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Communication

Copper(I) Iodide-Catalyzed Synthesis of *N*,*N*′-Disubstituted Guanidines from *N*-Substituted Cyanamides*

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A facile and effective synthesis of *N*-alkyl-*N*′-arylguanidines was accomplished by the reaction of *N*-arylcyanamides with various primary and secondary alkylamines, under the catalysis of copper(I) iodide and Xantphos in DMF. This methodology provides a direct access to versatile *N*,*N*′-disubstituted guanidine derivatives from *N*-arylcyanamides that can be readily prepared from the corresponding nitriles via Tiemann rearrangement.

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Guanidine is an important nitrogen-containing functionality and characteristic structural motif which commonly exists in natural products and biologically active compounds.[1–3] In addition, *N*-substituted guanidines have been extensively used as reactive CN_3 building blocks and organocatalysts[4–6] in organic synthesis, as well as bidentate ligands in coordination chemistry. Despite their versatile applications, only a few synthetic approaches for the preparation of *N*-substituted guanidines have been practically utilized in the literature. The most straightforward approach involves the direct nucleophilic attack of amines to various activated CN_2 guanidinylating reagents, usually derived from ureas or thioureas.[7,8] Unactivated carbodiimides and cyanamides are less reactive CN_2 guanidinylating reagents.[9] Their reactions with amines require higher temperature,[10–13] acidic condition,[14–19] or the assistance of nucleophilic reagents such as fluoride ion or *N*-hetero-azoles (pyrazoles, imidazoles, or benzotriazoles).[20]

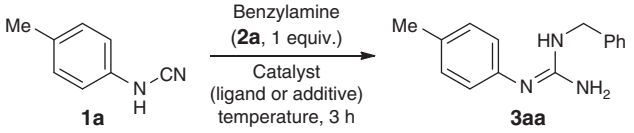
Recent studies have shown that guanidine formation from the reaction of carbodiimides with amines can be effectively catalyzed by various metal salts or metal complexes, including zinc,[21] aluminium,[22,23] titanium,[24] vanadium,[25] and several rare earth metals.[26,27] In contrast, the metal-catalyzed guanidine formation from cyanamides and amines was only recently reported by Li and Neuville, in which the trisubstituted guanidines can be obtained from copper(II) chloride-catalyzed three-component reaction of cyanamides, arylboronic acids, and amines.[28] Lately, we reported a general procedure for the preparation of *N*-substituted cyanamides via Tiemann rearrangement.[29] In a continuous effort to explore the potential synthetic application of cyanamides, we embarked on an investigation of a general and practical synthesis of guanidines via metal-catalyzed reaction.

Our study focussed on the reaction of *N*-arylcyanamides with amines and *N*-(4-methylphenyl)cyanamide (**1a**) and benzylamine (**2a**) were chosen as model substrates to investigate the guanidine formation reaction. In our initial attempts, the direct addition of benzylamine (**2a**) to *N*-(4-methylphenyl)cyanamide (**1a**) under the catalysis of tertiary amines and *N*-heterocycles was examined. The results showed that the reactions gave only poor to moderate yields (entries 1–5 in Table 1). We rationalized that, unlike the carbodiimides, *N*-monosubstituted cyanamides possess an acidic proton that gets deprotonated under these conditions, thus deactivating the cyanamides from the nucleophilic addition of amines. We then shifted our focus to metal-catalyzed guanidine formation from cyanamides and amines. The screening of the reaction conditions started with copper, nickel, and iron salts as the catalysts with various solvents, temperatures, and ligands/additives (part of the results are summarized in Table 1). The survey of the conditions concluded that maximal yield was obtained when the reaction was carried out in DMF with copper(I) iodide as the catalyst, and Xantphos as the ligand under argon atmosphere at 140°C (entry 16 in Table 1). We postulated that the copper(I) salt played the role of a Lewis acid to activate the cyano group to facilitate the addition reaction.

With the optimized condition established, the scope and generality of the reaction was explored. A wide variety of *N*-arylcyanamides **1a**–**k**, prepared from the corresponding carbonitriles via Tiemann rearrangement,[29] were subjected to the reaction, under the optimized condition (entry 16 in Table 1), with various primary and secondary amines **2a**–**g**. Our investigation showed that *N*-arylcyanamides **1a**–**j** could react with primary and secondary alkylamines **2a**–**f** to give good yields of the targeted *N*,*N*′-disubstituted guanidines in free-base form.

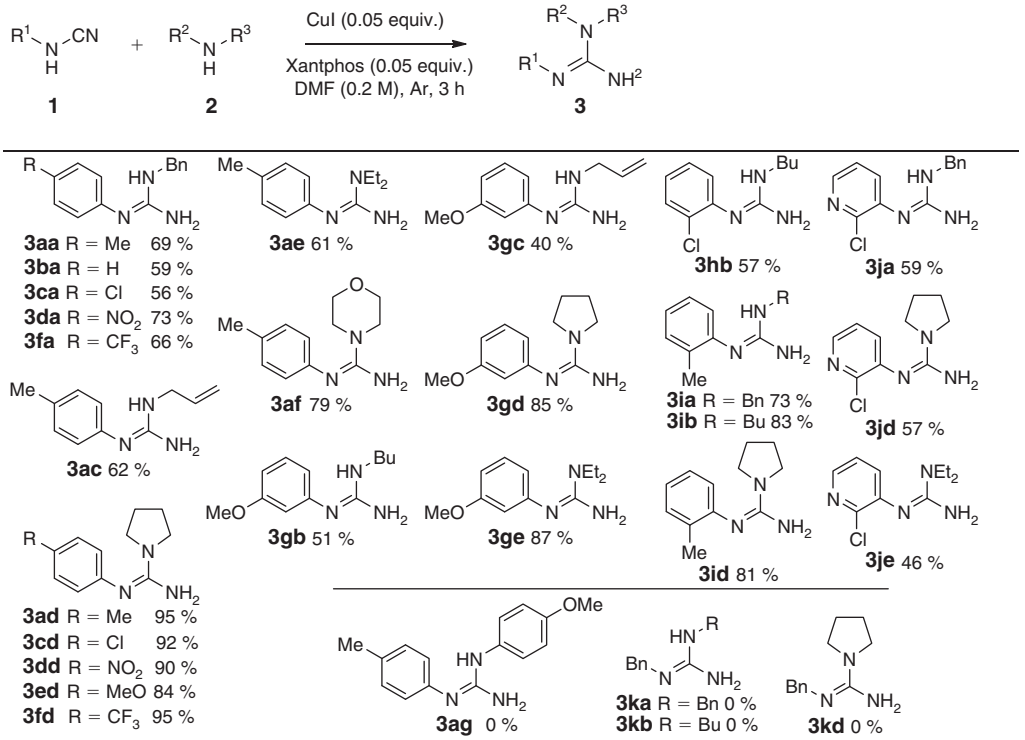
*This paper is dedicated to Professor Ming-Chang P. Yeh on the occasion of his 60th birthday.

Table 1. Survey and optimization of the reaction conditions

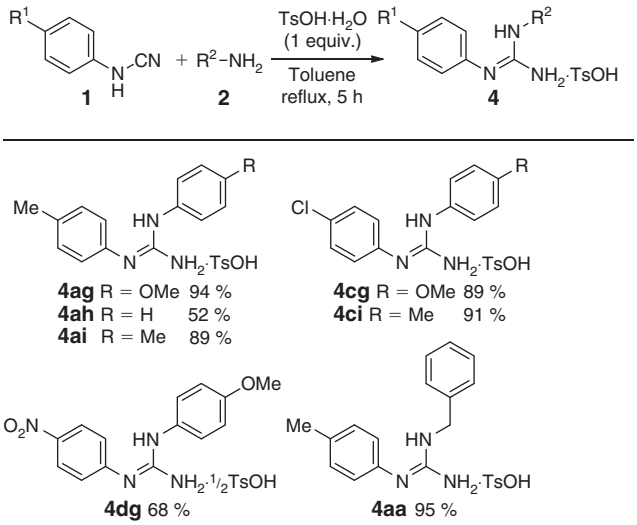


Entry	Catalyst [equiv.]	Ligand or additive [equiv.]	Temperature [°C]	Solvent	Yield [%][A,B]
1	–	Et_3N (1)	100	Dioxane	50 (11)
2	–	DABCO (1)	100	Dioxane	46 (17)
3	–	DBU (1)	100	Dioxane	28 (33)
4	–	Benzotriazole (1)	100	Dioxane	50 (17)
5	–	DMAP (0.1)	100	Dioxane	39 (26)
6	$CuCl_2$ (0.1)	Xantphos (0.1)	100	Dioxane	50 (18)
7	CuCl (0.1)	Xantphos (0.1)	100	Dioxane	53 (14)
8	CuI (0.1)	Xantphos (0.1)	100	Dioxane	56 (9)
9	$NiCl_2$ (0.1)	Xantphos (0.1)	100	Dioxane	40[C]
10	$FeCl_3$ (0.1)	Xantphos (0.1)	100	Dioxane	13[C]
11	CuI (0.1)	Xantphos (0.1)	110	Toluene	31
12	CuI (0.1)	Xantphos (0.1)	120	Chlorobenzene	15
13	CuI (0.1)	Xantphos (0.1)	120	DMF	60 (20)
14	CuCl (0.1)	Xantphos (0.1)	120	DMF	56 (7)
15	CuI (0.1)	Xantphos (0.1)	140	DMF	66
16	CuI (0.05)	Xantphos (0.05)	140	DMF	69[C]
17	CuI (0.05)	–	140	DMF	16
18	$CuCl_2$ (0.1)	Xantphos (0.1)	140	DMF	51

[A]Unless specified otherwise, the yields were determined by ^1H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard.
[B]Numbers in parentheses represent the unreacted cyanamides, if denoted.
[C]Isolated yield.



Scheme 1.



Scheme 2.

The yields of the reaction can be correlated with the electrophilicity of the cyanamide carbon and the nucleophilicity of the amine nitrogen. In general, the *N*-arylcyanamides possessing electron-withdrawing substituents as the electrophiles or the secondary amines as the nucleophiles could result in better yields (Scheme 1). It is notable that, although the reactions of *N*-arylcyanamides with alkylamines proceeded flawlessly under the optimized condition, our attempts to apply the same condition to the reaction with primary arylamines were unsuccessful. In contrast to the primary and secondary alkylamines, we speculated that this failure could be attributed to the reduced nucleophilicity of the arylamines. Moreover, the reaction of *N*-alkylcyanamides **1k** with primary and secondary alkylamines also failed to give the desired *N*,*N*′-dialkylguanidines. (Scheme 1)

In a continuous screening of catalytic conditions for the reaction of *N*-(*p*-tolyl)cyanamide (**1a**) with *p*-anisidine (**2g**), we found that only the commonly used acid-catalyzed reactions[14–19] could give an acceptable yield of the desired product, while the copper salts were unable to effectively catalyse the guanidine formation. The acid-catalyzed guanidine formation gave the product in its salt form and our attempts to remove the acidic counterpart were unsuccessful. Nevertheless, our investigation chose a stoichiometric amount of *p*-toluenesulfonic acid (TsOH) as the catalyst, by which the counterion of the resulted guanidine salts can be quantitated by ^{1}H NMR spectroscopy. Hence, the reaction of *N*-arylcyanamides **1a**, **c**, **d** with anilines **2 g**–**i** was carried out in the presence of TsOH in toluene under reflux temperature to afford a series of *N*,*N*′-diphenylguanidine · TsOH salts **4** in good yields. The reaction protocol is also applicable to alkylamines as nucleophiles (Scheme 2).

In summary, our investigation has provided a facile and practical synthesis of *N*-alkyl-*N*′-arylguanidine derivatives, in which copper(I) iodide and Xantphos were used as catalysts for the nucleophilic addition of primary or secondary alkylamines to *N*-arylcyanamides. *N*-Arylcyanamides are readily available via Tiemann rearrangement of amidoximes that were prepared directly from the corresponding nitriles.[29] Although the CuI-catalyzed reaction was not applicable to the synthesis of *N*,*N*′-diarylguanidines, we have also demonstrated that the TsOH-catalyzed nucleophilic addition of anilines to *N*-aryl cyanamides could be employed as a supplementary route. Our investigation successfully provided a viable synthesis which is amenable to the preparation of various *N*,*N*′-disubstituted guanidine derivatives.

Experimental

General Procedure for the Preparation of N-*Alkyl*-N′-*arylguanidines* ***3*** *from* N-*Arylcyanamides* ***1*** *(Scheme 1)*

To a solution of *N*-arylcyanamide[29] (**1**, 1.0 mmol) in DMF (5 mL) was added Xantphos (0.05 mmol, 0.05 equiv.), CuI (0.05 mmol, 0.05 equiv.), and amine (**2**, 1.0 mmol, 1 equiv.). The resulting mixture was stirred under argon atmosphere at 140°C for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography.

General Procedure for the Preparation of N,N′-*Diarylguanidines* ***4*** *from* N-*Arylcyanamides* ***1*** *(Scheme 2)*

A mixture of *N*-arylcyanamide[29] (**1**, 1.0 mmol), amine (**2**, 1.0 mmol, 1 equiv.), and *p*-TsOH · H_2O (1.0 mmol, 1 equiv.) in toluene (5 mL) was stirred at reflux temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography.

Supplementary Material

^{1}H and ^{13}C NMR spectra of representative compounds are available on the Journal's website.

Acknowledgements

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