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Nanoparticulate Copper(II) Oxide Catalyzed Synthesis of Guanidine Derivatives and Their Conversion into Functionalized Iminoguanidines

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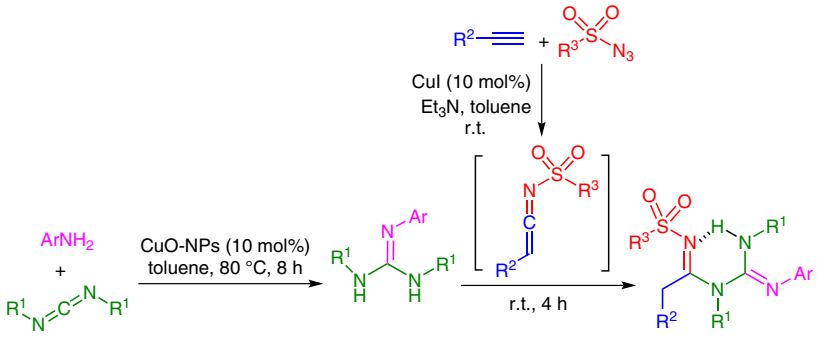

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Abstract A simple synthesis of functionalized iminoguanidines from *N*-sulfoketenimines and *N*,*N*′,*N*′′-trisubstituted guanidines, generated by nanoparticulate copper(II) oxide-catalyzed hydroamination of di(cyclo)alkylcarbodiimides, is described.

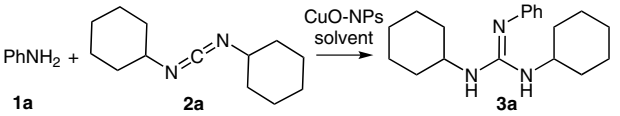
Key words imines, guanidines, ketenes, tandem reactions, azides, alkynes, carbodiimides

Guanidines have a wide range of applications as therapeutic agents in medicine.[1,2] Moreover, guanidine derivatives are used as organocatalysts or as ancillary ligands in many transformations.[3] Consequently, there is increasing interest in the synthesis of guanidines.[4–6] Recently, direct catalytic guanylation of amines with carbodiimides has received much interest because it provides a convenient and atom-economic approach to guanidines.[7]

There has also been much recent interest in the synthesis and application of transition-metal oxide nanoparticles, because of their large specific surface areas and their high activities in many catalytic processes.[8] Among the various nanoparticulate metal oxides, nanoparticulate copper(II) oxide is an effective catalyst for many reactions.[9–12] In continuation of our interest in the applications of nanoparticulate copper(II) oxide as a catalyst for organic reactions, we have prepared nanoparticulate copper(II) oxide[13] and have used it as a new, simple, and efficient catalyst for the guanylation of amines with carbodiimides under mild conditions.

Initially, we examined various copper catalysts, including copper(I) iodide, copper(I) bromide, copper(II) acetate, copper(II) chloride, nanoparticulate copper(I) oxide, bulk copper(II) oxide, and nanoparticulate copper(II) oxide, for the synthesis of *N*,*N*′,*N*′′-trisubstituted guanidines from amines and carbodiimides. Only the nanoparticulate copper(II) oxide gave acceptable results. We therefore optimized the reaction conditions for hydroamination of carbodiimides by using nanoparticulate copper(II) oxide as a catalyst for the model reaction of aniline (**1a**) with *N*,*N*′-dicyclohexylcarbodiimide (**2a**; DCC). A brief screening of solvents in the presence of 5 mol% of catalyst under reflux showed that acetonitrile, tetrahydrofuran, dichloromethane, and hexane were less effective than toluene (Table 1, entries 2–6). *N*,*N*′-Dicyclohexyl-*N*′′-phenylguanidine (**3a**)

Table 1 Optimization of the Conditions for the Hydroamination of *N*,*N*′-Dicyclohexylcarbodiimide with Nanoparticulate Copper(II) Oxide as Catalyst[a]



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	–	toluene	reflux	24	–
2	5	toluene	reflux	24	80
3	5	CH_2Cl_2	reflux	24	35
4	5	hexane	reflux	24	45
5	5	MeCN	reflux	24	75
6	5	THF	reflux	24	60
7	10	toluene	r.t.	24	–
8	10	toluene	60	24	65
9	10	toluene	80	8	94
10	10	toluene	100	8	94
11	20	toluene	80	8	94

[a] Reaction conditions: DCC (1 mmol), $PhNH_2$ (1 mmol).
[b] Isolated yield.

was obtained efficiently after eight hours in the presence of 10 mol% of nanoparticulate copper(II) oxide at 80 °C. Increasing the catalyst loading to 20 mol% did not affect the yield. Therefore, the use of 10 mol% of nanoparticulate copper(II) oxide (8 mg) in toluene at 80 °C was considered to be the best choice for hydroamination of DCC (entry 9).

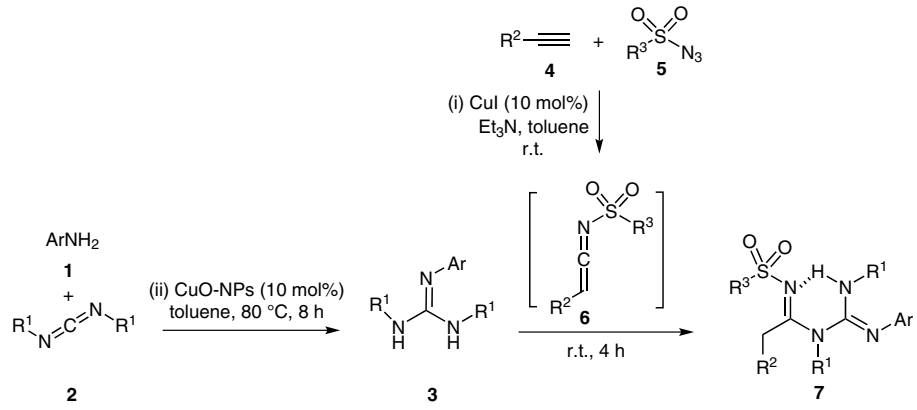
As part of our current studies on the development of new applications of *N*-sulfoketenimines in organic synthesis,[14–16] we used the optimized conditions to construct highly functionalized iminoguanidines from *N*-sulfoketenimines and the *N*,*N*′,*N*″-trisubstituted guanidines prepared by the nanoparticulate copper(II) oxide catalyzed hydroamination of dialkylcarbodiimides.

To investigate the scope of this transformation, we examined the reactions of a wide range of anilines containing various electron-donating and electron-withdrawing groups to give 1,3-dialkyl-2-arylguanidines **3**. Subsequently, these intermediates were treated with *N*-sulfoketenimines to give the corresponding iminoguanidines **7a**–**k** in good yields (Table 2).[17]

These reactions gave good yields regardless of whether electron-withdrawing or electron-donating substituents were present on the aromatic ring. The catalytic system showed good functional-group tolerance. Both *N*,*N*′-di(cyclo)alkylcarbodiimides **2** reacted with aromatic amines bearing bulky and electron-withdrawing substituents in the *ortho*- or *para*-position of the phenyl ring to give the corresponding iminoguanidines in good yields. Aliphatic alkynes readily participated in the coupling to give the corresponding iminoguanidines **7a**–**j** (Table 2). Aromatic and aliphatic sulfonyl azides reacted efficiently, and the corresponding products were obtained in good yields.

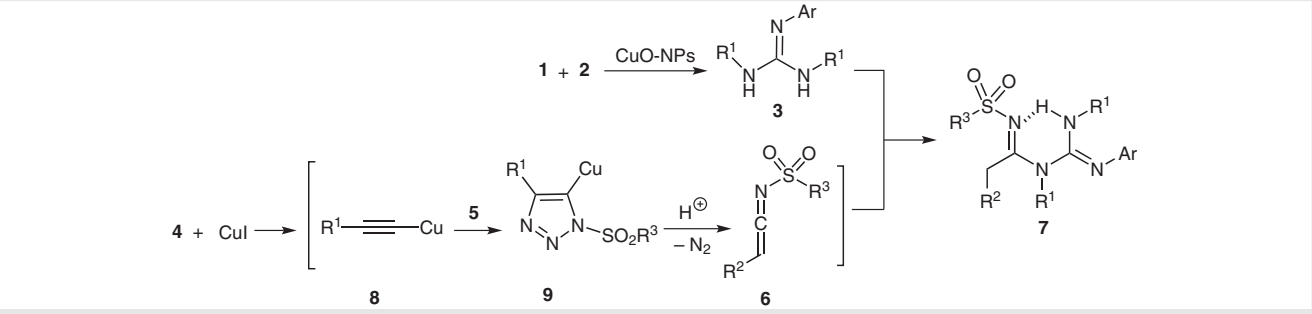
A plausible mechanism for the formation of products **7** is shown in Scheme 1. The copper acetylide **8**, formed from alkyne **4** and copper(I) iodide, undergoes a 1,3-dipolar cycloaddition reaction with sulfonyl azide **5** to give the triazole derivative **9**. This intermediate can undergo a ring-opening reaction to give the *N*-sulfonylketenimine **6**. Guanidine derivative **3**, formed from arylamine **1** and *N*,*N*′-di(cyclo)al-

Table 2 Synthesis of Iminoguanidine Derivatives **7a**–**k**[a]



Entry	Ar	R^1	R^2	R^3	Product	Yield[b] (%)
1	Ph	Cy	Bu	Ph	**7a**	84
2	4-Tol	*i*-Pr	Bu	Ph	**7b**	80
3	2,4-$Cl_2C_4H_6$	*i*-Pr	Bu	Ph	**7c**	74
4	4-Tol	Cy	Pr	4-Tol	**7d**	70
5	4-ClC_6H_4	Cy	Pr	Ph	**7e**	81
6	Ph	Cy	Pr	4-Tol	**7f**	78
7	4-$O_2NC_6H_4$	Cy	Bu	4-Tol	**7g**	79
8	4-ClC_6H_4	Cy	Pr	Me	**7h**	80
9	4-Tol	Cy	Pr	Me	**7i**	83
10	Ph	Cy	Bu	4-Tol	**7j**	85
11	4-ClC_6H_4	*i*-Pr	Ph	Ph	**7k**	70

[a] Reaction conditions: (i) **1** (1.0 mmol), **2** (1.0 mmol), nanoparticulate CuO (8 mg, 20 mol%), toluene (2 mL), 80 °C, 8 h; (ii) **5** (1.2 mmol), **4** (1 mmol), CuI (0.019 g, 0.1 mmol), Et_3N (101 mg, 1 mmol), toluene (2 mL), r.t, 4 h.
[b] Isolated yield.



Scheme 1 A plausible mechanism for the formation of products **7**

kylcarbodiimide **2**, undergoes a nucleophilic addition reaction with the *N*-sulfonylketenimine **6** to give the iminoguanidine **7**.

In conclusion, we have developed a multicomponent protocol for the synthesis of a novel class of iminoguanidine derivatives through a nanoparticulate copper(II) oxide catalyzed tandem reaction of anilines, di(cyclo)alkylcarbodiimides, sulfonyl azides, and terminal alkynes. The advantages of this catalytic system are its operational simplicity, simple workup, substrate and catalyst availability, and low cost.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380349.

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(17) ***N*-(Cyclo)alkyl-*N*-{[(cyclo)alkylamino](arylimino)methyl}-*N′*-(arylsulfonyl)hexanimidamides 7; General Procedure**
Aniline **1** (1 mmol), carbodiimide **2** (1.2 mmol), and nanoparticulate CuO (10 mol%) were stirred in toluene (2 mL) at 80 °C for 8 h. A mixture of sulfonyl azide **5**, (1.2 mmol), alkyne **4** (1 mmol), CuI (0.019 g, 0.1 mmol), and Et_3N (0.101 g, 1 mmol) in toluene (2 mL) was slowly added, and the mixture was stirred at r.t. under N_2. When the reaction was complete [~4 h; TLC (EtOAc–hexane, 1:5)], the mixture was diluted with aq NH_4Cl (3 mL) and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane–EtOAc (5:1)].
***N*-Cyclohexyl-*N*-[(cyclohexylamino)(phenylimino)methyl]-*N′*-(phenylsulfonyl)hexanimidamide (7a)**
Colorless crystals; yield: 0.45 g (84%); mp 134–137 °C. IR (KBr): 3329, 3053, 2930, 1652, 1590, 1513, 1448, 1343, 1266, 1146, 1092, 752 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 6.8 Hz, 3 H), 1.23–2.38 (m, 28 H), 3.27 (quint, ^3J = 6.8 Hz, 1 H), 3.62 (quint, ^3J = 6.8 Hz, 1 H), 6.73–6.83 (m, 3 H), 6.96 (s, 1 H), 7.18 (d, ^3J = 7.9 Hz, 2 H), 7.42–7.61 (m, 3 H), 7.88 (d, ^3J = 7.9 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.6 (Me), 21.5 (CH_2), 22.3 (2 CH_2), 24.9 (CH_2), 25.5 (2 CH_2), 26.0 (CH_2), 29.1 (CH_2), 30.4 (CH_2), 31.0 (CH_2), 31.3 (CH_2), 32.6 (CH_2), 34.0 (CH_2), 43.6 (CH_2), 50.8 (CH), 57.8 (CH), 122.0 (3 CH), 125.1 (2 CH), 126.4 (2 CH), 128.5 (2 CH), 132.4 (CH), 143.2 (C), 144.7 (C), 154.8 (C), 155.5 (C). MS: *m/z* (%) = 536 (8) [M^+], 478 (20), 395 (24), 362 (40), 238 (36), 141 (88), 91 (38), 77 (100). Anal. Calcd for $C_{31}H_{44}N_4O_2S$ (536.77): C, 69.37; H, 8.26; N, 10.44. Found: C, 69.81; H, 8.32; N, 10.51.