

Cu-nanoparticles: a chemoselective catalyst for the aza-Michael reactions of *N*-alkyl- and *N*-arylpiperazines with acrylonitrile

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Abstract—A novel method for effecting the aza-Michael reactions of *N*-alkyl- and *N*-arylpiperazines with acrylonitrile using Cu-nanoparticles is described. The method features the use of 10 mol % Cu (14–17 nm) nanoparticles under mild reaction conditions to afford the addition products in good to excellent yields. The Cu-nanoparticles selectively catalysed the aza-Michael reaction of *N*-alkyl- and *N*-arylpiperazines in the presence of aromatic amino or aliphatic hydroxy groups.
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The conjugate addition of amines to carbon–carbon double bonds is a useful protocol in synthetic organic chemistry.^{1,2} It is used extensively in the synthesis of pharmaceutical intermediates, peptide analogues, antibiotics and other biologically active molecules and drugs.^{3–5}

In the past few years, a number of alternative procedures have been developed, and in particular, various catalysts have been investigated such as palladium,⁶ InCl₃,⁷ CeCl₃·7H₂O–NaI,⁸ Bi(NO₃)₃,⁹ Bi(OTf)₃,¹⁰ bmimBF₄,¹¹ activated silica gel¹² and clay.¹³ However, their use in stoichiometric amounts often poses severe environmental problems in waste disposal. Moreover, the high cost of ionic liquids, elevated temperatures and apprehension regarding the toxicity of some of them have led us to develop a selective, simpler, cheaper and efficient metal catalyst.

Recent work in the field of metal nanoparticles as catalysts in synthetic organic chemistry has gained much interest.^{14–31} Pioneering work includes: (i) the Mizoroki–Heck reaction using palladium nanoparticles,^{14–16} (ii) Suzuki cross-coupling reactions using palladium

nanoparticles,^{14,16–23} (iii) Stille type reactions,^{24–26} (iv) Sonogashira coupling reactions,²¹ (v) Tsuji–Trost allylation and Pauson–Khand reactions^{27,28} and other reactions catalysed by nanoparticles^{29–31} prompted this account. Current literature shows that the application of Cu-nanoparticles as catalysts in organic synthesis has been little explored. Copper nanoparticles are particularly attractive, being cheap (they can be prepared from CuSO₄), are high yielding, need mild reaction conditions and are recyclable.^{17,32} Rothenberg and co-workers have recently reported the use of copper nanoparticles, which are less harmful to the environment than any other metals in Suzuki cross coupling reactions.³³

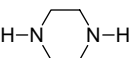
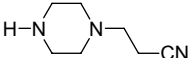
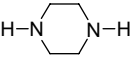
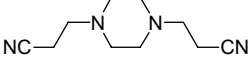
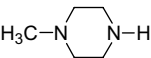
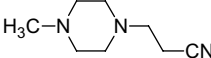
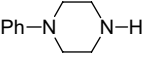
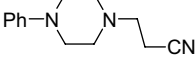
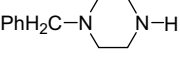
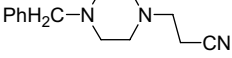
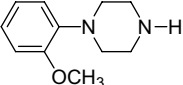
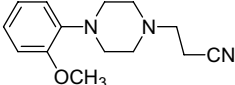
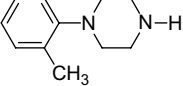
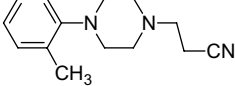
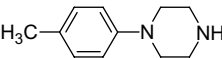
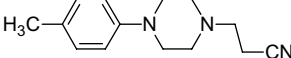
Herein, we report a novel protocol that employs Cu-nanoparticles as an efficient and selective catalyst in aza-Michael reactions of *N*-alkyl- and *N*-arylpiperazines with acrylonitrile. Additionally, in our protocol, the copper nanoparticles catalysed the aza-Michael reaction selectively in the presence of aromatic amino or aliphatic hydroxy groups. To the best of our knowledge a report by Deshpande and co-workers using a clay catalyst, is the only other example of a chemoselective aza-Michael reaction in the presence of aromatic amino groups.¹³

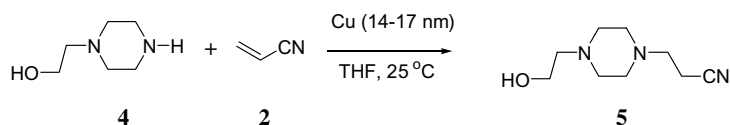
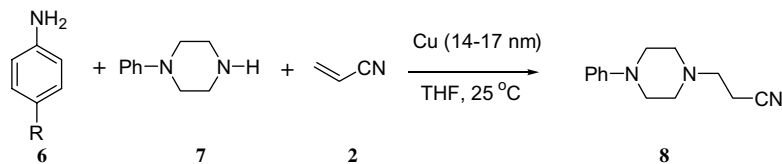
Reduction of Cu²⁺ ions to Cu(0) in a reverse micellar system was employed to prepare the copper nanoparticles (Scheme 1).^{34–36} The sizes of the Cu-nanoparticles

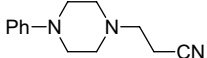
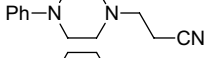
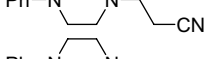
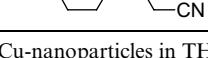
Keywords: Cu-nanoparticles; Aza-Michael reaction; Piperazine; Cyanoethylation; Acrylonitrile.

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Table 1. The aza-Michael reaction of *N*-alkyl- and *N*-arylpiperazines with acrylonitrile using Cu-nanoparticles (10 mol %)^a

Entry	1	3	Time (h)	Yield ^b (%)
1			7	80
2			16	70 ^c
3			9	85
4			8	82
5			8	78
6			8	90
7			8	86
8			8	88

^a Reaction conditions: 1.0 equiv of **1**, 1.20 equiv of **2**, 10 mol % of Cu (14–17 nm) nanoparticles in THF at room temperature stirred under an inert atmosphere.^b Isolated yield.^c Reaction conditions for entry 2: 1.0 equiv of **1**, 2.4 equiv of **2**, 15 mol % of Cu (14–17 nm) nanoparticles in THF at 25 °C stirred under an inert atmosphere.**Scheme 3.** A chemoselective aza-Michael reaction of 2-piperazin-1-ylethanol with acrylonitrile using Cu-nanoparticles.**Table 2.** A chemoselective aza-Michael reaction of *N*-alkyl- and *N*-arylpiperazines in the presence of aromatic amines with acrylonitrile using copper nanoparticles^a

Entry	R	Product 8	Yield ^b (%)
1	H		80
2	OCH ₃		87
3	CH ₃		79
4	OH		89

^a Reaction conditions: 1.0 equiv of **6**, 1 equiv of **7**, 2.5 equiv of **2** and 15 mol % Cu-nanoparticles in THF at room temperature stirred under an inert atmosphere.^b Isolated yield.

piperazines that such transformations can be readily achieved chemoselectively in the presence of an aromatic amino or aliphatic hydroxy groups. Our protocol avoids the use of expensive reagents and high temperatures and the catalyst can be recovered. Additional applications are currently under investigation.

Acknowledgements

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Supplementary data

Experimental procedures and characterisation of Cu-nanoparticles. Supplementary data associated with this article can be found, in the online version at doi: 10.1016/j.tetlet.2005.05.108.

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- (a) *General procedure for the aza-Michael reaction of N-alkyl- and N-arylpiperazines (Scheme 2)*: To a stirred solution of amine (1.0 equiv) and acrylonitrile (1.2 equiv) in THF (30 mL), Cu-nanoparticles (14–17 nm, 10 mol %) were added at room temperature and stirring was continued for 8–16 h under nitrogen. After completion of the reaction (TLC), THF was removed in vacuo, the reaction mixture was treated with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and after the removal of the solvent in vacuo, the residue was purified by column chromatography (silica gel 250–400 mesh size)
- 3-Piperazin-1-ylpropanenitrile, yellow oil; ¹H NMR (CDCl₃, 300 MHz): δ (ppm) 2.89 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.53–2.47 (m, 8H), 1.80 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ (ppm) 119.18 (CN), 53.87, 51.16, 45.84, 15.62; TOF-MS ES⁺ *m/z*: 140 (M+1).