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Copper(I)-Induced Addition of Amines to Unactivated Nitriles: The First General One-Step Synthesis of Alkyl Amidines.

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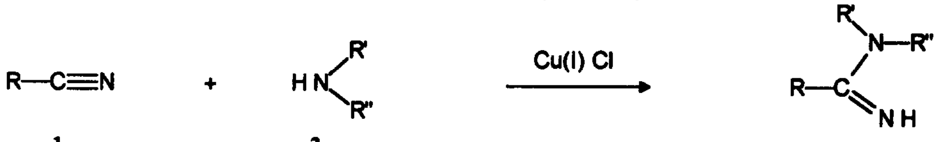
Key Words: Amidines; nitriles; amines; copper(I)-catalyzed condensation.

***Abstract** : Cu(I)Cl promotes the condensation of acetonitrile **1a** and benzonitrile **1b** with primary and secondary amines **2a-g** into amidines **3a-j** under mild conditions, in high to quantitative yields. Stoichiometric formation of Cu(I)-amidines complexes allows to control the degree of substitution of resulting amidines.*

Direct synthesis of amidines from nitriles and amines: R-C≡N + R'R"NH → R-C(=NH)NR'R" can be achieved only if nitriles are substituted by electron-withdrawing groups,[1] e. g. Cl_3C-C≡N. On the contrary, unactivated nitriles have to be reacted in presence of Lewis acids ($AlCl_3$, $ZnCl_2$..) at 150-200° C,[2] or with aluminium amides,[3] or transformed in a first step into alkyl imidates, which are in turn reacted with amines (Pinner's synthesis).[4] Lanthanide (III) triflates catalyze condensation of nitriles with primary amines and diamines into *N,N'*-disubstituted and cyclic amidines,[5] but monosubstituted amidines cannot be obtained from primary amines, and further condensations yield eventually heterocyclic compounds (triazines, pyrimidines) from secondary amines, thus limiting the scope of the method.

We report here that the transformation of ordinary unactivated nitriles **1a-b** (R = CH_3, C_6H_5) and amines **2a-f** (R', R" = H, alkyl) into amidines **3a-j** is easily performed in high to quantitative yields (80-100%) in the presence of Cu(I)Cl [or Cu(I)Br], under mild conditions (see Table).



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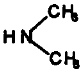
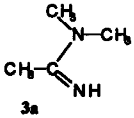
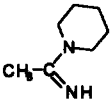
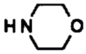
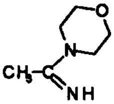
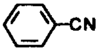
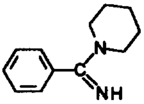
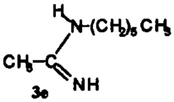
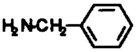
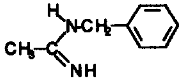
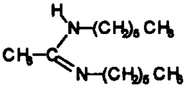
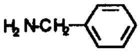
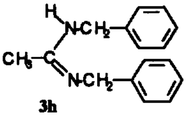
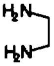
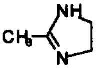
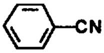
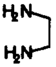
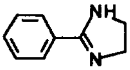
The reaction takes place either with the nitrile as solvent, or in alcohols (EtOH, MeOH) or even in DMSO below ca. 80° C under an inert atmosphere. After completion, Cu(I) is precipitated by excess concentrated aqueous NaOH and the crude mixture is extracted with Et_2O to yield pure amidines; the majority of them, although structurally quite simple, are original compounds. Structures have been established by NMR and/or GC-MS analysis,[6] and confirmed when possible by comparison with known compounds. The amount of reacted nitrile **1a-b** (even when used in large excess, as solvent) is at most equal to the quantity of Cu(I)Cl engaged.

Nitrile	Amine	Solvent	Amidine	Yield
CH_3-CN **1a**	 $HN(CH_3)_2$ **2a**	CH_3-CN	 **3a**	100%
CH_3-CN **1a**	 **2b**	CH_3-CN	 **3b**	100% (75 % in EtOH)
CH_3-CN **1a**	 **2c**	CH_3-CN	 **3c**	80%
 **1b**	 **2b**	Φ-CN	 **3d**	100% (90% in EtOH)
CH_3-CN **1a**	$H_2N-(CH_2)_5CH_3$ **2d**	CH_3-CN	 **3e**	90%
CH_3-CN **1a**	 **2e**	CH_3-CN	 **3f**	80%
CH_3-CN **1a**	$H_2N-(CH_2)_5CH_3$ **2d**	DMSO	 **3g**	90% (80% in EtOH)
CH_3-CN **1a**	 **2e**	DMSO	 **3h**	80% (75% in EtOH)
CH_3-CN **1a**	 **2f**	MeOH	 **3i**	40%
 **1b**	 **2f**	MeOH	 **3j**	60%

Thus, *N,N* disubstituted amidines **3a-d** are readily obtained as single products from secondary amines **2a-c**, used in a 1/1 [amine] / [Cu(I)Cl] ratio.

In contrast, primary amines **2d-e**, when submitted to the preceding procedure, generally give rise to a mixture of mono and *N,N'* disubstituted amidines **3e/3g** and **3f/3h** respectively; nevertheless, selective synthesis of each one of the latter can be achieved according to the ratio [amine]/[Cu(I)Cl] : 1 equi. amine **2d-e** and 1.2 equi. Cu(I)Cl in acetonitrile solvent **1a** lead to monosubstituted amidines **3e-f** in high yields (reported to **2d-e**).

On the other hand, 4 equi. **2d-e**, 1 equi. Cu(I)Cl and 1 equi. **1a** in alcohol solvent or better in DMSO provide chiefly in 48h *N,N'* disubstituted amidines **3g-h**, with displacement of NH_3.

The condensation of nitriles with ethylenediamine **2f** does not take place in excess nitrile, where the catalyst is unstable; it can be achieved in alcoholic solvents, in which the same disproportionation of Cu(I)Cl/diamine complex into Cu(II) and Cu(0) becomes obviously reversible: 2-methyl and 2-phenyl-Δ^2-imidazolines **3i-j** are obtained from **1a-b** in 40-60% yield (MeOH solvent) in 20h (1 equi. **2f**,.1 equi. Cu(I)Cl for 1 equi **1a-b**), and the reaction proceeds as well when starting from 0.5 equi. $Cu(II)Cl_2$ + 0.5 equi. Cu(0) as catalyst.

Coordination with Cu(I) therefore activates nitriles **1a-b** towards nucleophilic attack of amines; this catalysis, due to a relatively weak interaction, becomes no longer effective in presence of excess competitive strong complexing reagents. So behave amidines **3a-j** themselves, since conversion culminates at a [**3**]/[Cu(I)] ratio equal to unity when no more Cu(I) is available as catalyst, being totally engaged in a stoichiometric complex, orange-red coloured in solution. Such 1/1 Cu(I)-amidine complexes have been previously described,[7] but their limited stability and ill-defined molecular weight (cyclic dimers or linear polymers) generally precluded precise structural analysis.[8]

Amines **2a-f**, when used in great excess (solvent), as well as DMF or *N*-methyl pyrrolidinone, also coordinate to Cu(I) and reduce its catalytic ability, decreasing the yields to ca. 50%, whereas pyridine totally inhibits the reaction.

We have therefore in hand a general and very mild synthetic method yielding amidines from nitriles and various amines, except aromatic amines like aniline, less nucleophilic than aliphatic ones.

References and Notes :

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6. In a typical experiment, a solution of nitrile **1** (4 mmol) and amine **2** (4 mmol) in absolute ethanol (3 ml) is added under nitrogen to Cu(I)Cl (4 mmol) at room temperature. The mixture is refluxed for 20 hours, and the resulting red solution poured in ether (50 ml) and vigorously stirred for 2 minutes with 5 ml of NaOH (30% aq.). The organic layer is dried (Na_2SO_4), filtered and evaporated. Resulting amidines **3** are pure enough (GLC/MS) to render further vacuum distillation unnecessary. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra (standard $SiMe_4$) were obtained in $CDCl_3$ unless otherwise stated.

- *N,N*-**Dimethylacetamidine**[5] **3a** : liquid, ^{1}H NMR δ (ppm): 2.08 (s, 3H), 2.90 (s, 6H), 5.20 (broad, 1H). ^{13}C NMR δ (ppm): 23.5 (CH_3), 38.1 (CH_3), 165.4 (s). MS: 86 ($M^{+\cdot}$), 71, 57, 44, 42.
- **Piperidinoacetamidine 3b** : liquid, ^{1}H NMR δ (ppm): 1.45-1.65 (m, 6H), 2.08 (s, 3H), 3.45-3.55 (m, 4H), 5.8 (broad, 1H). ^{13}C NMR δ (ppm): 23.9 (CH_3), 24.7 (CH_2), 25.7 (CH_2), 45.8 (CH_2), 164.7 (C=N). MS: 126 ($M^{+\cdot}$), 111, 97, 84, 56, 42.
- **Morpholinoacetamidine 3c** : liquid, ^{1}H NMR δ (ppm): 2.08 (s, 3H), 3.35-3.45 (m, 4H), 3.65-3.75 (m, 6H), 5.8 (broad, 1H). ^{13}C NMR δ (ppm): 23.4 (CH_3), 45.1 (CH_2), 66.6 (CH_2), 165.2 (C=N). MS: 128 ($M^{+\cdot}$), 98, 86, 71, 57, 42.
- **Piperidinobenzamidine**[2] **3d** : liquid, ^{1}H NMR δ (ppm): 1.5-1.7 (m, 6H), 3.2-3.4 (m, 4H), 5.8 (broad, 1H), 7.3-7.45 (m, 5H). ^{13}C NMR δ (ppm): 24.7 (CH_2), 25.8 (CH_2), 47.1 (CH_2), 126.7 (CH), 128.5 (CH), 128.9 (CH), 138.9 (s), 169.8 (s). MS: 188 ($M^{+\cdot}$), 187, 104, 84, 77.
- *N*-**Hexylacetamidine 3e** : oil, ^{1}H NMR δ (ppm): 0.8-0.9 (t, 3H, J = 6.5 Hz), 1.2-1.4 (m, 6H), 1.5-1.65 (m, 2H), 1.95 (s, 3H), 3.15 (t, 2H, J = 7 Hz), 4.85 (broad). ^{13}C NMR δ (ppm): 13.9 (CH_3), 22.4 (CH_2), 23.4 (CH_3), 26.7 (CH_2), 29.3 (CH_2), 31.4 (CH_2), 41.9 (CH_2), 161.9 (s). MS: 142 ($M^{+\cdot}$), 127, 113, 99, 85, 72, 58, 42.
- *N*-**Benzylacetamidine 3f** : oil, ^{1}H NMR (DMSO) δ (ppm): 1.85 (s, 3H), 4.0 (H_2O, DMSO), 4.15 (s, 2H), 7.1-7.4 (m, 5H). ^{13}C NMR (DMSO) δ (ppm): 22.6 (CH_3), 42.1 (CH_2), 126.1 (CH), 127.5 (CH), 128.0 (CH), 141.3 (s), 158.9 (s). MS: 148 ($M^{+\cdot}$), 147, 106, 91, 42.
- *N,N'*-**Dihexylacetamidine 3g** : oil, ^{1}H NMR δ (ppm): 0.8-1.0 (t, 6H, J = 6.8 Hz), 1.2-1.4 (m, 12H), 1.45-1.6 (m, 4H), 1.85 (s, 3H), 3.0-3.15 (t, 4H, J = 7.2 Hz). ^{13}C NMR δ (ppm): 13.8 (CH_3), 22.4 (CH_2), 26.4 (CH_2), 30.6 (CH_2), 31.6 (CH_2), 45.5 (CH_2), 155.9 (s). MS: 226 ($M^{+\cdot}$), 211, 197, 183, 169, 155, 99, 85, 56, 43, 42.
- *N,N'*-**Dibenzylacetamidine 3h** : oil, ^{1}H NMR δ (ppm): 1.9 (s, 3H), 4.45 (s, 4H), 7.1-7.35 (m, 10H). ^{13}C NMR δ (ppm): 17.9 (CH_3), 48.9 (CH_2), 126.5 (CH), 127.4 (CH), 128.2 (CH),140.9 (s), 158.5 (s). MS: 238 ($M^{+\cdot}$), 147, 106, 91.
- **2-Methyl Δ^2-imidazoline 3i** : mp 103° C (lit.[9] 103° C), ^{1}H NMR δ (ppm): 1.9 (s, 3H), 3.55 (s, 4H), 4.5 (broad, 1H). ^{13}C NMR δ (ppm): 14.9 (CH_3), 49.9 (CH_2), 164.0 (s). MS: 84 ($M^{+\cdot}$), 83, 55, 42.
- **2-Phenyl Δ^2-imidazoline 3j** : mp 99° C (lit.[10] 99° C), ^{1}H NMR δ (ppm): 3.75 (s, 4H), 4.4 (broad, 1H), 7.3-7.5 (m, 3H), 7.7-7.8 (m, 2H). ^{13}C NMR δ (ppm): 50.4 (CH_2), 126.8 (CH), 128.3 (CH), 130.4 (CH), 138.0 (s), 164.5 (s). MS: 146 ($M^{+\cdot}$), 117, 77.

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