

Simple and Efficient Procedure for Synthesis of *N'*-Arylamidines Using Trimethylaluminum

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Amidines are an important class of compounds that have wide range of application in the fields of catalyst design,¹ material science,² medicinal chemistry and also shown the promising anti-inflammatory and analgesic activity.³⁻⁵ They are valuable synthons for synthesis of various heterocyclic compounds.⁶ In addition, recent studies have demonstrated their capacity to fix carbon dioxide.^{7,8}

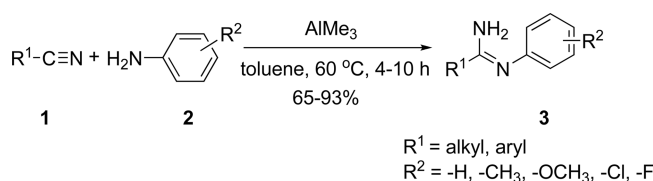
As a result of their importance, various methods have been reported in the literature for their synthesis. Traditionally, they are synthesized by the addition of amines to nitriles by Pinner reaction.⁹ Amidines are also synthesized by the condensation reaction of amines with amides,¹⁰ carboxylic acids¹¹ or orthoformate¹² in the presence of condensation agents such as POCl₃, P₂O₅, PCl₅ respectively. In the recent years, rare earth metal triflates and halides have found to be effective Lewis acids for promoting the amination of nitriles affording amidines in good yields.¹³

Organoaluminum compounds can easily reacts with various heteroatoms in organic molecules, particularly with oxygen and nitrogen, to generate 1:1 acid-base complexes.^{14,15} Aluminum derivatives has been reported for direct conversion of ester or acid to amides,^{16,17} synthesis of pyrazoles,¹⁸ aluminoisoxazoles,¹⁹ methylation of tertiary alcohols²⁰ and carbamates to amides.²¹

The synthesis of amidines from the reaction of nitrile and amine in the presence of AlCl₃ has been reported,²² however it requires longer reaction time and harsh reaction condition. In 1990, Garigipati reported the conversion of alkyl and aryl nitriles to unsubstituted amidines in a single step using methylchloroaluminum amide which prepared by addition of ammonium chloride to commercially available trimethylaluminum.²³ However, the scope of this procedure is limited only to the synthesis of unsubstituted amidines.

As a part of ongoing research on solution and solid-phase synthesis of small organic molecules, we have utilized aluminum-amide reagent which prepared from amine and trimethylaluminum. And this aluminum-amide reagent was utilized to introduce further diversity onto the core scaffold during release of product from resin-bound ester and carbamate to afford amides and ureas.²⁴ Here we wish to report a simple and efficient protocol for the synthesis of *N'*-arylamidines using nitrile, aryl amines and AlMe₃ (Scheme 1).

Initially, this research began with the finding that; when



Scheme 1



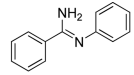

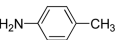
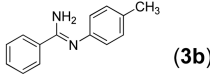


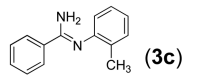

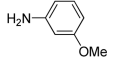
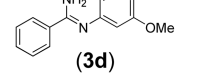

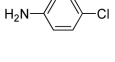
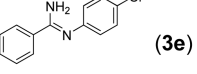


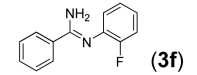

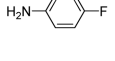
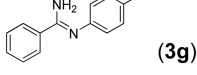

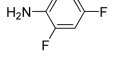
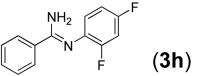

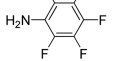
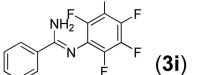
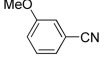

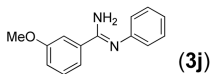


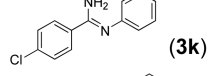
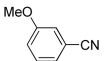
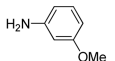
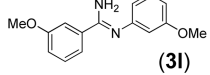


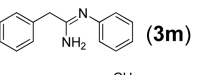


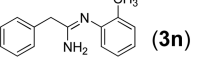

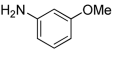
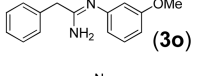

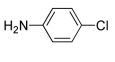
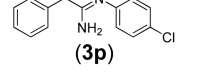

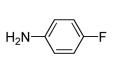
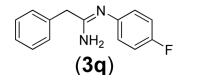

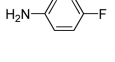
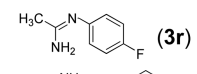

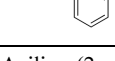
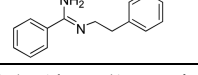
Table 1. Optimization of amidation reaction conditions

Entry	Amine:AlMe ₃ :Nitrile	Temp (°C)	Yield (%)
1	1:1:1	rt	30
2	2:0:1	60	NR
3	2:1:1	60	60
4	2:1.5:1	60	85
5	2:2:1	60	84

treated with dimethylaluminum amide reagent, the cyano substituent on the core structure was transformed to unexpected functional moiety, presumably an adduct which containing amine moiety by ¹H NMR and Mass analysis (data not shown here). To confirm this transformation, simple nitrile (benzotrile) was reacted with dimethylaluminum amide at room temperature to give the corresponding amidine in 30% yield (Table 1, entry 1). Encouraged with this result, various reaction parameters were tested such as amount of AlMe₃, stoichiometric mole ratio of reactants and temperature. This conversion didn't proceed in the absence of AlMe₃ (Table 1, entry 2). A little bit excess of both reagent (1.5-2.0 equiv.) and elevated reaction temperature (60 °C) were essential for full conversion of starting nitrile and give the desired amidine in high yield (Table 1, entry 3-5).

To study the scope and limitation of this procedure, variety of aryl amines in combination with aromatic and aliphatic nitriles were tested on the optimized reaction conditions. The reactivity of the substrate is relevant to the electronic effects of the substituent on the benzene ring of the aryl amine. Generally, unsubstituted aryl amines and those with and electron-donating substituents reacted with benzonitrile to afford the products in good yield (Table 2, entries 1-4).

Table 2. Synthesis of *N'*-arylamidines from nitriles and anilines using trimethylaluminum^a

Entry	Nitrile	Amine	Amidine	Yield ^c (%)
1			 (3a)	85
2			 (3b)	82
3			 (3c)	78
4			 (3d)	75
5			 (3e)	88
6			 (3f)	90
7			 (3g)	93
8			 (3h)	85
9			 (3i)	91
10			 (3j)	80
11			 (3k)	83
12			 (3l)	72
13 ^b			 (3m)	81
14 ^b			 (3n)	77
15 ^b			 (3o)	75
16 ^b			 (3p)	90
17 ^b			 (3q)	85
18 ^b			 (3r)	65
19				NR

^aReaction conditions: Aniline (2 equiv.), AlMe₃ (1.5 equiv.), nitrile (1 equiv.) and toluene (3 mL), 60 °C, 4 h. ^bAniline (2 equiv.), AlMe₃ (1.5 equiv.), nitrile (1 equiv.) and toluene (3 mL), 60 °C, 10 h. ^cIsolated yield.

The aryl amines with electron-withdrawing substituents (chloro and mono, di and pentafluoro) gave the corresponding products in better yields (Table 2, entries 4-9). Reactions of the aryl amine with ortho-substituent also proceeded to afford the product in good yield (Table 2, entry 3). The substitution pattern as well as the electronic effect of substituted benzonitrile did not have any significant effect on the yields of the product (Table 2, entries 10-12). Aliphatic nitriles also found to be good substrate for this conversion and transformed to corresponding amidines when reacted with variety of aromatic amines (Table 2, entries 13-17), although prolonged reaction time (10 h) was required. In addition, simple acetonitrile reacted well with the 4-fluoroaniline to afford the desired product in 65% yield (Table 2, entry 18). Unfortunately, the reaction did not proceed when aliphatic amines were used and the starting material was recovered (Table 2, entry 19).

In conclusion, we have developed simple and efficient procedure for the synthesis of *N'*-arylamidines using trimethylaluminum, nitriles and aryl amines under mild condition. Aliphatic, aromatic nitriles were reacted well with a variety of aromatic amine to afford corresponding amidines in good to high yields.

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Supporting Information. Experimental details, general information and characterization data for all compounds and copies of ¹H and ¹³C NMR spectra.

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