Tetrahedron Letters 50 (2009) 4467–4469

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Nanocrystalline copper(II) oxide catalyzed aza-Michael reaction and insertion of α-diazo compounds into N–H bonds of amines

M. Lakshmi Kantam[a,*], Soumi Laha[a], Jagjit Yadav[a], Shailendra Jha[b]

[a] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India
[b] Department of Chemistry, Jadavpur University, Kolkata, India

ARTICLE INFO

Article history:
Received 24 April 2009
Revised 14 May 2009
Accepted 16 May 2009
Available online 23 May 2009

Keywords:
Nanocrystalline copper(II) oxide
Heterogeneous catalyst
Aza-Michael addition
α,β-Unsaturated compounds
Insertion
Diazoacetate

ABSTRACT

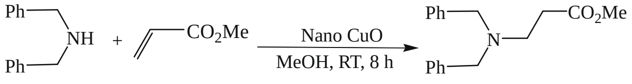
Nanocrystalline copper(II) oxide efficiently catalyzed the conjugate addition of aliphatic amines to α,β-unsaturated compounds to produce β-amino compounds with excellent yields under mild reaction conditions. Similarly, Glycine esters are obtained in good yields by the insertion of α-diazoacetate into N–H bonds of amines. The catalyst is used for three cycles with minimal loss of activity.

β-Amino carbonyl compounds are important intermediates in the synthesis of various complex natural products, antibiotics, β-amino alcohols, and chiral auxillaries[1,2,14] and can be prepared by conjugate addition of amines to α,β-unsaturated compounds. A number of methods have been reported for the 1,4-addition of amines to electron-deficient olefins through the activation of amines by stoichiometric or catalytic Lewis acids such as $Bi(NO)_3$,[3] $Bi(OTf)_3$,[4] $Yb(OTf)_3$,[5] $La(OTf)_3$,[6] $InCl_3$,[7] $FeCl_3{\cdot}6H_2O$, $Co(OAc)_2$,[8] $Ni(ClO_4)_2{\cdot}6H_2O$,[9] $LiClO_4$,[10] and copper salts.[11] Different heterogeneous catalysts such as transition-metal doped montmorillonite and kaolinite clays,[12] silica gel[13] and alumina-supported $CeCl_3{\cdot}7H_2O$–NaI[14] have been used for aza-Michael reactions. More recently, a green approach in ionic liquids has been employed for the conjugate addition of amines to α,β-unsaturated compounds.[15] On the other hand, insertion of α-diazo compounds into X–H (X = C, N, S) bonds is a reaction of considerable importance for the synthesis of α-amino acids, peptides, and β-lactam antibiotics.[16,17] The N–H insertion reaction is reported with catalysts such as copper bronze,[18] CuCN,[19] $Rh(OAc)_2$ and its derivatives,[20] ruthenium complexes,[21] and Cu(I) homoscorpionate complexes.[22] Using Cu(I) and Ag(I) carbenoids, asymmetric version of this reaction has also been developed.[23]

Industry favors catalytic processes induced by heterogeneous catalysts over homogeneous processes in view of the ease of handling, simple work-up, and regenerability. Nanocrystalline metal oxides have attracted attention due to their unusual magnetic, physical, and surface chemical and catalytic properties.[24] These high reactivities are due to high surface areas combined with unusually reactive morphologies. Copper oxide nanoparticles have been of considerable interest due to the role of CuO in catalysis, in metallurgy, and in high-temperature superconductors.[25]

As part of our ongoing research on nanocrystalline metal oxide-catalyzed organic transformations,[26] we herein report our results on the use of recoverable nanocrystalline CuO (nano CuO) catalyst for the aza-Michael addition of dibenzylamine with methyl acrylate to produce methyl-3-(dibenzylamino) propionate in good yields at room temperature (Scheme 1) and the reaction of piperidine with ethyl diazoacetate (EDA) at room temperature resulted in the formation of ethyl-4-piperidinylacetate with moderate yields (Scheme 2).

Initially, nano CuO as well as commercially available bulk CuO and Cu_2O was evaluated for the aza-Michael reaction of dibenzylamine and methyl acrylate and the results are summarized in Table 1. The nano CuO was found to be a more active catalyst than

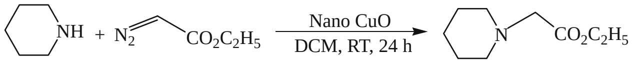


Scheme 1.

---

* Corresponding author. Tel./fax: +91 40 27160921.
E-mail address: mlakshmi@iict.res.in (M.L. Kantam).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.059



Scheme 2.

Table 1
Screening of reaction parameters for aza-Michael reaction[a]

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Nano CuO	Toluene	12	Trace
2	Nano CuO	MeCN	12	5
3	Nano CuO	DCM	12	Trace
4	Nano CuO	THF	12	10
5	Nano CuO	MeOH	8	74, 70[c]
6	Bulk CuO	MeOH	8	38
7	Bulk Cu_2O	MeOH	8	42
8	None	MeOH	8	25

[a] Reaction conditions: dibenzylamine(1 mmol), methyl acrylate (1.2 mmol), catalyst (10 mol %), solvent (4 mL), room temperature.

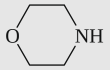
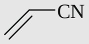
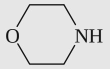
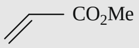
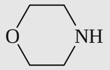
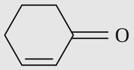
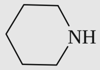
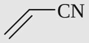
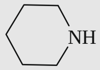
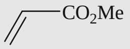
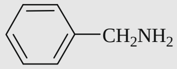
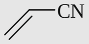
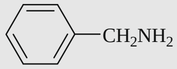
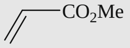
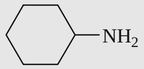
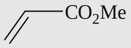
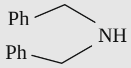
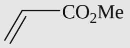
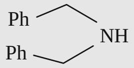
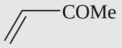
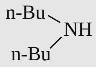
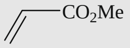
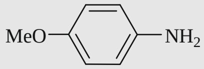
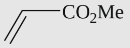
[b] Isolated yields.

[c] Yield after third cycle.

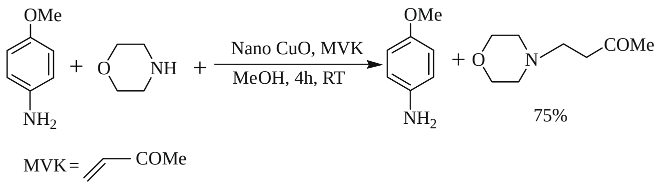
the commercial CuO and Cu_2O. The use of solvents such as toluene, acetonitrile, dichloromethane, and THF was less effective in place of methanol. Catalyst-recycling experiments were also carried out, using dibenzylamine and methyl acrylate as Michael acceptor. As can be seen in (Table 1, entry 5), nano CuO can be used for three cycles with minimal loss of activity.

A variety of α,β-unsaturated compounds such as methyl acrylate (MA), acrylonitrile (AN), methyl vinyl ketone (MVK), and cyclohexenone underwent 1,4-addition with a wide range of cyclic and acyclic aliphatic amines in the presence of nano CuO at room temperature to give the corresponding β-amino compounds or nitriles in high yields (Table 2). Cyclic α,β-unsaturated ketone such as cyclohexenone reacted with morpholine to give the corresponding 1,4-adduct in good yield (Table 2, entry 3). Other amines such as piperidine (Table 2, entries 4 and 5), benzylamine (Table 2, entries 6 and 7), cyclohexylamine (Table 2, entry 8), and dibutylamine (Table 2, entry 11) were reacted in equal ease with MA and AN and gave 77–85% yields in 3–8 h. In case of primary amines, 8–12% of the bis adduct was also formed (Table 2, entries 6, 7, and 8). Sterically hindered amine, for example, dibenzylamine (Table 2, entries 9 and 10) with MA and MVK offered 1,4-addition products in 70–74% yields in 8 h. Though it can be seen from Table 2 that the reaction proceeds well within 3–8 h for all substrates while aromatic amine such as *p*-methoxy aniline (Table 2, entry 12) when treated with MA furnishes trace amount of product. The inertness of aromatic amine is further exemplified by taking MVK and an equimolecular mixture of *p*-methoxy aniline and morpholine under a similar condition. As expected, aliphatic amine gave addition product in good yields (Scheme 3). This clearly shows that nano CuO catalyst fails in the case of aromatic amines for aza-Michael addition reaction.

Table 2
The aza-Michael reaction of amines with alkenes in the presence of nano CuO[a]

Entry	Amine	Olefin	Time (h)	Isolated yield (%)
1			4	81
2			4	79
3			6	78
4			3	85
5			4	82
6			6	77
7			7	78
8			8	80
9			8	74
10			8	70
11			6	82
12			10	Trace

[a] Reaction conditions: amines (1 mmol), α,β-unsaturated compounds (1.2 mmol), nano CuO (10 mol %), MeOH (4 mL), room temperature.

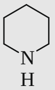
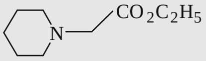
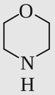
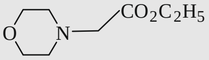
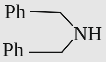
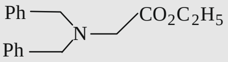
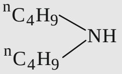
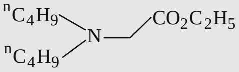
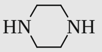
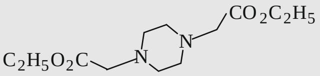
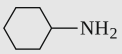
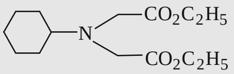
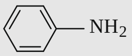
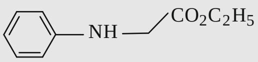
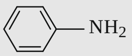
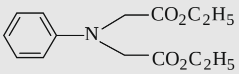
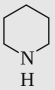
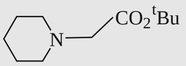


Scheme 3.

Encouraged by the high catalytic activity of nano CuO in the aza-Michael reaction, we tried the catalytic insertion of α-diazo compounds into N–H bonds of amines using nano CuO and ethyl diazoacetate (EDA). As illustrated in Table 3, the catalytic system (10 mol % of nano CuO and DCM as solvent at room temperature) proved to be efficient with a variety of amines including primary, secondary, aliphatic, aromatic, acyclic, and cyclic amines underwent reaction with EDA. Interestingly, cyclic amines such as morpholine and piperidine (Table 3, entries 1 and 2) were found to be more active and gave the corresponding products in moderate yields. Bulky amines, such as dibutyl and dibenzyl amine also afforded the products in moderate yields (Table 3, entries 3 and 4). In case of primary amines and piperazine, bis-insertion products were obtained in the presence of two equivalent of EDA (Table 3, entries 5, 6, and 8). Interestingly, bulky glycine ester can also be synthesized in moderated yields (Table 3, entry 9).

In conclusion, we have developed nano CuO catalyzed aza-Michael reaction of aliphatic amines with α,β-unsaturated compounds and synthesis of glycine esters via N–H insertion of diazoacetate. The high catalytic activity of nano CuO may be attributed to the higher surface area (S.A: 136 m^2/g) and a higher porosity compared to that of commercial CuO (S.A: 1.952 m^2/g) as well

Table 3
Insertion of diazoacetate into N–H bonds of amines using nano CuO[a]

Entry	Amine	Product	Time (h)	Yield[b] (%)
1			24	62, 58[c]
2			24	66
3			36	54
4			36	56
5			36	52[d]
6			36	52[d]
7			36	60
8			36	55[d]
9			24	51[e]

[a] Reaction conditions: amine (1 mmol), EDA (1 mmol), nano CuO (10 mol %), DCM (4 mL), room temperature.
[b] Isolated yields.
[c] Yield after third cycle.
[d] 2 mmol of EDA is used.
[e] 1 mmol *tert*-butyldiazoacetate is used as carbine source.

as the higher surface concentration of reactive sites. The catalyst is used for three cycles with minimal loss of activity.

General experimental procedure for aza-Michael addition reaction: In an oven dried 10 mL Schlenk flask, a mixture of dibenzylamine (1 mmol), methyl acrylate (1.2 mmol), and nano CuO (10 mol %) in methanol (4 mL) was maintained at room temperature under vigorous stirring for appropriate time. After the completion of the reaction, monitored by TLC, the reaction mixture was centrifuged and washed with ethyl acetate to recover the catalyst for reuse. The combined ethyl acetate extracts were concentrated in vacuo, and the resulting product was directly charged on silica gel column to obtain the product. Isolated yield of methyl-3-(dibenzylamino) propionate was 74%.

H^1 NMR: 2.48–2.58 (t, 2H), 2.80–2.92 (t, 2H), 3.62 (s, 3H), 3.73 (s, 4H), 7.20–7.44 (m, 10H).

General experimental for insertion of diazo compounds into amines: Nano CuO (10 mol %) in DCM (4 mL) was placed in an oven dried 10 mL Schlenk flask, at room temperature under N_2 atmosphere. Piperidine (1 mmol) was added. To the reaction mixture ethyl diazoacetate (1 mmol) was added dropwise for 10 min and stirring was continued. After the completion of the reaction, as monitored by TLC, the reaction mixture was centrifuged to separate the catalyst. The catalyst was washed with diethyl ether and reused for another cycle after vacuum drying. The centrifugate was diluted with diethyl ether and the solvent was removed under reduced pressure. Then it was subjected to column chromatography to get the pure product. Isolated yield of ethyl-4-piperidinylacetate was 62%.

H^1 NMR: 1.24–1.31 (t, 3H), 1.38–1.48 (m, 2H), 1.57–1.65 (m, 4H), 2.51 (t, 4H), 3.12 (d, 2H), 4.19 (q, 2H).

Acknowledgments

S.L. and J.Y. thank CSIR, New Delhi for the award of research fellowships. Nanocrystalline metal oxide samples were obtained from Nanoscale Materials Inc., Manhattan, KS 66502, USA.

References and notes

1. (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328; (b) Wang, Y. F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465; (c) Wabnitz, T. C.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484; (d) Liu, M.; Sibi, M. P. *Tetrahetron* **2002**, *58*, 7991.
2. (a) Hayashi, Y.; Rode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502; (b) Eliel, E. L.; He, X. *J. Org. Chem.* **1990**, *55*, 2114.
3. Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109.
4. Vala, R.; Alam, M. M.; Adapa, S. R. *Synlet* **2003**, 720.
5. Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233.
6. Matsubara, M.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827.
7. Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975.
8. Xu, L. W.; Li, L.; Xia, C. G. *Helve. Chim. Acta* **2004**, *87*, 1522.
9. Fadini, L.; Tongi, A. *Chem Commun.* **2003**, 30.
10. Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383.
11. Xu, L. W.; Li, J. W.; Xia, C. G.; Zhou, S. L.; Hu, X. X. *Synlett* **2003**, 2425.
12. (a) Cabral, J.; Laszlo, P.; Mahe, L.; Montaufier, M. T.; Randriamahefa, S. L. *Tetrahedron Lett.* **1989**, *30*, 3969; (b) Shaikh, N. S.; Despande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045.
13. Basu, B.; Das, P.; Hossain, I. *Synlett* **2004**, 2630.
14. Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169.
15. (a) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2003**, 988; (b) Xu, L.-W.; Li, J.-W.; Zhou, S.-L.; Xia, C.-G. *New J. Chem.* **2004**, *28*, 183.
16. (a) Ye, T.; McKarvey, M. A. *Chem. Rev.* **1994**, *94*, 1091; (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.
17. For pharmaceutical application of carbenoid chemistry, see: (a) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984; (b) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293; (c) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron* **1980**, *21*, 31; (d) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765; (e) Wentrup, C.; Winter, H. -W. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
18. Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.
19. (a) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* **1966**, *7*, 6131; (b) Nicoud, J. -F.; Kagan, H. B. *Tetrahedron Lett.* **1971**, *12*, 2065.
20. (a) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1974**, *15*, 607; (b) Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Berger, K. *Tetrahedron Lett.* **1996**, *37*, 615; (c) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2879; (d) Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2885; (e) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J. *Chem. Soc., Perkin Trans.* **2002**, *1*, 1672.
21. Galardon, E.; Maux, P. l.; Simonneaux, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2455.
22. Morilla, M. E.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Chem. Commun.* **2002**, 2998.
23. Bachmann, S.; Fielenbach, D.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 3044.
24. (a) Itoh, H.; Utamapanya, S.; Stark, J. V.; Klabunde, K. J.; Schlup, J. R. *Chem. Mater.* **1993**, *5*, 71; (b) Jiang, Y.; Decker, C.; Mohs, C.; Klabunde, K. J. *J. Catal.* **1998**, *180*, 24; (c) Guzman, J.; Gates, B. C. *Nano Lett.* **2001**, *1*, 689; (d) Choudary, B. M.; Mulukutla, R. S.; Klabunde, K. J. *J. Am. Chem. Soc.* **2003**, *125*, 2020; (e) Shi, F.; Tse, M. K.; Pohl, M.-M.; Brückner, A.; Zhang, S.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8866; (f) Polshettiwar, V.; Varma, R. S. *Chem. Eur. J.* **2009**, *15*, 1582; (g) Polshettiwar, V.; Varma, R. S. *Org. Biomol. Chem.* **2009**, *7*, 37; (h) Polshettiwar, V.; Baruwati, B.; Varma, R. S. *Green Chem.* **2009**, *11*, 127; (i) Polshettiwar, V.; Baruwati, B.; Varma, R. S. *Chem. Commun.* **2009**, 1837.
25. (a) Larsson, P.; Andersson, A. *J. Catal.* **1998**, *179*, 72; (b) Chikán, V.; Molnár, Ä.; Balázsik, K. *J. Catal.* **1999**, *184*, 134; (c) Raveau, B.; Michel, C.; Herview, M.; Groult, D. *Crystal Chemistry of High-T_c Superconducting Copper Oxides*; Springer: Berlin, 1991; (d) Poole, C. P.; Datta, T.; Farach, H. A.; Rigney, M. M.; Sanders, C. R. *Copper Oxide Superconductors*; John Wiley & Sons: NewYork, 1988.
26. (a) Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369; (b) Kantam, M. L.; Laha, S.; Yadav, J.; Choudary, B. M.; Sreedhar, B. *Adv. Synth. Catal.* **2006**, *348*, 867; (c) Kantam, M. L.; Shiva Kumar, K. B.; Sridhar, Ch. *Adv. Synth. Catal.* **2005**, *347*, 1212; (d) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167.