Synthesis S. H. Kwak et al. Paper

Copper-Mediated Intramolecular N–N Bond Coupling Using Cerium(IV) Sulfate as the Oxidant for the Synthesis of 5-Thio-Substituted 1,2,4-Triazoles

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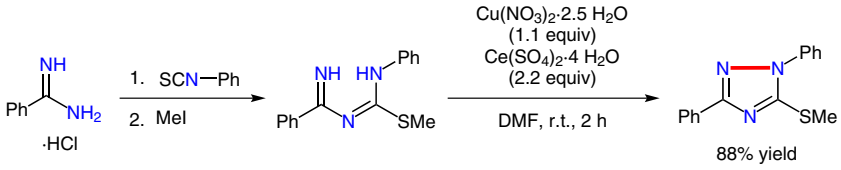


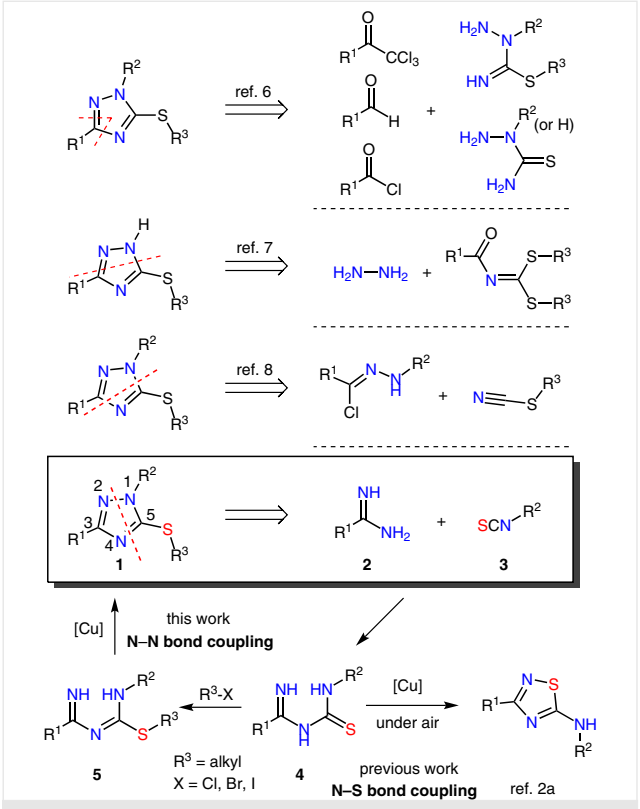
Received: 10.07.2015
Accepted after revision: 06.09.2015
Published online: 22.09.2015
DOI: 10.1055/s-0035-1560349; Art ID: ss-2015-f0427-op

Abstract A method for copper(II)-mediated N–N bond formation of *N*-imidoylisothioureas has been developed for the synthesis of 1,2,4-triazoles. The reaction requires cerium(IV) sulfate as an oxidant and proceeds at room temperature. This approach provides access to a variety of substituted 1,2,4-triazoles.

Key words copper, triazole, N–N coupling, cerium sulfate, heterocycles

Copper-catalyzed or -mediated heteroatom–heteroatom bond formation, such as the formation of N–N[1] and N–S bonds,[2] has been recently utilized for the construction of heterocycles and azo compounds.[3] This strategy has several advantages: it does not require either a leaving group on the heteroatom or prefunctionalization to create the bond between the two heteroatoms, which makes the oxidative heteroatom–heteroatom bond-coupling reaction step- and atom-economical.[4] In addition, building blocks containing an N–N bond that are challenging to prepare and handle can be avoided. Therefore, this transformation could expand the library of heterocycles. Furthermore, copper salts are inexpensive, less toxic, and readily available. Our laboratory has already reported the synthesis of 1,2,4-thiadiazoles by copper-catalyzed N–S bond formation.[2a] In continuation of our work, we report herein the copper-mediated synthesis of 1,2,4-triazoles with cerium(IV) sulfate as the oxidant.

1,2,4-Triazoles are a pharmaceutically important class of heterocycles[1c,5] that are synthesized by various routes. In the case of triazole **1**, several routes are known.[6–8] Our approach employs amidine **2** and isothiocyanate **3** for the preparation of *N*-imidoylthiourea **4** that is subjected to alkylation to give *N*-imidoylisothiourea **5** containing two NH groups that are subsequently coupled (Scheme 1). This new synthetic approach could complement previous methods especially, when their necessary components are challenging to prepare.

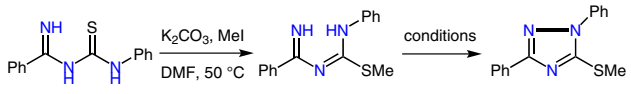


Scheme 1 Previous strategies and our work

At the outset, we optimized the reaction conditions for the oxidative N–N bond coupling of *N*-imidoylisothiourea **5a** (Table 1), which was prepared by S-methylation of *N*-im-

idoylthiourea **4a** generated from amidine **2** and isothiocyanate **3**. Initially, the conditions known for N–N bond formation using copper salts were examined, but they failed to provide **1a** (entry 1 and 2).[1] Addition of Oxone as an oxidant with copper(II) acetate showed the feasibility of this transformation (entry 3). Copper salts and oxidants were screened (entries 4–12) and we eventually found that cerium(IV) sulfate and copper(II) nitrate gave **1a** in good yield (entry 10). When the amount of copper(II) nitrate was reduced without changing the amount of cerium(IV) sulfate, the yields showed that this reaction could be carried out under catalytic conditions (entry 13 and 14); however, the yields decreased as the amount of copper(II) nitrate was reduced. The reactions under acidic conditions, in which cerium(IV) becomes the stronger oxidant, afforded better results than in the absence of acids with substoichiometric amounts of copper(II) nitrate, but the yield of **1a** did not surpass that obtained with a near stoichiometric amount of copper(II) nitrate (entry 10 vs. entries 15–17). The addition of 1,10-phenanthroline (1,10-phen) resulted in a lower yield (entry 18). Cerium(IV) sulfate in the absence of copper(II) nitrate did not produce **1a** (entry 19), implying that cerium(IV) sulfate plays a role as an oxidant in the formation of *N*-imidoylisothiourea–copper complexes. Hyperva-

Table 1 Optimization of N–N Bond Formation



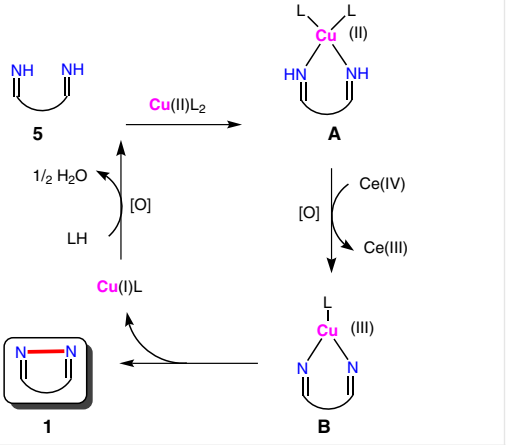
4a **5a** **1a**

Entry	Cu salt (equiv)	Oxidant (equiv)	Temp (°C), time (h)	Yield[a,b] (%) of **1a**
1	$Cu(OAc)_2$ (1.1)	–	60, 2	–
2[c]	CuBr (0.2)	–	100, 2	dec.
3	$Cu(OAc)_2$ (1.1)	Oxone (2)	r.t., 0.5	9
4	$Cu(OTf)_2$ (1.1)	Oxone (1.1)	r.t., 0.5	30
5	$CuSO_4$ (1.1)	Oxone (1.1)	60, 0.5	35
6	$CuSO_4$ (1.1)	CAN (1.1)	r.t., 0.5	39
7	CuO (1.1)	CAN (1.1)	r.t., 0.5	8
8	$CuSO_4$ (1.1)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	65
9	CuOSe (1.1)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 4	73
10	**$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (1.1)**	**$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)**	**r.t., 2**	**89 (88)[d,e]**
11	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (1.1)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (1.5)	r.t., 4	68[f]
12	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (1.1)	O_2 (1 atm)	r.t., 4	–
13	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.5)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	80
14	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.2)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	63
15[g]	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.2)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	72
16[h]	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.2)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	67
17[i]	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.2)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 3	78
18[j]	$Cu(NO_3)_2{\cdot}2.5\,H_2O$ (0.2)	$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 5	25
19		$Ce(SO_4)_2{\cdot}4\,H_2O$ (2.2)	r.t., 2	–
20[k]		$PhI(OAc)_2$ (1.5)	r.t., 1	22
21[l]		$PhI(OCOCF_3)_2$ (1.5)	r.t., 1	dec.

[a] Reaction condition: **5a** (0.2 mmol) and DMF (1 mL).
[b] NMR yield using an internal standard.
[c] DMSO was used as the solvent.
[d] **5a** (1 mmol).
[e] Isolated yield.
[f] 5% imidoyl isothiourea **5a** remained.
[g] Pivalic acid (0.2 equiv) was added.
[h] Pivalic acid (0.5 equiv) was added.
[i] Formic acid (0.2 equiv) was added.
[j] 1,10-Phen (0.2 equiv) was added.
[k] CH_2Cl_2 was used as the solvent.
[l] 2,2,2-Trifluoroethanol was used as the solvent.

lent iodine reagents known for oxidative N–N bond formation,[9] (diacetoxyiodo)benzene and [bis(trifluoroacetoxy)iodo]benzene, were also tested to compare them with copper-based reactions in yield. Interestingly, (diacetoxyiodo)benzene generated the desired product, but the yield of **1a** was disappointing and there were intractable byproducts in the mixture that hampered purification (entries 20 and 21).

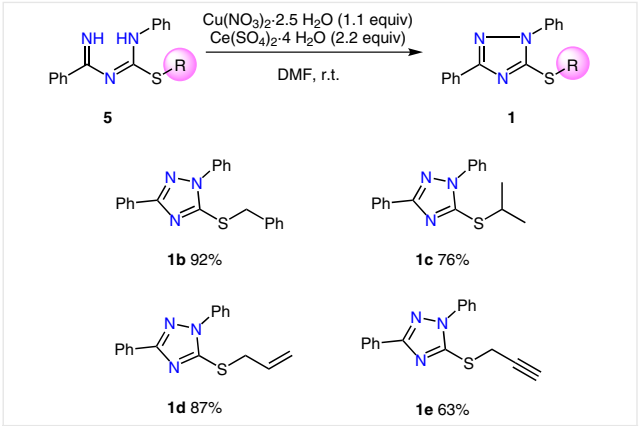
On the basis of the obtained results and literature reports,[1b,f,2a,c] a plausible pathway for the copper(II)-mediated formation of N–N bond is depicted in Scheme 2. Coordination of copper(II) **A** is followed by oxidation using one-electron oxidant Ce(IV) to generate copper complex **B**.[10] Reductive elimination of the copper species forms the N–N bond affording the triazole **1** and reduced copper, the latter is oxidized under the air atmosphere to copper(II).



Scheme 2 Proposed pathway for N–N bond formation to give 1,2,4-triazoles **1**

Having found an appropriate combination, copper(II) nitrate and cerium(IV) sulfate, we next explored various substrates (Schemes 3 and 4). At first, we investigated substrates with different alkyl groups at the sulfur atom in **5** (Scheme 3); 1,2,4-triazoles substituted with the benzyl **1b** and isopropyl **1c**, allyl **1d**, and propargyl **1e** groups were obtained in good yields.

Various *N*-imidoylisothioureas **5f**–**x** were reacted under the optimized conditions to investigate whether the transformation would be applicable to the synthesis of 1,2,4-triazoles bearing aryl, heteroaryl, and alkyl groups at the N1 and C3 positions (Scheme 4). 1,2,4-Triazoles **1f**–**n** substituted at N1 by an aryl group containing electron-donating or electron-withdrawing groups were formed in good yields. 1,2,4-Triazoles **1q**,**t**,**u** substituted at C3 by 2-, 3-, and 4-pyridyl groups were also formed in good yields. However, alkyl groups at N1 or C3, including methyl, cyclohexyl, and benzyl, were not tolerated and the products were formed in low yields or trace amounts; only 3-*tert*-butyl-1,2,4-triazole **1x** was formed in 73% yield. In case of **1s**, a higher loading of the copper salt and oxidant were necessary to complete the reaction; while **5r** was unreactive to the conditions.



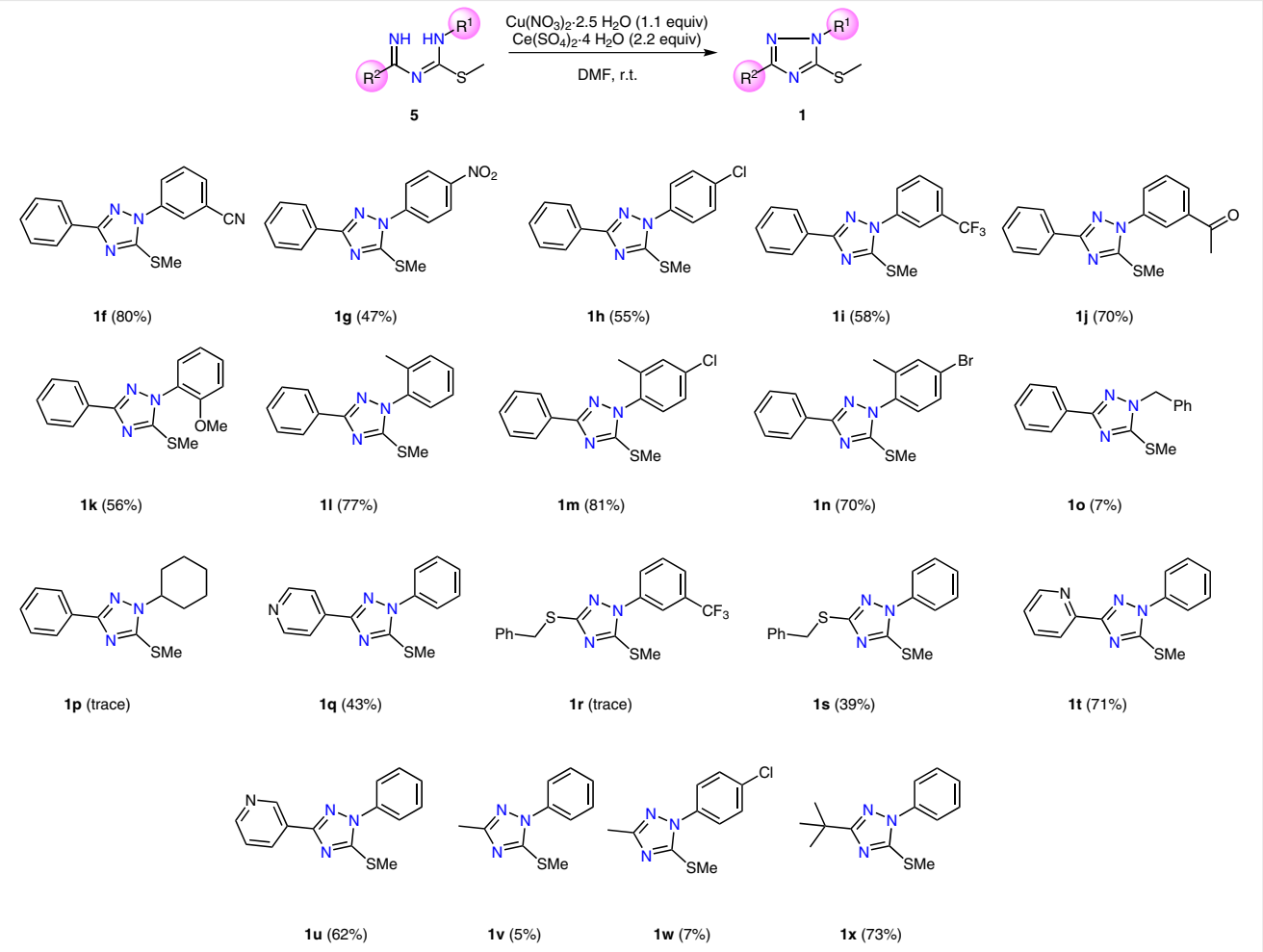
Scheme 3 Variation of the substituent at the sulfur atom. *Reagents and conditions*: **5** (0.4 mmol), DMF (2 mL).

We hoped to apply the optimized conditions to other substrates having an oxygen and nitrogen atom instead of the sulfur atom because, if we succeed in the cyclization of **6** and **7**, it could facilitate the production of diverse 1,2,4-triazoles (Scheme 5). However, the intermediates did not give the desired products. The indirect route towards 1,2,4-triazole-3-one **8** using the oxidation of the sulfide **1a** to the sulfone **9** and hydrolysis was employed to give the product **8**.[5b]

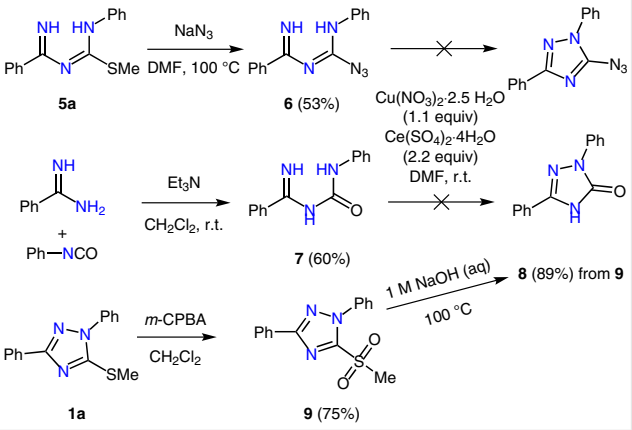
In summary, the formation of the N–N in *N*-imidoylisothioureas for the synthesis of 1,2,4-triazoles has been investigated. The combination of copper(II) nitrate and cerium(IV) sulfate was the best choice for the transformation. Various functional groups were tolerated under the conditions, but *N*-imidoylisothioureas involving alkyl groups, *N*-imidoyl azidoformamidine **6**, and *N*-imidoylurea **7** were not suitable. Bond coupling of the N–N in unreactive intermediates is currently under investigation in our laboratory.

All reactions were carried out under open-flask conditions in which no precautions were taken to exclude air and moisture from the reaction mixture. All commercial reagents and solvents were used as received without further purification. The reactions were monitored by TLC. Column chromatography was performed with silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer referenced to TMS at $\delta = 0.00$ as an internal standard. LR-MS were obtained on a Triple Quadrupole Mass spectrometer using a technique of electron spray ionization. HRMS were obtained using a TOF LC/MS system.

The preparations of imidoyl thioureas **4**,[2a] imidoyl isothioureas **5**, and compounds **6**–**9** are given in the Supporting Information.



Scheme 4 Variation of the substituent at the N1 (R^1) and C3 (R^2) positions. *Reagents and conditions*: **5** (0.4 mmol), $Cu(NO_3)_2·2.5\ H_2O$ (1.5 equiv), $Ce(SO_4)_2·4\ H_2O$ (3 equiv), DMF (2 mL).



Scheme 5 Variation of the substituent at the C5 position instead of the sulfur atom

Triazoles 1; General Procedure

To a solution of 2-alkylated *N*-imidoylisothiourea **5** (0.4 mmol) in DMF (2 mL) were added $Cu(NO_3)_2·2.5\ H_2O$ (102 mg, 0.44 mmol) and $Ce(SO_4)_2·4\ H_2O$ (356 mg, 0.88 mmol); the suspension was stirred at r.t. After completion of the reaction as indicated by TLC, water was added to the mixture and it was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered. After removal of the solvent under vacuum, the residue was purified by column chromatography to afford the product.

5-(Methylsulfanyl)-1,3-diphenyl-1,2,4-triazole (1a)[8b]

White solid; yield: 235 mg (88%); mp 51–52 °C.

IR (ATR): 2931, 1598, 1524, 1498, 1390, 1339, 1140, 1096, 1069, 1000, 754, 715, 685 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.21–8.12 (m, 2 H), 7.71–7.60 (m, 2 H), 7.52 (t, *J* = 7.8 Hz, 2 H), 7.48–7.37 (m, 4 H), 2.79 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.23, 154.27, 137.52, 130.88, 129.54, 129.53, 128.74, 128.69, 126.60, 123.99, 16.02.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3S$: 268.0903; found: 268.0910.

5-(Benzylsulfanyl)-1,3-diphenyl-1,2,4-triazole (1b)

Pale yellow oil; yield: 126 mg (92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24–8.16 (m, 2 H), 7.61–7.54 (m, 2 H), 7.52–7.36 (m, 8 H), 7.35–7.22 (m, 3 H), 4.59 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 183.59, 162.03, 152.85, 137.24, 136.51, 130.70, 129.62, 129.41, 129.26, 129.20, 128.66, 128.58, 128.51, 127.76, 126.43, 123.93, 37.98.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}N_3S$: 344.1216; found: 344.1218.

5-(Isopropylsulfanyl)-1,3-diphenyl-1,2,4-triazole (1c)

Colorless oil; yield: 90 mg (76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23–8.12 (m, 2 H), 7.68–7.60 (m, 2 H), 7.54–7.47 (m, 2 H), 7.47–7.36 (m, 4 H), 4.09 (hept, *J* = 6.8 Hz, 1 H), 1.47 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.18, 152.98, 137.42, 130.79, 129.32, 129.21, 128.52, 128.48, 126.42, 124.20, 39.60, 23.31.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3S$: 296.1216; found: 296.1219.

5-(Allylsulfanyl)-1,3-diphenyl-1,2,4-triazole (1d)

White solid; yield: 102 mg (87%); mp 61–62 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22–8.10 (m, 2 H), 7.67–7.59 (m, 2 H), 7.54–7.48 (m, 2 H), 7.47–7.38 (m, 4 H), 6.01 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1 H), 5.34 (dd, *J* = 16.9, 1.3 Hz, 1 H), 5.16 (d, *J* = 10.0 Hz, 1 H), 3.99 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.07, 152.64, 137.30, 132.63, 130.68, 129.38, 129.30, 128.56, 128.55, 126.41, 124.02, 119.03, 36.38.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}N_3S$: 294.1059; found: 294.1066.

1,3-Diphenyl-5-(prop-2-ynylsulfanyl)-1,2,4-triazole (1e)

White solid; yield: 73 mg (63%); mp 124–125 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.1 Hz, 2 H), 7.63 (d, *J* = 7.7 Hz, 2 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 7.49–7.38 (m, 4 H), 4.15 (d, *J* = 2.4 Hz, 2 H), 2.27 (t, *J* = 2.2 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.24, 151.49, 137.05, 130.47, 129.50, 129.42, 128.75, 128.57, 126.44, 123.90, 78.30, 72.25, 22.09.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3S$: 292.0903; found: 292.0904.

3-[5-(Methylsulfanyl)-3-phenyl-1,2,4-triazol-1-yl]benzonitrile (1f)

White solid; yield: 94 mg (80%); mp 142–144 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.9, 1.5 Hz, 2 H), 8.08–8.03 (m, 1 H), 7.97 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.9 Hz, 1 H), 7.51–7.41 (m, 3 H), 2.84 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.47, 154.52, 138.15, 131.42, 130.34, 130.11, 129.77, 128.65, 127.27, 126.57, 126.50, 117.67, 113.68, 15.98.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4S$: 293.0855; found: 293.0862.

5-(Methylsulfanyl)-1-(4-nitrophenyl)-3-phenyl-1,2,4-triazole (1g)

Pale yellow solid; yield: 59 mg (47%); mp 134–135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45–8.33 (m, 2 H), 8.16 (dd, *J* = 7.8, 1.6 Hz, 2 H), 8.05–7.91 (m, 2 H), 7.54–7.40 (m, 3 H), 2.86 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.57, 155.05, 146.39, 142.30, 129.99, 129.91, 128.67, 126.59, 124.96, 123.00, 16.14.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_4O_2S$: 313.0754; found: 313.0759.

1-(4-Chlorophenyl)-5-(methylsulfanyl)-3-phenyl-1,2,4-triazole (1h)

White solid; yield: 66 mg (55%); mp 117–119 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.1 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.55–7.36 (m, 5 H), 2.80 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.13, 154.37, 135.49, 133.27, 129.98, 129.71, 129.64, 128.84, 125.95, 125.60, 15.57.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClN_3S$: 302.0513; found: 302.0520.

5-(Methylsulfanyl)-3-phenyl-1-[3-(trifluoromethyl)phenyl]-1,2,4-triazole (1i)

Pale yellow solid; yield: 78 mg (58%); mp 76–78 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 8.1, 1.4 Hz, 2 H), 8.00 (s, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.71–7.60 (m, 2 H), 7.51–7.37 (m, 3 H), 2.82 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.36, 154.44, 137.83, 131.98 (q, *J* = 33.1 Hz), 130.31, 129.97, 129.63, 128.61, 126.49, 126.43, 124.87 (q, *J* = 3.7 Hz), 123.45 (q, *J* = 272.6 Hz),120.54 (q, *J* = 3.9 Hz), 15.91.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}F_3N_3S$: 336.0777; found: 336.0781.

1-{3-[5-(Methylsulfanyl)-3-phenyl-1,2,4-triazol-1-yl]phenyl}ethanone (1j)

White solid; yield: 87 mg (70%); mp 115–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.17 (d, *J* = 7.7 Hz, 2 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.52–7.37 (m, 3 H), 2.82 (s, 3 H), 2.67 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.73, 162.24, 154.32, 138.16, 137.76, 130.42, 129.72, 129.53, 128.58, 127.87, 127.79, 126.45, 123.27, 26.76, 15.89.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}N_3OS$: 310.1009; found: 310.1014.

1-(2-Methoxyphenyl)-5-(methylsulfanyl)-3-phenyl-1,2,4-triazole (1k)

Colorless oil; yield: 67 mg (56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.4 Hz, 2 H), 7.52–7.35 (m, 5 H), 7.13–7.01 (m, 2 H), 3.83 (s, 3 H), 2.71 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.37, 156.23, 154.77, 131.49, 131.02, 129.31, 128.73, 128.61, 126.54, 125.77, 120.98, 112.43, 55.95, 15.90.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3OS$: 298.1009; found: 298.1013.

5-(Methylsulfanyl)-1-(*o*-tolyl)-3-phenyl-1,2,4-triazole (1l)

Pale yellow oil; yield: 87 mg (77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22–8.10 (m, 2 H), 7.47–7.28 (m, 7 H), 2.73 (s, 3 H), 2.19 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.22, 155.35, 135.92, 135.69, 131.37, 130.79, 130.22, 129.28, 128.54, 127.45, 126.84, 126.33, 17.57, 15.35.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3S$: 282.1059; found: 282.1063.

1-(4-Chloro-2-methylphenyl)-5-(methylsulfanyl)-3-phenyl-1,2,4-triazole (1m)

White solid; yield: 102 mg (81%); mp 88–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20–8.06 (m, 2 H), 7.50–7.39 (m, 3 H), 7.36 (s, 1 H), 7.33–7.22 (m, 2 H), 2.74 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.44, 155.58, 137.90, 135.92, 134.21, 131.33, 130.58, 129.43, 128.73, 128.58, 127.05, 126.33, 17.59, 15.36.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClN_3S$: 316.0670; found: 316.0673.

1-(4-Bromo-2-methylphenyl)-5-(methylsulfanyl)-3-phenyl-1,2,4-triazole (1n)

Yellow solid; yield: 101 mg (70%); mp 109–111 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.11 (m, 2 H), 7.54 (s, 1 H), 7.51–7.37 (m, 4 H), 7.21 (d, *J* = 8.3 Hz, 1 H), 2.75 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.47, 155.51, 138.18, 134.76, 134.31, 130.59, 130.05, 129.42, 128.96, 128.58, 126.34, 124.13, 17.55, 15.39.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}BrN_3S$: 360.0165; found: 360.0169.

1-Benzyl-5-(methylsulfanyl)-3-phenyl-1,2,4-triazole (1o)

Colorless oil; yield: 8 mg (7%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14–8.03 (m, 2 H), 7.45–7.40 (m, 2 H), 7.39–7.32 (m, 3 H), 7.32–7.27 (m, 3 H), 5.30 (s, 2 H), 2.72 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.82, 153.57, 135.18, 130.96, 129.10, 128.77, 128.48, 128.14, 127.68, 126.24, 52.34, 15.92.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3S$: 282.1059; found: 282.1063.

4-[5-(Methylsulfanyl)-1-phenyl-1,2,4-triazol-3-yl]pyridine (1q)

White solid; yield: 46 mg (43%); mp 59–61 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 4.6, 1.4 Hz, 2 H), 8.02 (dd, *J* = 4.5, 1.5 Hz, 2 H), 7.68–7.61 (m, 2 H), 7.54 (t, *J* = 7.7 Hz, 2 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 2.79 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.93, 155.04, 150.34, 138.01, 137.02, 129.46, 128.91, 123.80, 120.49, 15.80.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4S$: 269.0855; found: 269.0859.

3-(Benzylsulfanyl)-5-(methylsulfanyl)-1-phenyl-1,2,4-triazole (1s)

Pale yellow oil; yield: 49 mg (39%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.8 Hz, 2 H), 7.51–7.43 (m, 4 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.28–7.22 (m, 1 H), 4.39 (s, 2 H), 2.70 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.63, 154.28, 137.50, 137.01, 129.30, 129.13, 128.46, 128.43, 127.32, 123.44, 36.30, 15.75.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3S_2$: 314.0780; found: 314.0785.

2-[5-(Methylsulfanyl)-1-phenyl-1,2,4-triazol-3-yl]pyridine (1t)

Colorless oil; yield: 76 mg (71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.78 (d, *J* = 4.4 Hz, 1 H), 8.20 (d, *J* = 7.9 Hz, 1 H), 7.80 (t, *J* = 7.7 Hz, 1 H), 7.68 (d, *J* = 7.9 Hz, 2 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.36–7.29 (m, 1 H), 2.83 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.64, 154.88, 150.07, 149.51, 137.10, 136.73, 129.26, 128.76, 124.03, 123.92, 121.84, 15.83.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4S$: 269.0855; found: 269.0864.

3-[5-(Methylsulfanyl)-1-phenyl-1,2,4-triazol-3-yl)pyridine (1u)

Pale yellow solid; yield: 66 mg (62%); mp 114–115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 1.5 Hz, 1 H), 8.65 (dd, *J* = 4.8, 1.7 Hz, 1 H), 8.41 (dt, *J* = 7.9, 1.9 Hz, 1 H), 7.69–7.61 (m, 2 H), 7.58–7.50 (m, 2 H), 7.49–7.41 (m, 1 H), 7.37 (ddd, *J* = 7.9, 4.8, 0.6 Hz, 1 H), 2.79 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.73, 154.67, 150.28, 147.97, 137.08, 133.60, 129.42, 128.73, 126.69, 123.73, 123.39, 15.80.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4S$: 269.0855; found: 269.0860.

3-Methyl-5-(methylsulfanyl)-1-phenyl-1,2,4-triazole (1v)

Pale yellow oil; yield: 4 mg (5%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.53 (m, 2 H), 7.52–7.45 (m, 2 H), 7.43–7.37 (m, 1 H), 2.70 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.02, 153.34, 137.19, 129.28, 128.35, 123.65, 15.64, 14.02.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}N_3S$: 206.0746; found: 206.0751.

1-(4-Chlorophenyl)-3-methyl-5-(methylsulfanyl)-1,2,4-triazole (1w)

Pale yellow solid; yield: 7 mg (7%); mp 114–115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.49 (m, 2 H), 7.49–7.40 (m, 2 H), 2.71 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.22, 153.50, 135.71, 134.01, 129.46, 124.76, 15.68, 13.99.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}ClN_3S$: 240.0357; found: 240.0360.

3-*tert*-Butyl-5-(methylsulfanyl)-1-phenyl-1,2,4-triazole (1x)

Yellow oil; yield: 72 mg (73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.8 Hz, 2 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 2.68 (s, 3 H), 1.41 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.02, 152.53, 137.46, 129.19, 128.08, 123.80, 33.04, 29.44, 15.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}N_3S$: 248.1216; found: 248.1219.

Acknowledgment

This research was financially supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) grant (No. 2014M3A9A9073847) and grant (No. 2012M3A9C1053532) funded by the Ministry of Science, ICT & Future Planning of the Korean Government.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560349.

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(10) The decreased product yields for **1a** were observed under the optimized conditions with either two equivalents 1,1-diphenylethene (66%) or *tert*-butylhydroxytoluene (37%) as a radical scavenger.