Tetrahedron Letters 53 (2012) 2518–2521

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2-N-substituted benzothiazoles via domino condensation-hetero cyclization process, mediated by copper oxide nanoparticles under ligand-free conditions

G. Satish, K. Harsha Vardhan Reddy, K. Ramesh, K. Karnakar, Y.V.D. Nageswar *

Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 9 January 2012
Revised 1 March 2012
Accepted 4 March 2012
Available online 16 March 2012

Keywords:
2-N-substituted benzothiazole
Carbon disulfide
Piperidine
CuO nanoparticles
Recyclability

ABSTRACT

A simple and highly practical method for the synthesis of 2-N-substituted benzothiazoles has been developed by using nanocopper oxide as a recyclable catalyst. The present tandem process allows to get access to a wide range of 2-N-substituted benzothiazoles in good to excellent yields by the reaction of 2-iodo aniline with carbon disulfide and piperidine in presence of KOH as a base and DMSO as a solvent under ligand-free conditions.

In the arena of heterocyclic chemistry, five-membered fused heterocycles with amine substituents are important structural scaffolds being widely employed in the context of medicinal chemistry and are applicable in the construction of synthetic reactive intermediates; for example, third generation antibiotics (cefdinir), and anti-inflammatory agent (meloxicam). 2-Aminothiazole derivatives are currently used as dopamine antagonists for Parkinson's disease (pramipexole).[1] These are also useful as pharmaceutically important molecular entities and are widely used as anti-HIV agents,[2] the PPAR agonists,[3] the H3-receptor ligands,[4] the nicotinic-acetylcholine-receptor ligands,[5] anti-bacterial compounds[6] (Fig. 1). Due to numerous applications associated with this heterocyclic core unit in diverse fields of therapeutic area, synthesis of N-substituted benzothiazoles attracted attention of research chemists. Generally the synthesis of 2-N-substituted benzothiazoles involves the substitution reaction between 2-halobenzothiazoles and corresponding nitrogen nucleophiles.[7]

However, the aforementioned method utilizes multi-step reaction sequence and harsh reaction conditions for getting desired products from the commercially available anilines. During the past decade metal catalyzed cross-coupling reactions have gained more significance in the synthesis of biologically active building blocks. This fascinating area of cross-coupling chemistry led many research groups to develop new catalytic systems to obtain libraries of new molecules. In this context, Punniyamurthy and co-workers described the synthesis of 2-aminobenzothiazoles by copper catalyzed intermolecular C–S bond formation from 2-aminobenzothioureas which were obtained from corresponding isothiocyanates and amine derivatives.[8] Other catalytic systems such as copper,[9] silver[10], and palladium[11] have also been developed to generate 2-aminobenzothiazoles. Very recently Ma et al. described an elegant protocol employing $CuCl_2{\cdot}2H_2O$ as a catalyst for the synthesis of 2-N-substituted benzothiazoles via domino intermolecular condensation reaction of dithiocarbamate salt with 2-iodoanilines.[12] Even though, the reported methods serve the purpose of obtaining 2-N-substituted benzothiazoles, these reported catalytic systems are not recyclable. In continuation of our work in the field of cross-coupling reactions,[13] herein we describe an inexpensive, air-stable, and recyclable nanocopper oxide as a catalyst for the

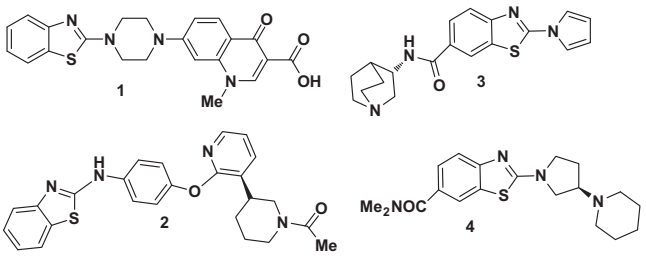
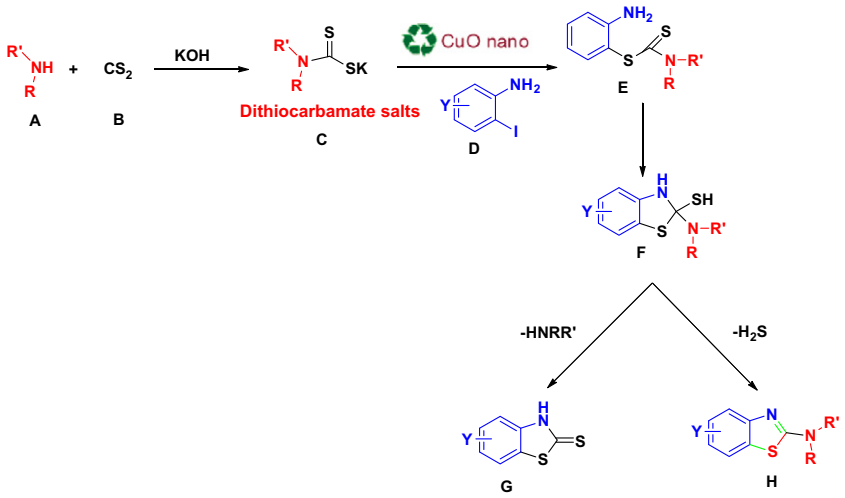


Figure 1. Structures of bioactive 2-N-substituted benzothiazoles.

* Corresponding author. Tel.: +91 40 27191654; fax: +91 40 27160512.
E-mail address: dryvdnageswar@gmail.com (Y.V.D. Nageswar).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.012



Scheme 1. Possible reaction course for the formation of 2-N-substituted benzothiazoles from N-nucleophiles, CS_2, and 2-haloanilines.

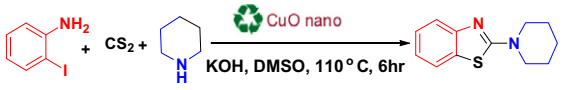
synthesis of 2-N-substituted benzothiazoles under ligand-free conditions.

In general, dithiocarbamate salts [C] are prepared by reacting amine with carbon disulfide in the presence of base (Scheme 1). These salts are tried as novel coupling partners to provide dithiocarbamates [E] on cyclization reaction with 2-haloanilines [D]. The amine group of [E] in turn on cyclization with the C–S group provide expected products [F] which yield cyclic dithiocarbamates [G] or 2-N-substituted benzothiazoles [H] upon elimination of an amine HNRR′or hydrogen sulfide, respectively.

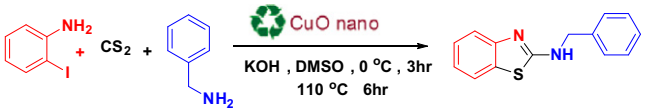
Recently heterogeneous catalysts have become attractive both from economic and industrial points of view when compared to homogeneous catalysts. The high surface area and reactive morphologies of nanomaterials allow them to be effective catalysts for organic synthesis. Copper oxide nanoparticles (CuOnps) have the advantages of recyclability, easy work-up, and cleaner reaction profiles apart from lack of necessity of external ligands which minimize the organic waste generation as compared to the conventional catalytic systems.

Initially, a model reaction was attempted with monosubstituted 2-iodoaniline with piperidine as a coupling partner. In general, the reaction proceeded well with these substrates to deliver the 2-substituted benzothiazole in good to excellent yields.[14] The result demonstrated that both the electronic features and the orientation of the additional substituent on the 2-haloaniline have limited influence on this cascade reaction. 2-Bromoanilines also underwent this transformation, although they required higher reaction temperatures than the corresponding iodides, and the products were formed in slightly lower yields. The synthesis of trisubstituted and disubstituted benzothiazoles indicate that this method enables the introduction of functional groups at 4-, 5- and 6-positions of benzothiazoles. We further explored the generality of the present method by varying the secondary amine and found that thiomorpholine, Boc-protected piperazine were also compatible with this process. Thus, benzothiazoles were formed in 61–80% yield in this process.

Another notable characteristic of this reaction is that, functional groups, such as chloro, fluoro, and trifluoromethyl substituent's also remain intact under the reaction conditions. This advantage makes our method a very useful tool for the assembly of bioactive benzothiazoles. Indeed, the product *tert*-butyl 4-(benzo[*d*]thiazol-2-yl)piperazine-1-carboxylate could be used for the synthesis of serotonin-receptor modulators, PDE4 inhibitors, modulators of metabotropic glutamate receptor 5 (mGluR5), and the anti-HIV agent compound.



Scheme 2. Screening of reaction conditions for the reaction of 2-iodoaniline, carbon disulfide, and piperidine.



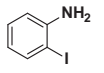
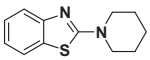
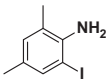
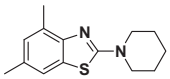
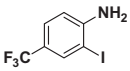
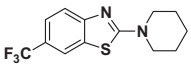
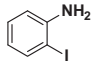
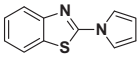
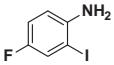
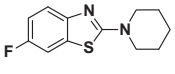
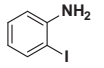
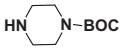
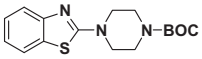
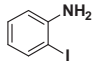
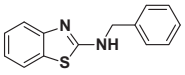
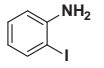
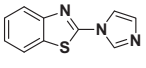
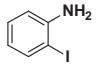
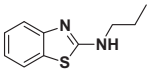
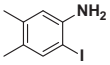
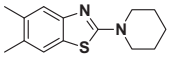
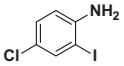
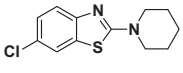
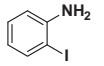
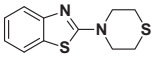
Scheme 3. Screening of reaction conditions for the reaction of 2-iodoaniline, carbon disulfide, and benzyl amine.

Various other N-nucleophiles were also examined for this protocol. When benzylamine was treated with 2-iodoaniline under the described reaction conditions, the desired product *N*-benzylbenzo[*d*]thiazol-2-amine was obtained in only 10% yield (Schemes 2 and 3) (Table 1).

It was observed that the yield could be improved to 80% if benzylamine was first treated with carbon disulfide at 0 °C, and the reaction mixture was heated after the addition of 2-iodoaniline. These modified conditions were found to be suitable for primary amines. Further investigations revealed that 2-(1*H*-pyrrol-1-yl)benzo[*d*]thiazole could be constructed from the corresponding pyrrole as a nucleophilic coupling partner. This method enables the formation of 2-N-substituted benzothiazoles with variable substituents and may find broad application in organic synthesis. All the products were confirmed by ^{1}H, ^{13}C NMR spectroscopy[12] and compared with authentic samples reported in the literature.[15]

The recyclability of nanocopper oxide was examined and the results are summarized in Table 2. To check the recyclability the catalyst, it was centrifuged from the reaction mixture and dried in vacuo and was reused for further catalytic reactions. The yields of 2-N-substituted benzothiazoles after two to three recycles were almost same without loss of catalytic activity. The native and used

Table 1
Formation of 2-N-substituted benzothiazoles by reacting with 2-iodobenzamine with carbon disulfide and N-nucleophiles

Entry	Reactant = I	Reactant = II	Product	Yield[c] (%)
1				70[a]
2				79[a]
3				69[a]
4				45[a]
5				75[a]
6				79[a]
7				80[b]
8				55[a]
9				75[b]
10				70[a]
11				70[a]
12				70[a]

[a] Reaction conditions: A mixture of 2-iodoaniline (0.5 mmol), CS_2 (0.6 mmol), an N-nucleophile (0.6 mmol), CuO nanoparticles (0.5 mmol), and KOH (1.5–2 mmol) in DMSO (3 mL) was stirred at 110 °C for 6 h.
[b] Reaction conditions: A mixture of an N-nucleophile (0.6 mmol), CS_2 (0.6 mmol), KOH (1.5–2 mmol) at 0 °C at 3 h after that 2-iodoaniline (0.5 mmol), CuO nanoparticles (0.5 mmol), in DMSO (3 mL) was stirred at 110 °C for 6 h.
[c] Isolated yields.

Table 2
Recyclability of CuO nanoparticles[a]

Recycles	Yield[b] (%)	Catalyst recovery (%)
Native	80	97
2	77	95
3	75	92

[a] Reaction conditions: A mixture of an N-nucleophile (0.6 mmol), CS_2 (0.6 mmol), KOH (1.5–2 mmol) at 0 °C for 3 h after that 2-iodoaniline (0.5 mmol), CuO nanoparticles (0.5 mmol), in DMSO (3 mL) was stirred at 110 °C for 6 h.
[b] Isolated yield.

CuO nanoparticles were analyzed by TEM analysis. It was observed from the TEM studies that the used CuO nanoparticles were intact in size and shape even after three cycles as compared to the native catalyst (Fig. 2).

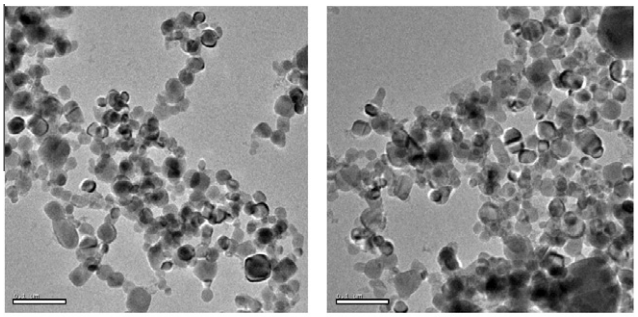


Figure 2. TEM images of (a) native CuO nanoparticles, (b) CuO nanoparticles after three cycles.

Conclusion

In conclusion, we have developed a nanocrystalline CuO catalyzed coupling of 2-iodoaniline, carbon disulfide, and nitrogen nucleophile under ligand-free conditions in good yields. This new coupling reaction underlines the potential of using nanocrystalline CuO as userfriendly, inexpensive, and efficient catalyst for the coupling of C–S. The catalyst can be easily recovered and reused.

Acknowledgments

We are grateful to CSIR, New Delhi, for research fellowships to G.S., K.H.V.R., K.K. and to the UGC, New Delhi, for fellowship to K.R.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.012.

References and notes

1. For a brief review, see: (a) Armstrong, A.; Collins, J. C. *Angew. Chem.* **2010**, *122*, 2332; (b) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282.
2. HIV = human immunodeficiency virus: Massari, S.; Daelemans, D.; Barreca, M. L.; Knezevich, A.; Sabatini, S.; Cecchetti, V.; Marcello, A.; Pannecouque, C.; Tabarrini, O. *J. Med. Chem.* **2010**, *53*, 641.
3. PPAR = peroxisome proliferator-activated receptor: Itai, A.; Muto, S.; Tokuyama, R.; Fukazawa, H.; Ohara, T.; Kato, T. WO 2007023882, 2007.
4. Black, L. A.; Cowart, M. D.; Gfesser, G. A.; Wakefield, B. D.; Altenbach, R. J.; Liu, H.; Zhao, C.; Hsieh, G. C. WO 2009085945, 2009.
5. Tehim, A.; Herbert, B.; Nguyen, T. M.; Xie, W.; Gauss, C. M. WO 2004029050, 2004.
6. Soneda, T.; Takeshita, H.; Kagoshima, Y.; Yamamoto, Y.; Hosokawa, T.; Konosu, T.; Masuda, N.; Uchida, T.; Achiwa, I.; Kuroyanagi, J.; Fujisawa, T.; Yokomizo, A.; Noguchi, T. WO 2009084614, 2009.
7. (a) Stewart, G. W.; Baxter, C. A.; Cleator, E.; Sheen, F. J. *J. Org. Chem.* **2009**, *74*, 3229; (b) Caleta, I.; Kralj, M.; Marjanovic, M.; Bertosa, B.; Tomic, S.; Pavlovic, G.; Karminski Zamola, G. *J. Med. Chem.* **2009**, *52*, 1744. and references therein.
8. Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719.
9. (a) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem.* **2009**, *121*, 9291; (b) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127; (c) Monguchi, D.; Fujiwara, T.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.
10. For a brief review, see: Armstrong, A.; Collins, J. C. *Angew. Chem.* **2010**, *122*, 2332.
11. (a) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792; (b) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147.
12. Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 1118–1121.
13. (a) Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *Eur. J. Org. Chem.* **2010**, *6*, 678; (b) Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *Eur. J. Org. Chem.* **2011**, *10*, 1940; (c) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Eur. J. Org. Chem.* **2009**, *34*, 5902; (d) Reddy, K. H. V.; Reddy, V. P.; Shankar, J.; Madhav, B.; Kumar, B. S. P. A.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2679; (e) Reddy, K. H. V.; Reddy, V. P.; Madhav, B.; Shankar, J.; Nageswar, Y. V. D. *Synlett* **2011**, 1268; (f) Reddy, K. H. V.; Reddy, V. P.; Kumar, A. A.; Kranthi, G.; Nageswar, Y. V.

D. *Beilstein J. Org. Chem.* **2011**, *7*, 886; (g) Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *Org. Biomol. Chem.* **2011**, *9*, 5978; (h) Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *Org. Biomol. Chem.* **2011**, *9*, 5989.

14. Typical procedure for the synthesis of 2-N-substituted benzothiazoles: A mixture of 2-iodoaniline (0.5 mmol), CS2 (0.6 mmol), an amine (0.6 mmol), CuO nanoparticles (0.5 mmol), and KOH (1.5–2 mmol) in DMSO (3 mL) was stirred at 110 °C for 6 h. The cooled solution was partitioned between ethyl acetate and water, and the organic layer was washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by silica-gel chromatography to give the desired benzothiazole.
Experimental procedure for recovering of CuO nanoparticles:
After work-up, the aqueous layer containing CuO nanoparticles was carefully centrifuged at 8000 rpm for 60 min and washed several times with water and acetone. The retrieved particles were oven dried at 80 °C and used for the next cycle. Likewise, the recovered CuO nanoparticles were recyclable up to three cycles. The native and used CuO nanoparticles were analyzed by powder XRD and TEM analysis. As observed from the powder XRD and TEM studies the used CuO nanoparticles are intact in size and shape even after three cycles, as compared to the native ones. The powder XRD spectra of both used and native are comparable, thus confirming the intactness of the particles even after three cycles.
15. Data for representative examples: 2-(1*H*-Pyrrol-1-yl)benzo[*d*]thiazole (Table 1, entry 3) ^{1}H NMR (300 MHz, $CDCl_3$) δ:7.84 (s, 1H), 7.58–7.48 (m, 2H), 3.72–3.60 (brs, 4H), 1.74 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 170.6, 155.4, 135.9, 130.5, 122.9, 118.1, 113.3, 52.9, 49.5, 25.8, 25.1, 24.4, 23.9; ESI-MS *m*/*z* 287 $(M+H)^+$.
6-Fluoro-2-(piperidin-1-yl)benzo[d]thiazole (Table 1, entry 5) ^{1}H NMR (300 MHz, $CDCl_3$) δ:7.48–7.41 (m, 1H), 7.31–7.25 (m, 1H), 7.04–6.98 (m, 1H), 3.58 (br s, 4H), 1.70 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 168159.4, 149.3, 119.1, 113.5, 113.2, 107.4, 107.1, 49.5, 30.8,29.6, 25.2; ESI-MS *m*/*z* 237 $(M+H)^+$.