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Addition of Amines to Nitriles Catalyzed by Ytterbium Amides: An Efficient One-Step Synthesis of Monosubstituted *N*-Arylamidines

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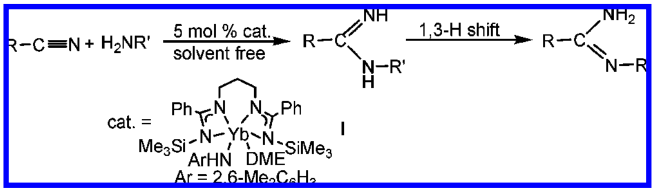
ABSTRACT



A one-step synthesis of monosubstituted *N*-arylamidinates via addition of amines to nitriles catalyzed by ytterbium amides is reported. The reactions with various substrates give the products in good to excellent yields with 5 mol % ytterbium at 100 °C under solvent-free conditions.

Amidinates are of interest as structural units with wide utility in drug design[1] and as synthons for the synthesis of heterocyclic compounds.[2] Several synthetic strategies have been developed[3,4] in which the nucleophilic addition of amine to nitrile is the most convenient and atom-economic method.[3] The one-step synthesis of amidines from nitriles and amines can be realized only if the nitriles are activated by electron-withdrawing groups[3a] or under more forcing conditions in the presence of Lewis acids[3b] or with aluminum amides[3c] for unactivated nitriles. Trivalent lanthanide triflates have been employed successfully as catalysts in the condensation

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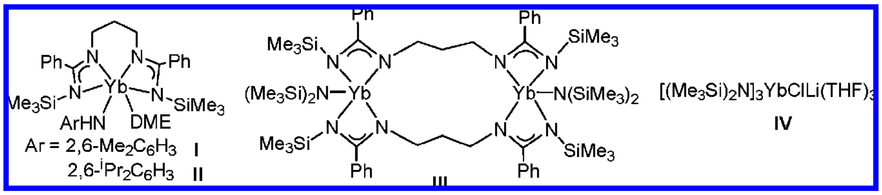
Scheme 1. Tested Amides

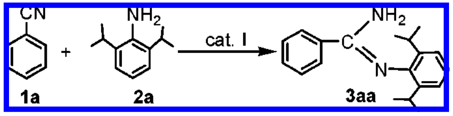


of nitriles with primary amines and diamines into *N*,*N*′-disubstituted and cyclic amidines, but monosubstituted amidines cannot be synthesized, and the reaction with secondary amines afforded triazines or pyrimidines via further condensations.[3d] SmI_2 can also catalyze the condensation reaction as a precatalyst, and the same problem as in the case with lanthanide triflates remains to be solved.[3e] Recently, the selective synthesis of monosubstituted alkylamidines from amines and nitriles can be achieved in the presence of CuCl. However, 1.2 equiv of CuCl to amines is needed in this process.[3f] Thus, the development of catalytic addition of amines to nitriles is still a challenge in monosubstituted amidine synthesis.

Prompted by recent successes obtained in C−N bond formation, reactions catalyzed by lanthanide amide complexes, including hydroamination,[5] monocoupling reaction of isocyanides with terminal alkynes,[6] a Cannizzaro-type disproportionation of aromatic aldehydes,[7] and the guanylation of amines[8] and amidination of alkyne,[3j,k] we turned our attention to the possible use of lanthanide amides as catalysts for addition reaction of amines to nitriles.

We have recently synthesized the novel amide complexes supported by a bridged bis(amidinate) **I**−**III** (Scheme 1) and found that amide complexes **I** and **II** show high reactivity for controlled polymerization of lactide.[9] Thus, complex **I** was first tested in the condensation reactions of nitriles and amines, and several reaction conditions were examined in the model reaction of **1a** with **2a** (Table 1). The reactions took place smoothly under solvent free conditions or in toluene to afford the monosubstituted amidine **3aa** in moderate to excellent yields depending on the conditions used. The reaction in THF provided the lowest yield (Table 1, entry 3). With the increasing temperature, the yields increased (Table 1, entries 2, 5, and 6). The ratio of amine to nitrile showed an effect on the reactivites, and the maximum yields were obtained in the range of 2−4 (Table 1, entries 8−10). The yields increased when the catalyst loading increased and an almost quantitative yield was obtained with 10 mol % of ytterbium (based on **1a**) under solvent-free conditions for 12 h (Table 1, entry 12).

Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (mol %)	solvent	**1a/2a**	*T* (°C)	time (h)	% yield[b]
1	5	toluene	1:1	60	12	35
2	5	toluene	1:1	60	24	45
3	10	THF	1:1	60	12	45
4	10	toluene	1:1	60	12	80
5	5	toluene	1:1	80	24	55
6	5	toluene	1:1	100	24	65
7	5		1:1	100	24	75
8	5		1:2	100	24	88
9	5		1:3	100	24	84
10	5		1:4	100	24	83
11	5		1:10	100	24	65
12	10		1:2	100	12	97

[a] All data were obtained using 1.90 mmol of nitrile. [b] Isolated yields.

Since **I** performed well in this reaction, we screened other lanthanide amides **II**−**IV**[10] (Scheme 1) in the reactions with several substrates. All reactions were conducted with 5 mol % of ytterbium at 100 °C in the absence of solvent (Table 2).

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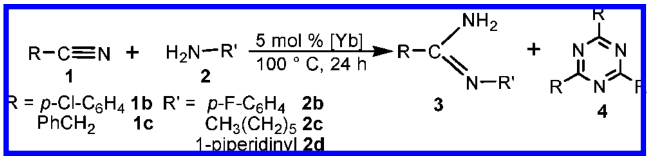
Table 2. Addition of Amines to Nitriles Catalyzed by Ytterbium Amides **I**−**IV**[a]



entry	1	2	product	amides[b] (%)			
				I	II	III	IV
1	**1a**	**2a**	**3aa**	88	90	55 (80[c])	45 (70[c])
2	**1b**	**2a**	**3ba**	83	84	70	20
			4b	0	0	0	35[d]
3	**1c**	**2b**	**3cb**	55	62	55	45
4	**1a**	**2c**	**3ac**	n.r.	n.r.	n.r.	0
			4a				30[d]
5	**1a**	**2d**	**3ad**	55	58	45	0
			4a	0	0	0	60[d]

[a] The reaction was performed by treating 1 equiv of nitrile with 2 equiv of amine. [b] Isolated yields. [c] 48 h. [d] The yield based on nitrile.

Inspection of Table 2 clearly revealed that **I** and **II** were the desired catalysts, displaying the best catalytic activity and selectivity giving monosubstituted amidines as the only products for all reactions tested. In general, the bimetallic amide **III** and amide **IV** were less active and required an extended period of reaction time for getting good yields (Table 2, entry 1). Quite interestingly, the product dependence on the amide complexes used were observed in some reactions (Table 2, entries 2, 4, and 5). For example, the addition reaction of **2a** to **1b** with **IV** gave a mixture of monosubstituted amidine and triazine in 1:1.7 mole ratio, while the same reaction with **I**(**II**) afforded only monosubstituted amidine **3ab** in 83(84)% yield (Table 2, entry 2); the reaction of **1a** with **2d** gave the amidine in 55% yield for **I** and 58% for **II**, and no triazine was detected for both cases, while the same reaction with **IV** gave triazine as the only product; the reaction of **1a** with **2c** by **IV** gave the triazine in 30% yield, whereas the same reaction by **I** and **II** went sluggishly. The different catalytic behavior observed between **I**(**II**) and **IV** might be attributed to the different coordinate environment around the center metal which leads to a difference in reactivity between the reactions of the active intermediate with amine and with nitrile (see Scheme 2).

Scheme 2. Proposed Mechanism for the Reaction of Nitriles with Amines

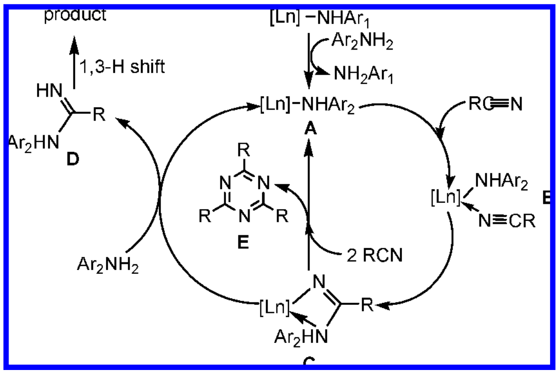
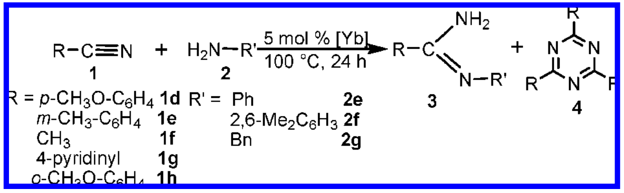


Table 3. One-Step Synthesis of Monosubstituted Amidines by **I**: Substrate Scope[a]



entry	1	2	product	% yield[b]
1	**1c**	**2a**	**3ca**	30 (75[d])
2	**1d**	**2a**	**3da**	92
3	**1a**	**2b**	**3ab**[c]	97
4	**1c**	**2b**	**3cb**	87[d]
5	**1d**	**2b**	**3db**[c]	98
6	**1e**	**2b**	**3eb**[c]	95
7	**1f**	**2b**	**3fb**	45 (75[d])
8	**1g**	**2b**	**4g**	95
9	**1a**	**2c**		trace
10	**1a**	**2e**	**3ae**	94
11	**1a**	**2f**	**3af**	91
12	**1a**	**2g**		trace
13	**1h**	**2b**		trace

[a] The reaction was performed by treating 1 equiv of nitrile with 2 equiv of amine under the given conditions. [b] Isolated yields. [c] 12 h. [d] Catalyst loading 10 mol %, 48 h.

According to the optimized conditions a range of other substrates were surveyed for the synthesis of monosubstituted amidines with **I** (Table 3). All tested aromatic nitriles which have electron-drawing or electron-donating groups at the meta and para position on the aryl ring, except 4-cyanopyridine, reacted smoothly with primary aromatic amines to give the corresponding monosubstituted aromatic amidines in isolated yields of 91−98%. The reaction with 4-cyanopyridine afforded triazine in 95% yield; no amidine was detected (Table 3, entry 8). The reaction with *o*-methoxybenzonitrile proceeded sluggishly (Table 3, entry 13). Aliphatic nitriles, such as **1c** and **1g**, showed much less activity. They reacted with **2b** to give the corresponding amidines in 55% and 45% yields, respectively (Table 2, entry 3, and Table 3, entry 7). The reactions with **2a** (Table 3, entry 1) were similar and required an extended period of reaction time and an increased catalytic loading for getting high yields (Table 3, entries 4 and 7). Apparently, the less active cyano group of aliphatic nitriles, in comparison with that of aromatic nitriles, retarded the reaction rate. The reaction of aromatic nitriles with aliphatic amines proceeded sluggishly, and only a trace of product was isolated (Table 3, entries 9 and 12). This may be attributed to much slower protonation reaction by aliphatic amines compared to that by aromatic amines, which was included in catalytic cycles (see the mechanism proposed, Scheme 2). All products were characterized by ^1H NMR and ^{13}C NMR to be amidines via 1,3-H shift and the structure of **3aa** was further confirmed by X-ray structural analysis (Figure 1). The crystal structure showed a double-bond character for the N(2)−C(1) bond with a distance of 1.290(3) Å.

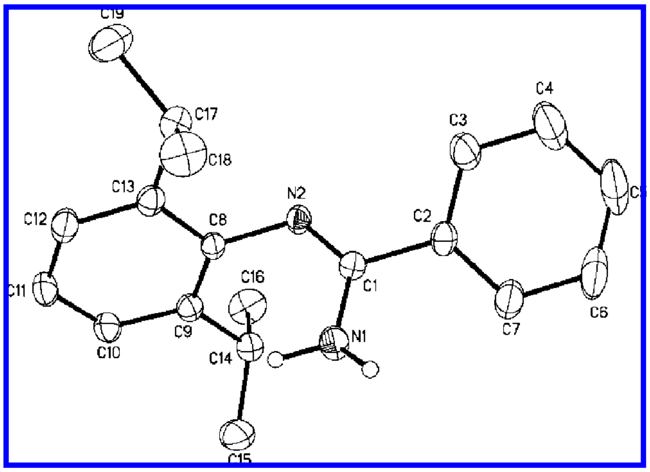


Figure 1. Molecular structure of **3aa**, drawn with 30% thermal ellipsoids.

The reaction mechanism was proposed as shown in Scheme 2. Reaction of an aniline with the lanthanide amide gave the new amido intermediate A through an acid−base reaction.[11] A nitrile then was coordinated to the center metal forming a complex B. An intramolecular insertion of amide to cyano of nitrile gave the corresponding intermediate **C** as reported previously.[12]

Intermediate **C** underwent protonation by amine to release the product and to generate the lanthanide amide active species **A**. When the reaction of intermediate **C** with additional nitrile is more favorable than that with amine, triazine **E** was produced as the main product.

In summary, we have developed an efficient protocol to the one-step synthesis of monosubstituted amidines in good to excellent yields via a nucleophilic addition of amines to nitriles catalyzed by ytterbium amides under solvent free conditions. The reactions of aromatic nitriles with aromatic primary amines proceed very well to give excellent yields. The present strategy can be viewed as a compensative method for the published intramolecular nucleophilic addition of amine to activated nitrile methods with $Ln(OTf)_3$ and/or SmI_2 as the catalysts,[3d,e] which frequently suffered from difficulty in synthesis of monosubstituted amidines. However, the reaction with aliphatic amines has not yet been successful. Efforts in this direction are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data; copies of ^1H NMR and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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