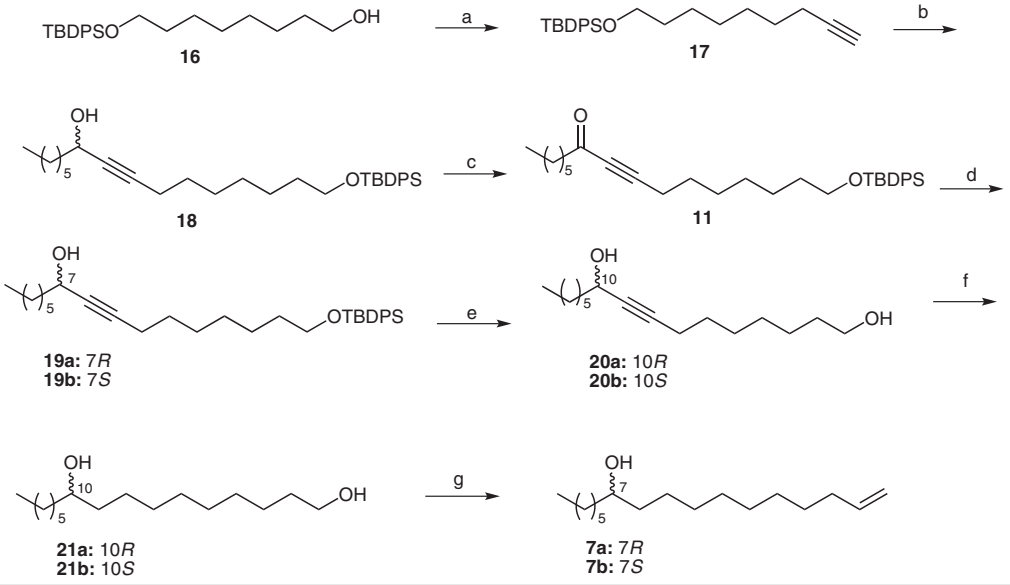
Next, we shifted our focus to the synthesis of the olefin fragments **7a** and **7b**. Selective protection of octane-1,8-diol by treatment with TBDPSCl and imidazole in CH_2Cl_2 gave the monoprotected derivative **16** in 80% yield. The primary alcohol group in compound **16** was oxidized under Swern conditions to afford the corresponding aldehyde, which upon Corey–Fuchs reaction[9] with CBr_4 and PPh_3 in CH_2Cl_2 at 0 °C gave a dibromo alkene; this was dehydrobrominated with BuLi at –78 °C to 0 °C to give the alkyne **17** in 68% yield over the three steps. Deprotonation of terminal alkyne **17** with BuLi, followed by addition of heptanal, gave the racemic propargylic alcohol **18** in 78% yield.

The ynol **18** was oxidized with Dess–Martin periodinane to afford the ynone **11** in 90% yield. Asymmetric reduction of the ynone by using the CBS reagent (*R*)-(–)-2-Me-CBS-oxazaborolidine and $BH_3{\cdot}Me_2S$ gave the chiral propargylic alcohol **19a** in 90% yield and 96% ee [by chiral HPLC: ChiralPak IA 250 × 4.6 mm, 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.129 min (2.05%), 10.558 min (97.94%)].[10] Similarly, reduction of ynone **11** with the CBS reagent (*S*)-(+)-2-Me-CBS-oxazaborolidine and $BH_3{\cdot}SMe_2$ gave the other isomer **19b** in 87% yield and 98% ee [by chiral HPLC: ChiralPak IA 250 × 4.6 mm, 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm, t_R = 10.154 min (99.32%), 10.583 min (0.68%)].[10] Next, deprotection of the TBDPS ether group of **19a** and **19b** with TBAF gave the required diols **20a** and **20b**, respectively, in 80% yield. These were subjected to hydrogenation independently in the presence of palladium on charcoal to give the saturated diols **21a** and **21b** (92% yield), respectively. Selective oxidation of the primary alcohol of the chiral diols **21a** and **21b** with TEMPO and [bis(acetoxy)iodo]benzene in CH_2Cl_2 gave the intermediate aldehydes, which on further one-carbon Wittig olefination with methylene(triphenyl)phosphorane [prepared in situ by treating methyl(triphenyl)phosphonium iodide with BuLi at –78 °C] gave the desired products **7a** and **7b**, respectively, in 66% yield over two steps. The spectral data of both the compounds were similar, except for the sign of rotation. Whereas $[\alpha]_D^{20}$ for **7a** was –7.8 (*c* 0.23, $CHCl_3$), that of **7b** was +9.0 (*c* 0.58, $CHCl_3$).

Finally, having successfully prepared the required lactone **6** and the olefin fragments **7a** and **7b**, we coupled lac-



Scheme 4



Scheme 3 *Reagents and conditions*: (a) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, then CBr_4, PPh_3, CH_2Cl_2, 0 °C, then BuLi, THF, –78 °C to –20 °C, 68% (three steps); (b) heptanal, BuLi, THF, –78 °C to 0 °C, 78%; (c) Dess–Martin periodinane, anhyd CH_2Cl_2, 0 °C, 90%; (d) [(*R*)-methyloxazaborolidine CBS catalyst for **19a**]/[(*S*)-methyloxazaborolidine CBS catalyst for **19b**], $BH_3{\cdot}SMe_2$, THF, –30 °C, 2–3 h, 90% (87% for **19b**); (e) TBAF, anhyd THF, 0 °C to r.t., 3 h, 80%; (f) H_2, Pd/C, EtOAc, r.t., 92%; (g) TEMPO, $PhI(OAc)_2$, anhyd CH_2Cl_2, r.t., 1 h; then $MePPh_3^+Br^-$, BuLi, anhyd THF, –78 °C to r.t., 2 h, 66% (two steps).

Table 1 ^{1}H and ^{13}C NMR Data[a] for the Natural Product and for the Synthetic Compounds **5a** and **5b**

Position	Natural Product		Synthetic product **5a**		Synthetic product **5b**	
	δ (^{13}C)	^{1}H (*J* Hz)	δ (^{13}C)	^{1}H (*J* Hz)	δ (^{13}C)	^{1}H (*J* Hz)
2	163.5		164.1		164.1	
3	121.3	6.03 br d (9.8)	121.3	6.02 dt (1.6, 9.7)	121.3	6.03 dt (1.6, 9.7)
4	145.0	6.90 m	145.1	6.89 m	145.1	6.89 m
5	29.2	2.44 m	29.2	2.44–2.40 m	29.3	2.46–2.40 m
6	72.5	4.69 m	75.9	4.56 m	75.9	4.57 m
1′, 5′	43.8, 32.9	1.79 m, 1.73 m 2.03 m	41.9, 32.0	1.79 m, 2.07–1.99 m 2.12 m	41.9, 32.1	1.79 m, 2.08–1.99 m 2.12 m
2′	63.3	4.63 m	69.7	4.37 q (6.8)	69.8	4.37 q (6.7)
3′	131.4	5.49 dd (7.0, 15.3)	131.6	5.46 tdd (1.3, 7.3, 15.2)	131.6	5.46 tdd (1.3, 7.3, 15.4)
4′	132.6	5.68 m	133.6	5.72 m	133.7	5.73 m
6′–11′ 15–16′	28.0, 29.6 29.6, 29.6 29.6, 29.6 29.6, 29.6	1.61–1.22 m	25.6, 25.6 28.9, 29.0 29.3, 29.4 29.4, 29.6	1.48–1.24 m	25.6, 25.6 29.0, 29.1 29.4, 29.5 29.5, 29.6	1.49–1.22 m
12′	42.1	1.61–1.49 m	37.5	1.48–1.24 m	37.5	1.49–1.22 m
13′	64.4	4.15 m	71.9	3.59 m	72.0	3.58 m
14′	42.1	1.61–1.49 m	37.4	1.8–1.24 m	37.4	1.49–1.22 m
17′	32.0	1.33–1.22 m	31.8	1.8–1.24 m	31.8	1.49–1.22 m
18′	22.8	1.33–1.22 m	22.6	1.8–1.24 m	22.6	1.49–1.22 m
19′	14.2	0.88 t (7.0)	14.0	0.88 t (6.8)	14.1	0.89 t (6.7)

[a] ^{1}H NMR in $CDCl_3$, 500 MHz; ^{13}C NMR in $CDCl_3$, 125 MHz.

tone **6** with the appropriate olefin fragment **7a** or **7b** by using Grubbs II catalyst[11] to afford the target C-13′ epimers **5a** and **5b**, respectively (Scheme4).

NMR analysis of the synthetic products **5a** and **5b** showed some differences from the reported NMR data. In particular, differences in the ^{1}H NMR spectra were observed with respect to the chemical shifts of the H-2′ and H-13′ protons (Table 1). The ^{1}H NMR chemical shifts of H-2′ and H-13′ of the natural product were reported to occur at δ = 4.43 and 4.15 ppm as multiplets, whereas those of H-2′ and H-13′ of the synthetic **5a** appeared as multiplets at δ = 4.37 and 3.59 ppm, respectively, and those of **5b** appeared as multiplets at δ = 4.37 and 3.58 ppm, respectively. Likewise, significant differences were noted in the ^{13}C chemical shifts of the chiral carbon atoms C6, C2′, and C13′. The ^{13}C chemical shifts of C6, C2′, and C13′ in the natural product occurred at δ = 72.5, 63.3, and 64.4 ppm, respectively, whereas the resonances of the same carbon atoms appeared at δ = 75.9, 69.7, and 71.9 ppm, respectively, for synthetic **5a** and at δ = 75.9, 69.8, and 72.0 ppm, respectively, for **5b**. Additionally, the ^{13}C chemical shifts for C12′ and C14′ also showed different chemical shifts for the natural and synthetic compounds.

The specific rotation for synthetic **5a** was $[\alpha]_D^{20}$ –4.8 (*c* 0.28, MeOH) and that of **5b** was $[\alpha]_D^{20}$ –10.0 (*c* 0.13, MeOH), compared with the reported value of $[\alpha]_D^{20}$ –25.0 (*c* 0.4, MeOH) for the natural product. It is pertinent to mention that the absolute stereochemistry of the two stereogenic carbons C6-OH and C2′-OH, were unequivocally assigned by Kingston et al.[2] and confirmed by us in the current study. However, because the configuration of the C13′ stereogenic center was not assigned, we synthesized both intermediates (**7a** and **7b**) by an unambiguous method and we obtained the epimeric targets **5a** and **5b**; nevertheless, the spectral data for the two synthetic compounds **5a** and **5b** did not match the reported data for the natural compound.

In conclusion, we have completed a synthesis of the two proposed structures of cryptorigidifoliol E: **5a** and **5b**. Noteworthy steps included an NIS- or I_2-assisted Bartlett–Smith halocyclization, a stereoselective ring-opening reaction, a Still–Gennari olefination, an acid-catalyzed one-pot deprotection–lactonization procedure, a CBS reduction, and, finally, an olefin cross-metathesis. The stereocontrolled synthesis of **5a** and **5b** suggests that a revision of the structure of natural cryptorigidifoliol E might be necessary.

NMR spectra were recorded on Bruker Avance spectrometers with $CDCl_3$ as solvent. ^1H NMR spectra were recorded at 300, 400, or 500 MHz, and ^{13}C NMR spectra were recorded at 100 or 125 MHz, as specified. Reactions were carried out under N_2 in anhydrous solvents. All reactions were monitored by TLC on silica-coated plates that were visualized by exposure to UV radiation and/or by α-naphthol charring. Organic solutions were dried (Na_2SO_4) and concentrated below 40 °C under reduced pressure. All column chromatographic separations were performed on silica gel (60–120 mesh) with EtOAc and hexane as eluents. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe and double-ended needle. Optical rotations were measured on an Anton Paar MCP-200 polarimeter. High-resolution mass spectra were recorded by using a Thermo Scientific Orbitrap.

tert-Butyl (1*S*)-1-{2-[(4-Methoxybenzyl)oxy]ethyl}but-3-en-1-yl Carbonate (12)

Di-*tert*-butyl dicarbonate (5.83 g, 25.42 mmol), DMAP (0.77 g, 6.35 mmol), and Et_3N (3.53 mL, 25.42 mmol) were added to a stirred solution of alcohol **10** (3.0 g, 12.71 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred at 0 °C to r.t. for 20 h. The mixture was then diluted with 3% aq HCl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic fractions were dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 3.84 g (90%); $[\alpha]_D^{20}$ +27.2 (*c* 1.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.78 (m, 1 H), 5.14–5.04 (m, 2 H) 4.88 (quint, *J* = 6.2 Hz, 1 H), 4.41 (s, 2 H), 3.79 (s, 3 H), 3.53–3.46 (m, 2 H), 2.40–2.33 (m, 2 H), 1.88 (q, *J* = 6.4 Hz, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.1, 133.3, 130.3, 129.2, 117.8, 113.6, 82.8, 73.8, 72.6, 66.1, 55.1, 38.8, 33.8, 27.7.

HRMS: *m/z* [M + NH_4]$^+$ calcd for $C_{19}H_{32}NO_5$: 354.2279; found: 354.2275.

(2*R*)-4-[(4-Methoxybenzyl)oxy]-1-[(2*R*)-oxiran-2-yl]butan-2-ol (9)

NIS (4.66 g, 20.8 mmol) was slowly added to a solution of carbonate **12** (3.5 g, 10.41 mmol) in anhyd MeCN (30 mL) at –40 °C. The mixture was then warmed to 0 °C and stirred for about 12h. When the reaction was complete (TLC), it was quenched with sat. aq $Na_2S_2O_3$ (20 mL). Sat. aq $NaHCO_3$ (20 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL), dried (Na_2SO_4), and concentrated by evaporation.

The residue was dissolved in MeOH (25 mL) and the solution was cooled to 0 °C. K_2CO_3 (3.36 g, 24.74 mmol) was added and the mixture was stirred at r.t. for 1 h. The solvent MeOH was removed under reduced pressure, and the crude residue was washed with H_2O (3 × 20 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless oil; yield: 1.74 g (66%, two steps); $[\alpha]_D^{20}$ –4.3 (*c* 1.0, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.45 (s, 2 H), 4.05 (m, 1 H), 3.80 (s, 3 H), 3.70 (m, 1 H), 3.63 (m, 1 H), 3.24 (m, 1 H), 3.09 (m, 1 H), 2.77 (m, 1 H), 2.50 (dd, *J* = 2.7, 4.8 Hz, 1 H), 1.91–1.58 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 129.8, 129.2, 113.7, 72.9, 69.4, 68.5, 55.2, 49.9, 46.5, 39.7, 36.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1255; found: 275.1253.

(3*R*,5*R*)-7-[(4-Methoxybenzyl)oxy]hept-1-ene-3,5-diol (13)

A 2.5 M soln of BuLi in THF (7.56 mL, 19.01 mmol) was added to a stirred mixture of trimethylsulfonium iodide (3.88 g, 19.01 mmol) in THF (25 mL) at –10 °C. The solution was stirred for 30 min, then a solution of epoxide **9** (1.6 g, 6.34 mmol) in THF (10 mL) was added and the mixture was stirred for 2 h at r.t. until the reaction was complete. The reaction was cautiously quenched with sat. aq NH_4Cl (5 mL), and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to a colorless liquid; yield: 1.26 g (75%); $[\alpha]_D^{20}$ –12.7 (*c* 0.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.86 (ddd, *J* = 5.8, 10.5, 17.1 Hz, 1 H), 5.25 (dt, *J* = 1.3, 17.1 Hz, 1 H), 5.08 (dt, *J* = 1.3, 10.3 Hz, 1 H), 4.45 (s, 2 H), 4.37 (m, 1 H), 4.09 (s, 1 H), 3.80 (s, 3 H), 3.72–3.60 (m, 2 H), 1.85–1.56 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 140.6, 129.8, 129.3, 114.1, 113.8, 73.1, 73.0, 72.0, 68.4, 55.2, 43.1, 36.8.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_4$: 289.1412; found: 289.1410.

(4*R*,6*R*)-4-{2-[(4-Methoxybenzyl)oxy]ethyl}-2,2-dimethyl-6-vinyl-1,3-dioxane (14)

2,2-Dimethoxypropane (1.05 mL, 8.64 mmol) and PPTS (0.217 g, 0.84 mmol) were added to a solution of diol **13** (1.15 g, 4.32 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred at r.t. for 3 h. The crude product was then mixed with CH_2Cl_2 (5 mL) and sat. aq $NaHCO_3$ (5 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 1.18 g (90%); $[\alpha]_D^{20}$ +12.6 (*c* 0.68, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.81 (ddd, *J* = 5.8, 10.5, 16.5 Hz, 1 H), 5.24 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.11 (dt, *J* = 1.3, 10.5 Hz, 1 H), 4.42 (d, *J* = 1.7 Hz, 2 H), 4.34 (m, 1 H), 4.07 (m, 1 H), 3.80 (s, 3 H), 3.60–3.47 (m, 2 H), 1.84–1.65 (m, 2 H), 1.53 (dt, *J* = 2.5, 12.8 Hz, 1 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 1.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 138.7, 130.5, 129.2, 115.2, 113.7, 98.6, 72.6, 70.2, 65.7, 55.2, 36.7, 36.4, 30.1, 19.8.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_4$: 329.1724; found: 329.1723.

2-[(4*R*,6*R*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]ethanol (15)

DDQ (1.63 g, 7.18 mmol) was added to a solution of dioxane **14** (1.1 g, 3.59 mmol) in 19:1 H_2O/CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at r.t. for 1 h. When the reaction was complete, sat. aq $NaHCO_3$ (25 mL) was added and the mixture was filtered. The filter was washed with CH_2Cl_2 (3 × 30 mL), and the combined filtrates were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless oil; yield: 0.58 g (87%); $[\alpha]_D^{20}$ +15.5 (*c* 0.89, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.27 (dq, *J* = 1.3, 17.2 Hz, 2 H), 5.14 (m, 1 H), 4.39 (m, 1 H), 4.17 (m, 1 H), 3.83–3.73 (m, 2 H), 1.81–1.70 (m, 2 H), 1.55 (dt, *J* = 2.6, 12.9 Hz, 1 H), 1.51 (s, 3 H), 1.48–1.38 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 115.4, 98.7, 70.3, 68.7, 60.5, 38.0, 36.4, 30.1, 19.7.

MS: *m/z* = 209 [M + Na]$^+$.

Methyl (2*Z*)-4-[(4*R*,6*R*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]but-2-enoate (8)

A solution of alcohol **15** (0.5 g, 2.68 mmol) in anhyd CH_2Cl_2 (10 mL) was cooled to 0 °C, Dess–Martin periodinane (1.36 g, 3.2 mmol) was added, and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (10 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the corresponding aldehyde, which was used in the next step without further characterization.

Methyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1.11 g, 3.49 mmol) was added to a stirred suspension of NaH (0.11 g, 4.58 mmol) in anhyd THF (10 mL) at 0 °C, and the resulting solution was stirred for 45 min at 0 °C then cooled to –78 °C. A solution of the aldehyde (0.43 mg, 2.33 mmol) in anhyd THF (5 mL) was added dropwise over 5 min and the resulting mixture was stirred at –78 °C for 1 h. The reaction was then quenched by adding NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 0.42 g (75%); $[\alpha]_D^{20}$ +32.9 (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dt, *J* = 7.9, 11.4 Hz, 1 H), 5.90–5.77 (m, 2 H), 5.25 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.12 (dt, *J* = 1.3, 10.5 Hz, 1 H), 4.35 (m, 1 H), 4.01 (m, 1 H), 3.71 (s, 3 H), 2.94 (m, 1 H), 2.76 (m, 1 H), 1.57 (dt, *J* = 2.5 Hz, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 145.9, 138.5, 120.6, 115.4, 98.7, 70.0, 68.1, 51.0, 36.2, 35.4, 30.1, 19.7.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{13}H_{20}NaO_4$: 263.1254; found: 263.1253.

(6*R*)-6-[(2*R*)-2-Hydroxybut-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (6)

A stirred solution of enoate **8** (0.3 g, 1.25 mmol) in THF (5 mL) was treated by dropwise addition of 3 M aq HCl (2 mL), and the solution was stirred for 12 h at r.t. When the reaction was complete, the mixture was carefully neutralized with sat. aq $NaHCO_3$ (20 mL) at 0 °C then extracted with EtOAc (3 × 30 mL). The organic extracts were dried (Na_2SO_4), concentrated, and purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless oil; yield: 0.165 g (79%); $[\alpha]_D^{20}$ +96.7 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (m, 1 H), 6.02 (dt, *J* = 1.8, 9.9 Hz, 1 H), 5.89 (m, 1 H), 5.31 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.17 (dt, *J* = 1.2, 10.3 Hz, 1 H), 4.60 (m, 1 H), 4.42 (q, *J* = 6.3, 13.0 Hz, 1 H), 2.47–2.41 (m, 2 H), 2.12 (m, 1 H), 1.84 (dt, *J* = 5.3, 14.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 145.2, 139.8, 121.1, 115.8, 75.8, 69.8, 41.1, 29.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_9H_{13}O_3$: 169.0861; found: 169.0859.

tert-Butyl(non-8-yn-1-yloxy)diphenylsilane (17)

DMSO (3.06 mL, 38.46 mmol) was added dropwise to a solution of oxalyl chloride (1.72 mL, 19.62 mmol) in CH_2Cl_2 (50 mL) at –78 °C under N_2. After 30 min, a solution of pyranone **16** (5.0 g, 13.08 mmol) in CH_2Cl_2 was added dropwise. After 1 h, Et_3N (10.92 mL, 78.51 mmol) was added, and the mixture was allowed to warm to r.t. over 1 h. The reaction was quenched with H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed sequentially with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography [silica gel, hexane–EtOAc (8:2)] to give a colorless liquid.

CBr_4 (7.74 g, 23.38 mmol) was added to a solution of PPh_3 (12.26 g, 46.79 mmol) in CH_2Cl_2 (60 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of the aldehyde prepared above (4.47 g, 11.7 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 1 h at 0 °C. Hexane (150 mL) was added to the mixture to precipitate a solid. The mixture was filtered through a pad of silica and the solvents were evaporated under reduced pressure to give the crude dibromoalkene, which was dissolved in THF. The solution was cooled to –78 °C and a 2.5 M solution of BuLi in hexane (8.37 mL, 0.93 mmol) was added dropwise. The mixture was allowed to warm to –20 °C and stirred at –20 °C for 1 h. The reaction was then quenched by addition of sat. aq NH_4Cl (15 mL), and the mixture was warmed to r.t. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 3.32 g (68%, three steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 3.65 (t, *J* = 6.4 Hz, 2 H), 2.17 (td, *J* = 2.5, 7.0 Hz, 2 H), 1.93 (t, *J* = 2.7 Hz, 1 H), 1.60–1.47 (m, 4 H), 1.41–1.23 (m, 6 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 134.1, 129.4, 127.5, 84.7, 68.0, 63.9, 32.4, 28.8, 28.7, 28.4, 26.8, 25.6, 19.2, 18.3.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{25}H_{35}OSi$: 379.2457; found: 379.2462.

16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (18)

Alkyne **17** (3.2 g, 8.46 mmol) was dissolved in THF (25 mL), and the solution was cooled to –78 °C. A 2.5 M solution of BuLi in hexane (4.06 mL, 10.15 mmol) was added slowly and the mixture was stirred for 30 min while the temperature was gradually increased to –10 °C. Heptanal (1.17 g, 10.08 mmol) was added dropwise, and the mixture was stirred for 1 h at r.t. The reaction was then quenched with sat. aq NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 3.24 g (78%).

The spectral data (^{1}H and ^{13}C NMR and HRMS) for **18** were identical to those of **19a**.

16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-one (11)

A solution of alcohol **18** (3.1 g, 6.3 mmol) in anhyd CH_2Cl_2 (30 mL) was cooled to 0 °C, Dess–Martin periodinane was added (3.2 g, 7.54 mmol), and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Purification of the crude product by column chromatography [silica gel, hexane–EtOAc (9:1)] gave a colorless liquid; yield: 2.77 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 3.69–3.64 (m, 2 H), 2.54–2.49 (m, 2 H), 2.34 (t, *J* = 7.1, Hz, 2 H), 1.70–1.62 (m, 2 H), 1.60–1.51 (m, 4 H), 1.44–1.24 (m, 12 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 135.4, 134.0, 129.4, 127.5, 94.1, 80.8, 63.8, 45.5, 32.4, 31.4, 28.7, 28.7, 28.6, 27.6, 26.8, 25.5, 24.0, 22.4, 19.1, 18.8, 13.9.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{32}H_{47}O_2Si$: 491.3345; found: 491.3350.

(7*R*)-16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (19a)

A 1 M solution of (*R*)-CBS reagent in toluene (5.34 mL, 5.34 mmol) was added to a stirred solution of ynone **11** (1.31 g, 2.65 mmol) in anhyd THF (15 mL) at –30 °C. BH_3·SMe_2 (1.25 mL, 13.33 mmol) was then added dropwise over 5 min, and the mixture was stirred for 1.5 h at –30 °C. The reaction was quenched by addition of MeOH (1 mL), and the mixture was stirred for another 10 min then concentrated under vacuum. The residue was purified by column chromatography [silica gel, hexane–EtOAc (6:4)] to give a colorless oil; yield: 1.18 g (90%, 96% ee); $[\alpha]_D^{20}$ +1.6 (*c* 0.9, $CHCl_3$).

HPLC: Chiral Pak IA (250 × 4.6 mm), 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.129 min (2.05%), 10.558 min (97.94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.44–7.35 (m, 6 H), 4.34 (t, *J* = 5.7 Hz, 1 H), 3.65 (t, *J* = 6.5 Hz, 2 H), 2.19 (td, *J* = 1.9 Hz, 2 H), 1.72–1.60 (m, 2 H), 1.59–1.24 (m, 18 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 134.1, 129.4, 127.5, 85.4, 81.3, 63.9, 62.7, 38.2, 32.4, 31.7, 28.9, 28.8, 28.7, 28.6, 26.8, 25.6, 25.1, 22.5, 19.2, 18.6, 14.0.

MS: *m/z* = 515 [M + Na]$^+$.

(7*S*)-16-{[*tert*-Butyl(diphenyl)silyl]oxy}hexadec-8-yn-7-ol (19b)

A 1 M solution of (*R*)-CBS reagent in toluene (5.34 mL, 5.34 mmol) was added to a stirred solution of ynone **11** (1.31 g, 2.65 mmol) in anhyd THF (15 mL) at –30 °C. BH_3·SMe_2 (1.25 mL, 13.33 mmol) was then added dropwise over 5 min, and the mixture was stirred for 1.5 h at –30 °C. The reaction was quenched by addition of MeOH (1 mL) and the mixture was stirred for another 10 min, then concentrated under vacuum. The residue was purified by column chromatography [silica gel, hexane–EtOAc (6:4)] to give a colorless oil; yield: 1.14 g (87%, 98% ee); $[\alpha]_D^{20}$ –2.1 (*c* 0.17, $CHCl_3$).

HPLC: Chiral Pak IA (250 × 4.6 mm), 2% *i*-PrOH–hexane (flow rate: 1 mL/min), 205 nm; t_R = 10.154 min (99.32%), 10.583 min (0.68%).

Spectral data (^{1}H and ^{13}C NMR and MS) for **19b** were identical to those of **19a**.

(10*R*)-Hexadec-8-yne-1,10-diol (20a)

To a stirred solution of ynol **19a** (1.0 g, 2.03 mmol) in anhyd THF (10 mL) was treated with a 1.0 M solution of TBAF in THF (3.04 mL, 3.04 mmol) at 0 °C, and the mixture was stirred for 1 h at r.t. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless liquid; yield: 0.412 g (80%); $[\alpha]_D^{20}$ +1.7 (*c* 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.34 (tt, *J* = 1.8, 6.5 Hz, 1 H), 3.64 (t, *J* = 6.7 Hz, 2 H), 2.20 (td, *J* = 1.9, 7.0 Hz, 2 H), 1.73–1.61 (m, 2 H), 1.61–1.47 (m, 4 H), 1.47–1.25 (m, 14 H), 0.89 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.2, 81.4, 62.8, 62.6, 38.1, 32.5, 31.7, 28.9, 28.7, 28.6, 28.4, 25.5, 25.1, 22.5, 18.5, 14.0.

MS: *m/z* = 277 [M + Na]$^+$.

(10*R*)-Hexadec-8-yne-1,10-diol (20b)

This was prepared by the same procedure as for **20a**; yield: 0.43 g (82%); $[\alpha]_D^{20}$ –2.8 (*c* 0.2, $CHCl_3$). Spectral data (^{1}H and ^{13}C NMR and MS) for **20b** were identical to those of **20a**.

(10*R*)-Hexadecane-1,10-diol (21a)

A solution of diol **20a** (0.3 g, 1.18 mmol) in EtOAc (8 mL) was stirred with 10% Pd/C (40 mg) under H_2 (balloon) for 3 h at r.t. The mixture was then filtered through Celite, which was washed with EtOAc (30 mL). The filtrate was evaporated in vacuo, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a white solid; yield: 0.28 g (92%); mp 64 °C; $[\alpha]_D^{20}$ +6.8 (*c* 0.17, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.64 (t, *J* = 6.7 Hz, 2 H), 3.58 (m, 1 H), 1.62–1.53 (m, 4 H), 1.49–1.22 (m, 22 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.0, 63.0, 37.5, 37.4, 32.7, 31.8, 29.6, 29.5, 29.3, 25.7, 25.6, 22.6, 14.0.

MS: *m/z* = 281 [M + Na]$^+$.

(*S*)-Hexadecane-1,10-diol (21b)

This was prepared by the same procedure as for **20a**; yield: 0.27 g (90%); $[\alpha]_D^{20}$ –5.9 (*c* 0.3, $CHCl_3$). The spectral data (^{1}H and ^{13}C NMR and MS) and mp for **21b** were identical to those of **21a**.

(7*R*)-Heptadec-16-en-7-ol (7a)

TEMPO (0.048 g, 0.307 mmol) and $PhI(OAc)_2$ (0.74 g, 2.32 mmol) were added to a solution of diol **21a** (0.2 g, 0.775 mmol) in anhyd CH_2Cl_2 (3 mL), and the mixture was stirred for 1 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 10 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give a crude product that was used in the next step without purification.

Methyltriphenylphosphonium bromide (0.62 g, 1.73 mmol) was dissolved in THF (8 mL) and the solution was cooled to –78 °C. A 2.5 M solution of BuLi in hexane (0.68 mL, 1.71 mmol) was added dropwise with stirring, and the solution was stirred for a further 30 min. A solution of the crude aldehyde product (0.15 g, 0.58 mmol) in anhyd THF (5 mL) was added, and the mixture was stirred for an additional 1 h. The reaction was then quenched with sat. aq NH_4Cl (15 mL), and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless liquid; yield: 0.13 g (66%, two steps); $[\alpha]_D^{20}$ –7.8 (*c* 0.23, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.04–4.90 (m, 2 H), 3.58 (m, 1 H), 2.09–1.98 (m, 2 H), 1.53–1.24 (m, 24 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.1, 114.0, 72.0, 37.4, 33.7, 31.8, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 25.6, 25.6, 22.6, 14.0.

MS: *m/z* = 277 [M + Na]$^+$.

(*S*)-Heptadec-16-en-7-ol (7b)

This was prepared by the same procedure as for **7a**; yield: 0.13 g (67%); $[\alpha]_D^{20}$ +9.0 (*c* 0.58, $CHCl_3$).

The spectral data (^{1}H and ^{13}C NMR and MS) for **7b** were identical to those of **7a**.

(6*R*)-6-[(2*R*,3*E*,13*R*)-2,13-Dihydroxynonadec-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (5a)

Grubbs II catalyst (0.01 g, 0.011 mmol) was added to a stirred solution of enol **7a** (0.03 g, 0.118 mmol) and lactone **6** (0.04 g, 0.238 mmol) in anhyd CH_2Cl_2 (2 mL), and mixture was stirred at r.t. for 5 h. When the reaction was complete, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless liquid; yield: 0.027 g (60%); $[\alpha]_D^{20}$ –4.8 (*c* 0.28, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89 (m, 1 H), 6.02 (dt, *J* = 1.6, 9.7 Hz, 1 H), 5.72 (m, 1 H), 5.46 (tdd, *J* = 1.3, 7.3, 15.2 Hz, 1 H), 4.56 (m, 1 H), 4.37 (q, *J* = 6.8 Hz, 1 H), 3.59 (m, 1 H), 2.44–2.40 (m, 2 H), 2.12 (m, 1 H), 2.07–1.99 (m, 2 H), 1.79 (m, 1 H), 1.48–1.24 (m, 24 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1, 145.1, 133.6, 131.6, 121.3, 75.9, 71.9, 69.7, 41.9, 37.5, 37.4, 32.0, 31.8, 29.6, 29.4 (2 C), 29.3, 29.2, 29.0, 28.9, 25.6 (2 C), 22.6, 14.0.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{42}NaO_4$: 417.2977; found: 417.2975.

(6*R*)-6-[(2*R*,3*E*,13*S*)-2,13-Dihydroxynonadec-3-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (5b)

Prepared from **7b** (0.028 g, 0.11 mmol) and lactone **6** (0.037 g, 0.22 mmol) by the same method as for **5a** as a colorless liquid; yield: 0.024 g (58%); $[\alpha]_D^{20}$ –10.0 (*c* 0.13, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89 (m, 1 H), 6.03 (dt, *J* = 1.6, 9.7 Hz, 1 H), 5.73 (m, 1 H), 5.46 (tdd, *J* = 1.3, 7.3, 15.4 Hz, 1 H), 4.57 (m, 1 H), 4.37 (q, *J* = 6.7 Hz, 1 H), 3.58 (m, 1 H), 2.46–2.40 (m, 2 H), 2.12 (m, 1 H), 2.08–1.99 (m, 2 H), 1.79 (m, 1 H), 1.49–1.22 (m, 24 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1, 145.1, 133.7, 131.6, 121.3, 75.9, 72.0, 69.8, 41.9, 37.5, 37.4, 32.1, 31.8, 29.6, 29.5 (2 C), 29.4, 29.3, 29.1, 29.0, 25.6 (2 C), 22.6, 14.1.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{42}NaO_4$: 417.2977; found: 417.2975.

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Supporting Information

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