A facile one-pot synthetic method for 1,2,4-triazoles and 1,3-disubstitued thioureas

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The reaction of arylisothiocyanates with triethylamine and acylhydrazides in the presence of mercuric acetate has been studied. The reaction proceeds through the formation of thiourea, followed by a sequential addition–dehydration with acylhydrazides. The initial detection of thiourea, which mediates the formation of disubstituted 1,2,4-triazoles, is explained by a plausible mechanism.

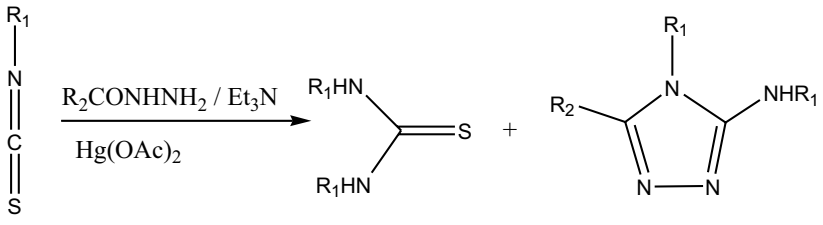
Keywords: triazole, thiourea, acyl hydrazide, arylisothiocyanate

1,2,4-Triazole ring systems constitute an important class of heterocycles.[1] This five-membered ring was also found in biologically active molecules such as active antimycobacterials[2] and potent, selective 5-HT1D receptor agonists.[3] 1,2,4-triazole derivatives have been used as mimics[4] of the amide bond in order to increase bioavailability of the parent bioactive molecules. Another interesting application of triazole was to employ it as a *cis*-amide bond surrogate in peptides.[5] These studies prompted us to further investigate the convenient synthetic methods of 1,2,4-triazoles as bioactive compounds of therapeutic potential.

A solid-phase synthetic method of 1,2,4-triazoles from acyl hydrazide resins and amidines in the presence of molecular sieves was reported by Katritzky *et al*.[6] Similarly, Larsen and DiPaolo converted *N*-resin-bound thioamides to amidrazones, which were then acylated by acyl halides and cyclised in the presence of acetic acid at room temperature to the triazoles of interest.[7] However, solid phase synthesis suffers from various problems, such as the heterogeneous nature of the reaction condition, reduced rate of reactions, and hindered mass transport of reagents. Recently, mercuric acetate and other mercuric salts have been reportedly used as thiophiles in the guanylation of amines by thioureas.[5a,8,9] Keeping these studies in mind and in continuation of our systematic studies on the synthesis of azole heterocycles,[10] we are reporting a facile synthesis of 1,2,4-triazoles from arylisothiocyanates catalysed by mercuric acetate in dioxane. The reaction process involves the formation of symmetrical thioureas from the corresponding arylisothiocyanates, which undergoes subsequent guanylation catalysed by mercuric acetate. The guanylated intermediate undergoes intramolecular ring cyclisation to yield the desired triazoles along with the thioureas as byeproducts.

Thioureas are also important compounds as building blocks in the synthesis of heterocycles such as 2-amino-1,3-thiazoles,[11] benzothiazoles,[12] iminothiazolines,[13] thiohydantoins,[14] 1,3,5-triazines,[15] and 2-amino oxazolidines.[16] Several new methods for the preparation of substituted thioureas have been recently reported.[17-21] However, these methods have several drawbacks such as the need for high reaction temperature, long reaction time, and using multistep reactions. The present method provides an efficient, easy and mild condition to afford the symmetrically substituted thioureas.

As a representative example, phenylisothiocyanate was stirred with triethylamine in anhydrous 1,4-dioxane for half an hour at room temperature. Addition of acylhydrazides in the presence of mercuric acetate and stirring the mixture for 5 h yields 1,3 diphenylthiourea **2a** and 1,2,4-triazole **3a,** in varying yields (Scheme 1). The yields are optimised with the product ratio of thiourea and triazole as 50:50 after stirring the reaction for 5–6 h. Interestingly, it was found that the yield of the thiourea (80%)was much more than the triazole if the reaction process was stopped after 1 h (monitored by TLC).



1a–c **2a–c** **3a–e**

Entry	R_1	R_2	% yield
2a	phenyl	H	50
2b	4-OMe-phenyl	H	58
2c	4-Cl-phenyl	H	52
3a	phenyl	H	50
3b	4-OMe-phenyl	H	42
3c	4-Cl-phenyl	H	48
3d	phenyl	Me	58
3e	phenyl	phenyl	52

Scheme 1

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It seems that the thiourea produced during the process gets converted to the triazole compound through the thiophilation in presence of the mercuric acetate. Based on this observation, a plausible mechanism is proposed as shown in Scheme 2.

In conclusion, we have developed a mild, efficient, and one-pot synthesis of two important compounds, namely, 1,2,4-triazoles and 1,3-disubstituted thioureas.

Experimental

The IR spectra were recorded on a Perkin Elmer 983 spectrometer in KBr pellets with absorption given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Varian EM-390 (300 MHz) spectrometer. The Chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to internal tetramethyl silane (TMS). The MS spectra were recorded on a Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Heraus CHN–O–Rapid Analyzer.

General procedure for preparation of **2a–c** *and* **3a–e**

1a-c (1 mmol) and triethylamine (5 mmol) were dissolved in anhydrous 1,4-dioxane (20 ml) and stirred at room temperature. After stirring for 20 minutes, the respective acylhydrazide (1.5 mmol) and $Hg(OAc)_2$ (1 mmol) was added. The reaction mixture was stirred at the same temperature for 5–10 h (monitored by TLC). The solid material was filtered and the filtrate was concentrated on a rotary vaccum evaporator. It was treated with water (100 ml) and extracted with chloroform (50 ml). The chloroform extract was dried (Na_2SO_4), evaporated and the residue was chromatographed on a silica gel column using ethylacetate/hexane (1:2) as eluent to yield **2a–c** and **3a–e**. The physical and spectral data of the compounds **2a–c** and **3a–e** are as follows.

1,3-Diphenylthiourea **(2a)**: 50%, m.p. 152–153°C (lit.[17] m.p. 152°C); IR (KBr): 3206, 3011, 1595, 1549, 1342, 1238 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.99 (brs, 2H), 7.23–7.75 (m, 10H); MS^+(EI): *m/z* 228. Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27. Found: C, 68.41; H, 5.32; N, 12.25%.

1,3-Di-(4-methoxyphenyl)thiourea lit.[18] **(2b):** 58%, colourless solid: m.p. 201–203°C; IR (KBr): 3200, 3001, 1585, 1543, 1336, 1228 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.40 (s, 2H), 7.27 (d, J = 8.8 Hz, 4H), 6.85 (d, J = 8.8 Hz, 4H), 3.70 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 181.2, 157.2, 132.9, 126.8, 114.5, 56.0; MS^+(EI): *m/z* 289 $[M + H]^+$.

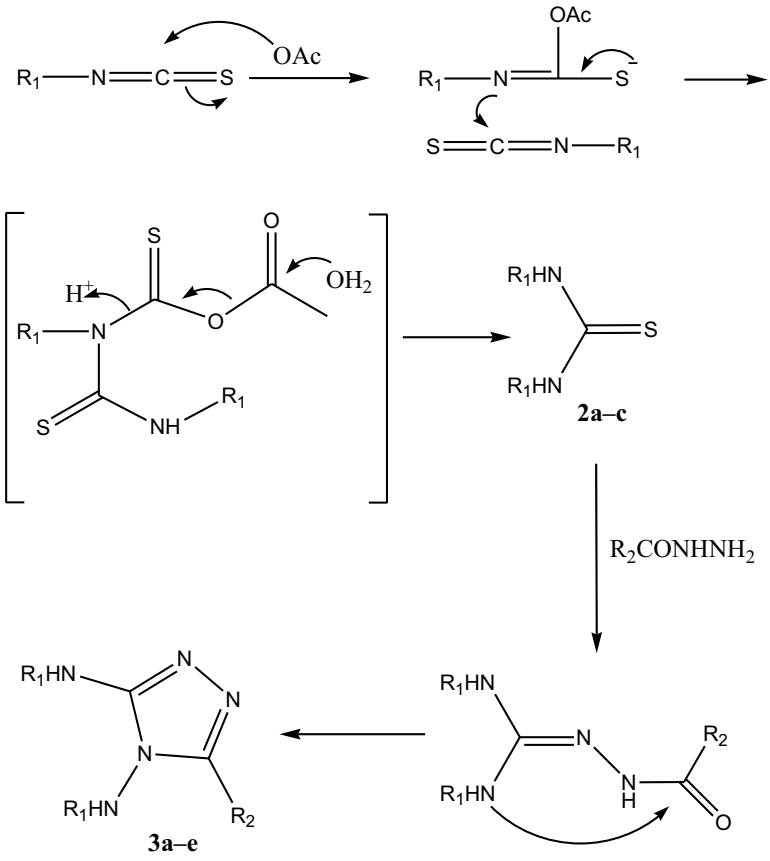
1,3-Di-(4-chlorophenyl)thiourea **(2c):** 52%, colourless solid: m.p. 166–168°C(lit.[17] m.p. 167°C); IR (KBr): 3203, 3011, 1596, 1543, 1332, 1215 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.42 (s, 2H), 7.35 (d, J = 9.0 Hz, 4H), 6.80 (d, J = 9.0 Hz, 4H); ^{13}C NMR (DMSO-d_6): δ 181.1, 157.2, 132.9, 126.8, 114.3, 55.9; MS^+(EI): *m/z* 297$[M + H]^+$. Anal. Calcd. for $C_{13}H_{10}Cl_2N_2S$: C, 52.54; H, 3.39; N, 9.43. Found: C, 52.50; H, 3.31; N, 9.52%.

N-Phenyl-(4-phenyl-4H-1,2,4-triazol-3-yl)-amine **(3a):** 50%, colourless solid: m.p. 214–216°C; 1H NMR (DMSO-d_6): δ 8.52 (bs, 1H), 8.49 (s, 1H), 7.57–7.55 (m, 2H), 7.51–7.44 (m, 3H), 7.40 (d, 2H, J = 8 Hz), 7.20 (t, 2H, J = 8 Hz), 6.82 (t, 1H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6): 150.7, 142.7, 142.2, 134.0, 130.6, 129.5, 129.5, 126.0, 120.9, 117.5; MS (EI): *m/z* 237 $[M + H]^+$; Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.95; H, 4.89; N, 23.77%.

(4-Methoxy-phenyl)-[4-(4-methoxy-phenyl)-4H-1,2,4-triazol-3-yl]-amine **(3b):** 42%, colourless solid: m.p. 183–185°C; ^1H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.12 (s, 1H), 7.43–7.37 (m, 4H), 7.08 (dd, J = 6.8, 2.0 Hz, 2H), 6.76 (dd, J = 6.8, 2.0 Hz, 2H), 3.80 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (DMSO-d_6): 159.5, 153.4, 150.9, 141.2, 134.9, 127.3, 125.9, 118.5, 114.9, 113.8, 55.5, 55.3; MS + (EI): *m/z* 296 $[M + H]^+$; Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.95; H, 5.69; N, 18.75%.

(4-Chloro-phenyl)-[4-(4-chloro-phenyl)-4H-1,2,4-triazol-3-yl]-amine **(3c):** 48%, colourless solid: m.p. 226–228°C; ^1H NMR (DMSO-d_6): δ 8.74 (s, 1H), 8.48 (s, 1H), 7.58–7.63 (m, 2H), 7.35–7.42 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 149.9, 141.3, 140.5, 133.5, 132.0, 129.8, 128.4, 127.6, 123.9, 118.5; MS (EI): *m/z* 305 $[M + H]^+$; Anal. Calcd for $C_{14}H_{10}Cl_2N_4$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.35; H, 3.29; N, 18.47%.

(5-Methyl-4-phenyl-4H-1,2,4-triazol-3-yl)-phenylamine **(3d):** 58%, colourless solid: m.p. 236–238°C; ^1H NMR (DMSO-d_6): δ 8.14 (s, 1H), 7.58–7.50 (m, 3H), 7.44–7.36 (m, 4H), 7.18–7.13 (m, 2H), 6.81–6.77 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 151.2, 148.2, 142.5, 133.7, 130.8, 130.0, 129.5, 128.3, 120.6, 117.1, 11.9; MS (EI): *m/z* 251 $[M + H]^+$; Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.78; H, 5.47; N, 22.41%.



Scheme 2

(4,5-Diphenyl-4H-1,2,4-triazol-3-yl)-phenyl-amine **(3e):** 52%, colourless solid: m.p. 201–203°C; ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 7.52–7.46 (m, 5H), 7.44–7.42 (m, 2H), 7.35–7.32 (m, 1H), 7.32–7.30 (m, 4H), 7.22 (t, J = 7.2 Hz, 2H), 6.87 (t, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 152.6, 150.7, 141.8, 133.9, 130.9, 130.8, 130.3, 129.5, 129.4, 129.3, 128.7, 127.9, 121.8, 118.5; MS (EI): *m/z* 313 $[M + H]^+$; Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.75; H, 5.10; N, 18.10%.

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References

1 (a) P.J. Garratt, In *Comprehensive Heterocyclic Chemistry II*, R.C. Storr, Ed.; Elsevier: Oxford, 1996; Vol. 4, pp 127, 905; (b) K. Turnbull, In *Progress in Heterocyclic Chemistry*, Elsevier: Oxford, 1998; Vol. 10, p 153.
2 I. Kucukguzel, S.G. Kucukguzel, S. Rollas and M. Kiraz, *Bioorg. Med. Chem. Lett.,* 2001, **11**, 1703.
3 L.J. Street, R. Baker, W.B. Davey, A.R. Guiblin, R.A. Jelley, A.J. Reeve, H. Routledge, F. Sternfeld, A.P. Watt, M.S. Beer, D.N. Middlemiss, A.J. Noble, J.A. Stanton, K. Scholey, R.J. Hargreaves, B. Sohal, M.I. Graham and V.G. Matassat, *J. Med. Chem.,* 1995, **38**, 1799.
4 G. Burrell, J.M. Evans, M.S. Hadley, F. Hicks and G. Stemp, *Bioorg. Med. Chem. Lett.,* 1994, **4**, 1285; (b) W.R. Tully, C.R. Gardner, R.J. Gillepsie and R. Westwood, *J. Med. Chem.,* 1991, **34**, 2060.
5 (a) Y. Hitotsuyanagi, S. Motegi, H. Fukaya and K.Takeya, *J. Org. Chem*., 2002, **67**, 3266; (b) J.V. Duncia, J.B. III Santela, A. Higley, M.K. VanAtten, P.C. Weber, R.S. Alexander, C.A. Kettner, J.R. Pruitt, A.Y. Liauw, M.L. Quan, R.M. Knabb and R.R. Wexler, *Bioorg. Med. Chem. Lett.,* 1998, **8**, 775.
6 A.R. Katritzky, M. Qi, D. Feng, G. Zhang, M.C. Griffith and K. Watson, *Org. Lett.,* 1999, **1**, 1189.
7 S.D. Larsen and B.A. DiPaolo, *Org. Lett.,* 2001, **3**, 3341.
8 C. Levallet, J. Lerpiniere and S. –Y. Ko, *Tetrahedron,* 1997, **53**, 5291.
9 (a) W. Su, *Synth. Commun.,* 1996, **26**, 407; (b) K.S. Kim and L. Qian, *Tetrahedron Lett.,* 1993, **34**, 7677.
10 (a) O.M. Singh, H. Ila and H. Junjappa, *J. Chem. Res*., 1999, 398; (b) O. Barun, H. Ila, H. Junjappa and O.M. Singh, *J. Org. Chem*., 2000, **65**, 1583; (c) O.M. Singh and M.F. Ahmed, *Ind. J. Chem*., 2004, **43B**, 1561.
11 (a) P.C. Kearney, M. Frenandez and J.A. Flygare, *J. Org. Chem.,* 1998, **63**, 196; (b) C. Boga, L. Forlani, C. Silvestroni, A.B. Corradi and P. Sagarabotto, *J. Chem. Soc., Perkin Trans., 1* 1999, 1363.
12 D.G. Patil and M.R. Chedekel, *J. Org. Chem.,* 1984, **49**, 997.
13 S. Kasmi, J. Hamelin and H. Benhaoua, *Tetrahedron Lett*., 1998, **39**, 8093.
14 (a) M. Kidwai, R. Venkataramanan and B. Dave, *Green Chem*., 2001, **3**, 278; (b) S. Paul, M. Gupta and A. Loupy, *Synthesis,* 2002, 75.
15 D. Anshu, A. Kapil and S. Meha, *Synth. Commun*., 2004, **34**, 1141.
16 U. Heinelt, D. Schultheis, S. Jager, M. Iindenmaire, A. Pollex and H.S.G. Beckmann, *Tetrahedron,* 2004, **60**, 9883.
17 J.B. Chattopadhyaya and A.V.R. Rao, *Synthesis,* 1974, 289.
18 N. Ramnath, V. Ramesh and V. Ramamurthy, *J. Org. Chem.,* 1983, **48**, 214.
19 C.R. Villani, F.J. Rasmussen, L.E. Weaner, B.E. Reynolds, A.R. Hood, L.R. Hecker, S.O. Nortey, A. Hanslin, M.J. Costanzo, E.T. Powell and A.J. Molinari, *Synthesis,* 1988, 456.
20 M. Kotetsu, Y. Fukuta and H. Ishihara, *Tetrahedron Lett.,* 2001, **42**, 6333.
21 (a) L. Ciszewski, D. Xu, O. Repic and T.J. Blacklock, *Tetrahedron Lett*., 2004, **45**, 8091; (b) J. Vazquez, S. Bernes, Y. Reyes, M. Maya, P. Sharma and C. Alvarez, Gutierrez, *Synthesis,* 2004, 1955; (c) A.R. Katritzky, N. Kirichenko, B.V. Rogovoy, J. Kister and H. Tao, *Synthesis,* 2004, 1799.