Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2381–2383
Tetrahedron Letters

First example of the coupling of α-diazoketones with thiourea: a novel route for the synthesis of 2-aminothiazoles

J. S. Yadav *, B. V. Subba Reddy, Y. Gopala Rao, A. V. Narsaiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 6 December 2007; revised 7 February 2008; accepted 13 February 2008
Available online 16 February 2008

Abstract

α-Diazoketones undergo smooth coupling with thiourea in the presence of 10 mol % of copper(II) triflate to produce the corresponding 2-aminothiazoles in excellent yields with high selectivity. The use of copper(II) triflate makes this method simple, convenient and practical. This method works well with both aryl and alkyl diazoketones to furnish a wide range of 2-aminothiazoles.

Keywords: Copper(II) salts; Carbene insertion reactions; 2-Aminothiazoles; Diazoketones

The 2-aminothiazole ring system is frequently found in drug molecules which are used for the treatment of allergies, hypertension, inflammation, schizophrenia and bacterial and HIV infections.[1–7] The Hantzsch synthesis is the most commonly used classical method for the synthesis of 2-aminothiazoles.[8–12] Due to their broad utility in the pharmaceutical industry, the development of novel methods for the synthesis of 2-aminothiazoles would provide additional lead molecules for drug discovery. Drug formulations containing 2-aminothiazoles are currently available for the treatment of inflammation, breast cancer, HIV-1 and rheumatoid arthritis (Fig. 1).[13–16]

The ready availability, relative stability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base and transition metal catalysis conditions make them useful intermediates in organic

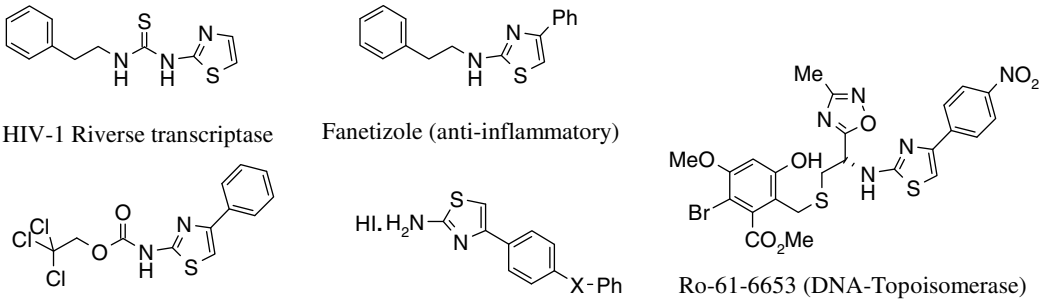


Fig. 1. Biologically active 2-aminothiazoles.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J. S. Yadav).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.068

synthesis.[17] Interestingly, α-diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H, X–H insertion reactions and cyclization reactions.[18–20] These reactions are chemoselective, which allow new carbon–carbon and carbon–heteroatom bond formation under mild conditions.[21,22] However, there have been no reports on the coupling of α-diazoketones with thiourea to generate biologically potent 2-aminothiazoles.

In this Letter, we report an efficient strategy for the synthesis of 2-aminothiazoles by means of $Cu(OTf)_2$-catalyzed coupling of α-diazoketones with thiourea under mild conditions. Initially, we attempted the coupling of diazoacetophenone (**1**) with thiourea (**2**) in the presence of 10 mol % $Cu(OTf)_2$ in dichloroethane. The reaction was complete within 2 h at 80 °C and the product, 2-amino-4-phenylthiazole **3a**, was isolated in 95% yield (Table 1, entry a, Scheme 1).

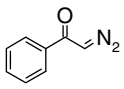
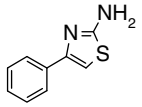
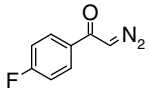
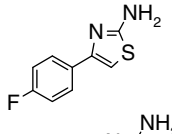
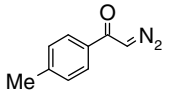
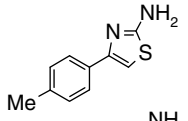
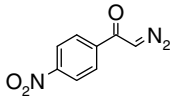
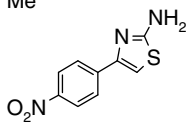
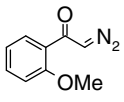
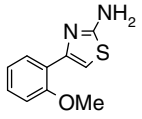
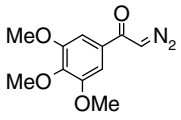
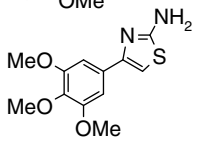
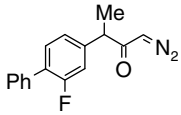
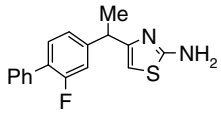
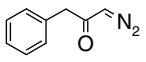
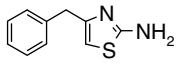
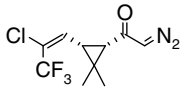
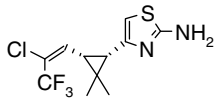
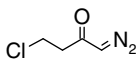
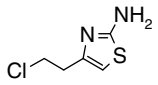
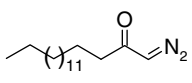
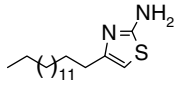
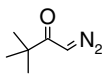
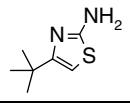
The remarkable catalytic activity of copper(II) triflate provided the incentive for further study with other α-diazocarbonyl compounds. Interestingly, various α-diazoketones reacted readily with thiourea to give the corresponding 2-amino-4-aryl- and 4-alkylthiazole derivatives as the products of sulfur insertion (Table 1). Both aromatic and aliphatic diazoketones participated well in this reaction (Table 1). The *cis*-cyhalothric acid-derived diazoketone also gave the sulfur insertion product **3i** in 90% yield (Table 1, entry i, Scheme 2).

Both electron-rich and electron-deficient aryl diazoketones participated in this reaction (Table 1, entries b–f). It is noteworthy to highlight that halo-substituted diazoketones were also selectively converted into their corresponding 2-aminothiazoles without affecting the halide functionality (Table 1, entries b, g, i and j). In all cases, the reactions proceeded smoothly in the presence of 10 mol % $Cu(OTf)_2$ at 80 °C in dichloroethane, and the products were obtained in high yields and with high selectivity.[23] No side products arising from Wolff rearrangement were observed under these reaction conditions. Other possible side products such as α-keto-*O*-triflates (the products of OTf insertion) arising from $Cu(OTf)_2$ were not identified under these conditions. The activity of various copper(II) salts such as $Cu(OAc)_2$, $Cu(BF_4)_2$ and $Cu(acac)_2$ was examined. Of these catalysts, $Cu(OTf)_2$ was found to be the most effective catalyst in terms of conversion and cleanliness. Other metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Bi(OTf)_3$ and $In(OTf)_3$ gave low yields of products (20–30%). However, solid acids such as Montmorillonite K10 and heteropoly acids, in particular, phosphomolybdic acid, failed to give the desired product. As solvent, dichloroethane gave the best results.

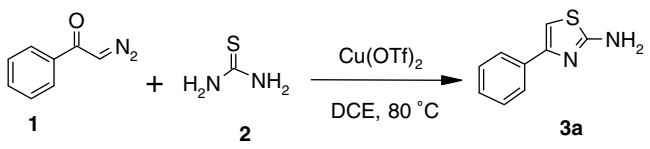
The reaction may proceed via initial formation of an imine followed by sulfur insertion resulting in the formation of 2-aminothiazole (Scheme 3).

In summary, we have described a novel synthesis of 4-aryl- and 4-alkylthiazoles via the coupling of α-diazoketones with thiourea using a catalytic amount of $Cu(OTf)_2$.

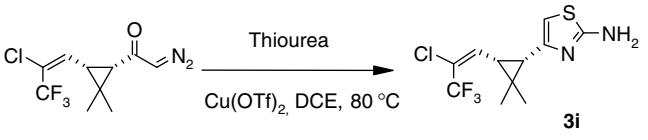
Table 1
$Cu(OTf)_2$-catalyzed synthesis of 2-aminothiazoles

Entry	α-Diazoketone	Product[a]	Time (h)	Yield[b] (%)
a			2.0	95
b			2.5	92
c			2.0	96
d			3.0	85
e			2.5	95
f			2.0	97
g			2.0	92
h			3.0	94
i			2.5	90
j			2.5	89
k			3.0	91
l			3.0	90

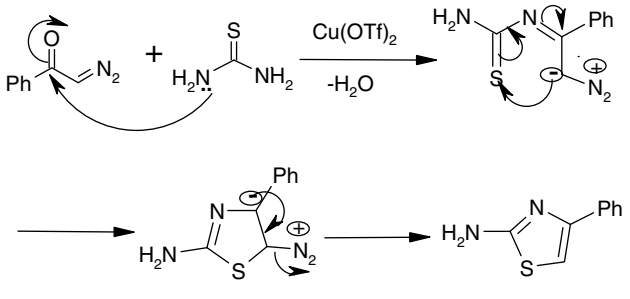
[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 1. Synthesis of 2-amino-4-phenylthiazole **3a**.



Scheme 2. Synthesis of 2-aminothiazole **3i**.



Scheme 3. A plausible reaction mechanism.

This method provides direct access to a wide range of 2-aminothiazoles from readily available diazoketones and thiourea. The present method offers significant advantages including mild reaction conditions, high conversions, short reaction times, cleaner reaction profiles and high selectivity making it a useful and attractive strategy for the preparation of biologically relevant 2-aminothiazole derivatives in a single step operation.

Acknowledgement

Y.G.R. thanks CSIR, New Delhi, for the award of fellowship.

References and notes

1. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
2. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562.
3. Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719.
4. Clemence, F.; Martret, O. L.; Delevallee, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453.
5. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 1453.
6. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.
7. Bell, F. W.; Cantrell, A. S.; Höberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noren, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.
8. Hantzsch, A. R.; Weber, J. H. *Ber* **1887**, *20*, 3118.
9. Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. *Tetrahedron* **2007**, *63*, 11066.
10. George, W. K.; Arjun, R. M. *Tetrahedron Lett.* **2006**, *47*, 5171.
11. Siddiqui, H. L.; Iqbal, A.; Ahmed, S.; Weaver, G. *Molecules* **2006**, *11*, 206;.
12. Karade, H.; Sathe, M.; Kaushik, M. P. *Catal. Commun.* **2007**, *8*, 741.
13. Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409.
14. Gorczynski, M. J.; Leal, R.; Mooberry, S. L.; Bushweller, J. H.; Brown, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 1029.
15. Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U. *J. Med. Chem.* **2001**, *44*, 619.
16. Smith, C. W.; Chakrabarti, J. K.; Williamson, W. R. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1673.
17. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds from Cyclopropanes to Ylides*; Wiley Inter-Science: New York, 1998.
18. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
19. Padwa, A.; Hornbuckle, S. A. *Chem. Rev.* **1991**, *91*, 263.
20. Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.
21. Regitz, M.; Mass, G. In *Diazo Compounds—Properties and Synthesis*; Academic Press: New York, 1986; p 90.
22. Jones, K.; Toutounji, T. *Tetrahedron* **2001**, *57*, 2427.
23. *General procedure*: (i) *Preparation of* α*-diazoketones*: The starting α-diazoketones were prepared by the condensation of the respective acid chlorides (1 eq) with diazomethane (4 eq) at 0 °C in diethyl ether. (ii) *Synthesis of thiazoles*: A mixture of α-diazoketone (1 mmol), thiourea (1 mmol) and $Cu(OTf)_2$ (0.1 mmol) in dichloroethane (10 mL) was stirred at 80 °C for the appropriate time (Table 1). After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude residue was purified on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford the pure 2-aminothiazole. Spectral data for selected products: *4-Phenylthiazol-2-amine (entry a)*: Pink coloured solid. Mp 149–150 °C. IR (KBr): *v* 3434, 3254, 3154, 3113, 2924, 2368, 1598, 1517, 1480, 1439, 1332, 1196, 1070, 1023, 909, 843, 770, 713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ 7.73 (d, 2H, $J = 7.8$ Hz), 7.36–7.17 (m, 3H), 6.63 (s, 1H) 6.21 (br s, 2H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$ + DMSO): δ 167.3, 149.1, 133.7, 127.2, 126.0, 124.5, 100.1. ESIMS: *m*/*z*: (M^++H): 177. HRMS calcd for $C_9H_8N_2S$: 177.0486. Found: 177.0488. *4-[3-(Z-2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropyl]thiazol-2- amine (entry i)*: Brown coloured solid. Mp 76–77 °C, IR (KBr): *v* 3285, 3125, 2957, 1615, 1523, 1458, 1295, 1186, 1141, 1048, 955, 893, 846, 817, 761, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.32 (s, 3H), 2.00 (t, 1H, $J = 9.0$ Hz), 2.19 (d, 1H, $J = 8.7$ Hz), 5.35 (br s, 2H), 6.09 (s, 1H), 6.55 (d, 1H, $J = 9.8$ Hz). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 166.9, 147.7, 133.1, 122.4, 118.8, 119.6, 105.3, 33.1, 29.6, 26.2, 28.7, 16.9. ESIMS: *m*/*z*: (M^++H): 297. HRMS calcd for $C_{11}H_{13}ClF_3N_2S$: 297.0440. Found: 297.0452. *4-Pentadecylthiazol-2-amine (entry k)*: Colourless solid. Mp 65–66 °C. IR (KBr): *v* 3430, 3233, 3065, 2920, 2850, 1607, 1541, 1511, 1467, 1377, 1317, 1112, 1021, 967, 847, 720, 698, 632 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 0.91 (t, 3H, $J = 7.0$ Hz), 1.29 (br s, 24H), 1.55–1.65 (m, 2H), 2.43 (t, 2H, $J = 7.0$ Hz), 5.90 (s, 1H), 6.31 (br s, 2H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$ + DMSO): δ 167.1, 151.5, 99.0, 33.2, 30.5, 30.3, 28.3, 27.4, 23.7, 21.3, 12.9. EIMS *m*/*z*: (M^++H): 311.40. HRMS calcd for $C_{18}H_{35}N_2S$: 311.2520. Found. 311.2536.