International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Synthesis of Amidines Via Nucleophilic Addition of Amine to Nitrile

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Abstract: ***Amidines are important classes of nitrogenous compounds, which have been widely used as antibiotics, diuretics, antiphlogistic drugs, anthelmintics, and acaricides. They represent an important pharmacophore in modern drug discovery. Many of the top-selling pharmaceuticals feature an amidine as a key structural component. They serve as key precursors in the preparation of many nitrogenous compounds of biological interest and play an essential role in the development of enzyme inhibitors, receptor ligands, and antimicrobial drugs. It can be found in DNA and RNA binding diamidine diminazene, Acid Sensing Ion Channel (ASIC) inhibitor, muscarinic agonists for the treatment of Alzheimer's disease, platelet aggregation inhibitors. Many research efforts have been carried out worldwide to develop efficient and sustainable synthetic approaches for the preparation of amidines. Consequently, numerous methods involving Lewis acids, transition metal catalysts have been reported for the preparation of amidines via the direct nucleophilic addition of amine to nitrile. In this paper, we summarize the general methods for the synthesis of amidine from nitrile and amine. The emphasis has been given in the use of Lewis acids and transition metal catalysts, highlighting recent advances in green synthetic strategies. The synthesis of a few amidines by the direct nucleophilic addition of amines to nitriles using NaH as a reagent has been discussed.***

Keywords: Benzonitrile, Aniline, Sodium hydride, Benzamidines, Lewis acid

1. Introduction

Amidines are an important functional group containing two nitrogen atoonms at 1, and 3-positions characterized by an imine nitrogen atom and singly bonded to a second nitrogen atom [1]. Its general formula RC(=NH) NR/2 (where R and R/ can be hydrogen atoms or various organic groups). They are strongly basic and highly polar, which allows them to easily bind to other molecules and form complexes. The specific Nitrogen-Carbon-Nitrogen (N-C-N) backbone provides a positive charge and excellent hydrogen-bonding capabilities, making them valuable structural components in biology and chemistry.

Amidines exhibited many biological activities including antibiotics, diuretics, antiphogistic drugs, anthelmintics, and acaricides [1,2]. They represent an important pharmacophore in modern drug discovery. In fact, many of the top-selling pharmaceuticals feature an amidine as a key structural component [3]. It can be found in DNA and RNA binding diamidine diminazene [4], Acid Sensing Ion Channel (ASIC) inhibitor [5], muscarinic agonists for the treatment of Alzheimer's disease [6], platelet aggregation inhibitors [7], and recently, used as serine protease inhibitors [8], for a few examples. Many compounds containing N-arylamidines have shown promise as treatment for inflammation and pain [9]. Amidines are also serve as ligands for transition metals due to their unique structure [10]. Recent studies revealed that amidine substrates have capability to fix carbon dioxide [11]. In synthetic organic chemistry, N-arylaminines have been used as valuable precursors for the preparation of biologically important azaheterocycles [12] such as imidazoles [13], benzimidazoles [14], quinazolines [15,16], pyrimidines [17], triazines [18], triazoles [19] etc.

Several synthetic methods have been developed, in which the nucleophilic addition of amine to nitrile [20] is the most convenient and atom-economic method. This one-step protocol for the synthesis of N-substituted amidines from nitriles and amines can be realized only if the nitriles are activated either by electron-withdrawing groups or by employing harsh conditions such as-high temperature or pressure in the presence of Lewis acids including anhydrous $AlCl_3$ [21], $ZnCl_2$ [21], SmI_2 [22], Ln(III) salt [23], and Ytterbium amide [24], or with aluminum amides [25] for unactivated nitriles.

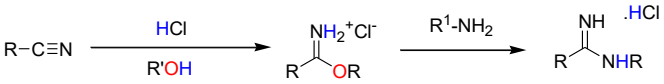
Recently, new synthetic approaches that do not require activation of nitrile with a stoichiometric reagent, based on a transition metal catalyst were developed [26-29]. Larhed and co-workers [28] have reported the palladium catalyzed synthesis of *N*-arylamidines from aryltrifluoroborates and cyanamides under microwave irradiation conditions. Recently, Bert et al. [29] have developed an interesting procedure for the synthesis of N-substituted amidines from arylboronic acids, isocyanides, and anilines catalyzed by palladium-catalyst under oxidative reaction conditions. The synthesis of monosubstituted amidines could also be achieved from amines and nitriles in the presence of CuCl [30]. However, 1.2 equivalent of CuCl to amines is required in this process. Thus, the search for a new protocol for the synthesis of amidines via transition metal catalyzed strategy under sustainable reaction conditions would be of high importance. In this work, we summarize the general methods for the synthesis of amidine derivatives, highlighting recent advances in green synthetic strategies using Lewis acids and transition metal catalysts. The synthesis of a few amidines by the direct nucleophilic addition of amines to nitriles has been discussed.

2. General methods for the synthesis of amidines

The Pinner reaction is an important classical method for the

synthesis of amidines from nitriles [31]. In this reaction, a nitrile is first treated with dry hydrogen chloride in an anhydrous alcohol to form the corresponding imidate salt, commonly called a Pinner salt. The Pinner salt then undergoes nucleophilic substitution with ammonia or an amine to give the desired amidines (Scheme 1). The reaction proceeds through acid-catalysed activation of the nitrile group, followed by addition of alcohol to generate the imidate intermediate. Subsequent treatment with ammonia, primary amines, or secondary amines affords amidines or their substituted derivatives. This method is widely used because it provides a direct route to amidines from readily available

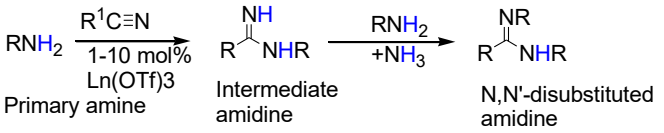
Pinner Reaction:



Scheme 1. Synthesis of amidines using Pinner reaction.

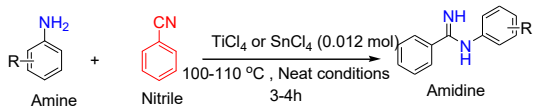
The Pinner reaction is one of the most useful methods for amidine preparation because it tolerates a wide range of nitrile substrates. It is especially valuable in heterocyclic and medicinal chemistry, where amidines serve as key intermediates and pharmacophores. Literature sources describe the method as a standard and reliable approach for amidine synthesis. Many modified Pinner reactions using Lewis acids have been developed for the preparation of amidines. A few recent updates in the amidine synthesis have been discussed below:

John H. Forsberg et al., observed that catalytic amounts of anhydrous lanthanide (III) trifluoromethanesulfonates (1–10 mol%) effectively promote the synthesis of *N, N*-disubstituted amidines by accelerating the direct reaction of amines to nitriles (Scheme 2) [32]. The strongly electrophilic lanthanide ions (Ln^{3+}) function as efficient Lewis acid catalysts, activating the nitrile group toward nucleophilic attack through enhanced polar–dipole interactions. Initially, the reaction of a primary monoamine with a nitrile produces an N-substituted amidine intermediate. This intermediate subsequently reacts with a second molecule of the amine to form the corresponding N, N′-disubstituted amidine in excellent yields, often exceeding 90%. The Ln^{3+}-catalyzed methodology offers a clean, efficient, and high-yielding synthetic route under mild reaction conditions while avoiding the explosive hazards associated with conventional lanthanide perchlorate catalysts.



Scheme 2. Synthesis of amidines using lanthanide (III) trifluoromethanesulfonates.

In 20212, Patil and Mahulikar reported that *N*-aryl benzamidines can be synthesized using $TiCl_4$- or $SnCl_4$ as Lewis catalyst under solvent-free through the coupling of amines with nitriles (Scheme 3). In this method, the nitrile is activated by the Lewis acid catalyst, increasing its electrophilicity and facilitating nucleophilic attack by the amine [33]. The reaction is carried out at 100–110 °C for 3–4 hours, followed by simple neutralization and purification to obtain the desired amidine products. Both $TiCl_4$ and $SnCl_4$ provide moderate to good yields. However, $TiCl_4$ exhibits superior catalytic performance over SnCl4. The protocol avoids the use of expensive samarium reagents and organic solvents, making it a simple, economical, and environmentally friendly approach for amidine synthesis.

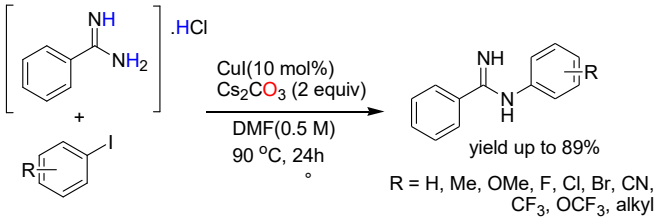


Lewis acid: $TiCl_4$: R = H (79%), 2-Me (59%), 4-Me (64%), 4-F (78%), 4-Cl (66%), 4-Br (81%), 3,4-Cl_2 (76%)
Lewis acid: $SnCl_4$: R = H (68%), 2-Me (64%), 4-Me (61%), 4-F (69%), 4-Cl (60%), 4-Br (65%), 3,4-Cl_2 (69%)

Scheme 3. Synthesis of amidines using TICl4 or SnCl4

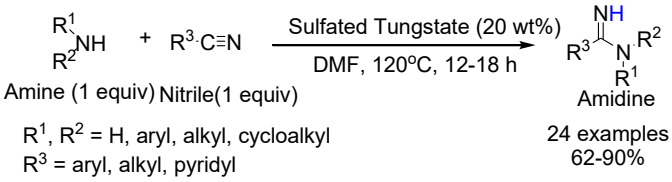
Recently, Stephen L. Buchwald et al. reported an efficient and highly selective method for the preparation of N-monoarylation of both aryl and alkyl amidines using palladium catalyst [34]. The reaction employs a catalyst system consisting of $Pd_2(dba)_3$ and the bulky, electron-rich bi-aryl phosphine ligand L2 (Brett-Phos), which enables the rapid coupling of amidine hydrochlorides with a broad range of aryl bromides, chlorides, and triflates. The reaction is carried out in tert-butanol (t-BuOH) using caesium carbonate (Cs_2CO_3) as the base. Under these optimized conditions, the desired N-monoarylated amidines are obtained in excellent yields (70–93%) with high selectivity, while effectively suppressing the formation of undesirable diarylated by-products. The use of the BrettPhos ligand plays a crucial role in promoting efficient monoarylation by enhancing catalyst activity and controlling reaction selectivity. The versatility of this methodology was further demonstrated through a one-pot cascade synthesis of quinazoline derivatives. After the initial palladium-catalysed N-arylation step, an aldehyde was added directly to the crude reaction mixture, triggering an intramolecular cyclization followed by oxidative aromatization. This sequential transformation provided quinazoline heterocycles efficiently in a single operational step without the need for intermediate purification, highlighting the practical and synthetic utility of the developed protocol.

In another attempt, Jon C. Antilla and co-workers developed a ligand-free, copper-catalyzed protocol for the synthesis of monoarylated amidines using 10 mol% CuI and 2 equivalents of Cs_2CO_3, providing an economical alternative to Pinner-type reactions and palladium-catalyzed methods (Scheme 4) [35]. Optimization studies showed that DMF is the optimal solvent for benzamidine hydrochlorides at 90 °C, while MeCN affords superior yields for acetamidine hydrochlorides at 80–90 °C of 24h reaction time. The reaction proceeds with high selectivity for *N*-monoarylation and accommodates a broad range of aryl iodides bearing both electron-donating and electron-withdrawing substituents, giving isolated yields of up to 89%. Furthermore, the methodology tolerates sterically hindered ortho-substituted aryl iodides and heterocyclic amidines such as isonicotinamidine, making it a robust and practical approach for synthesizing monoarylated amidines and bioactive diaryl guanidine analogues.



Scheme 4. Synthesis of substituted amidines from benzamidines and aryl iodide catalysed by CuI.

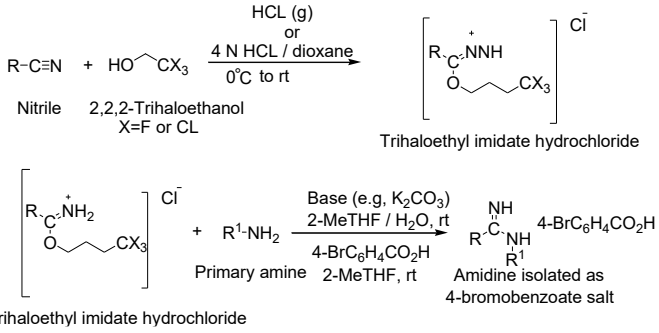
Krishnacharya G. Akamanchi and co-workers, developed an efficient and mild protocol for the synthesis of amidines through the nucleophilic addition of amines to nitriles using 20 wt% sulphated tungstate as a non-corrosive, stable, and reusable heterogeneous solid acid catalyst in DMF at 120 °C (Scheme 5) [36]. The method achieves 100% atom economy by activating inactivated nitriles without reducing the nucleophilicity of the amines. It exhibits a broad substrate scope, accommodating aromatic, aliphatic, heterocyclic, and secondary amines, while ammonium acetate enables the synthesis of unsubstituted amidines. The catalyst also demonstrates excellent chemoselectivity by preserving reactive functional groups such as aliphatic chlorine atoms. After 12–18 h of reaction, the protocol affords the desired amidines in isolated yields of up to 90%, with the added advantage of simple catalyst filtration and recovery.



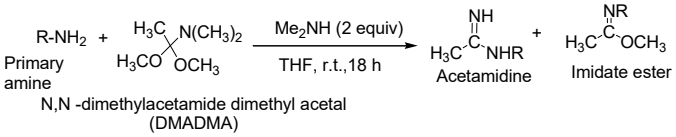
Scheme 5. Synthesis of amidines using sulphated tungstate as catalyst.

Caron et al. (2010) reported that amidines can be synthesized efficiently using 2,2,2-trifluoroethyl and 2,2,2-trichloroethyl imidates as key intermediates [37]. The corresponding nitrile is first converted into a trihaloethyl imidate hydrochloride through the Pinner reaction using hydrochloric acid and trihaloethanol. The activated imidate then undergoes nucleophilic substitution with a primary amine under mild reaction conditions to afford the desired amidine derivative (Scheme 6). The trihaloethyl group acts as an excellent leaving group, resulting in improved reactivity and high product yields. In several cases, the amidine products were isolated as p-bromobenzoate salts with high purity. This method is simple, cost-effective, and suitable for the synthesis of a wide range of amidine derivatives under mild conditions.

Harjani et al. (2011) reported that acetamidines can be synthesized efficiently by the condensation of primary amines with *N, N*-dimethylacetamide dimethyl acetal (DMADMA) [38]. In this reaction, the primary amine attacks the electrophilic carbon of DMADMA to form the desired acetamidine derivative (Scheme 7). The study showed that the reaction selectivity is significantly improved by carrying out the condensation in the presence of excess dimethylamine (Me_2NH), which suppresses the formation of the undesired imidate ester by-product. The optimized method proceeds under mild conditions, provides good to excellent yields, and eliminates the need for extensive purification. This protocol is compatible with a wide range of primary amines, including PEG-containing substrates, making it a practical and efficient approach for the synthesis of acetamidines.



Scheme 6. Synthesis of amidines using 2,2,2-trifluoroethyl and 2,2,2-trichloroethyl imidates as key intermediates.



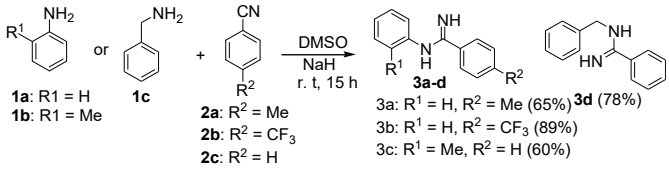
Scheme 7. Amidines from primary amines and N-dimethylacetamide dimethyl acetal.

3. Result and Discussion

In this work, we synthesized a few amidine derivatives via the direct nucleophilic addition of amine to nitrile using NaH as a regent at room temperature. In general, synthesis of amidines via nucleophilic addition of an amine to nitrile has been achieved by using different Lewis acids such as $AlCl_3$, $SnCl_4$, $TiCl_4$, Ln-based Lewis acids etc.. In this Lewis acid based protocol, in many cases a high temperature is required for the direct addition of an amine to an un-activated nitrile. Thus, the protocol is not general and restricted to the activated nitrile for the preparation of amidines. Recently, a few transition metal catalysts have been reported for the preparation of amidines via direct condensation of amines to nitriles. The mainstream of research in this area focuses on metals such as Pd and Cu which suffer from high costs and toxicity.

This work focuses on the synthesis of amidines from direct nucleophilic addition of amine to nitrile using sodium hydride as reagent (Scheme 8). The reaction proceeded in DMSO solvent at room temperature without use of transition metal or other catalysts, leading to high yield of amidine products. We started our investigation using aniline and 4-methyl benzonitrile. We screened many solvents like water, DMF, CF_3CH_2OH and DCM. The yield of the amidine has been achieved to 65% using DMSO as solvent and 1.2 equiv. of NaH (60%) at room temperature. Other amines tested such as *ortho*-methyl aniline and benzylamine were well tolerated under the reaction conditions. Benzonitriles with electron donating such as *p*-methyl benzonitrile and electron-withdrawing such as *para*-triflurometlhyl benzonitrile were well tolerated in the reaction conditions and leading to benzamidines in high yields. This process benefits from mild reaction conditions, easy work-up procedure, transition

metal-free catalyst, and high yields of the products, making it ideal protocol for the synthesis of benzamidines.



Scheme 8. Synthesis of amidines using NaH as reagent in DMSO.

4. Procedure for the Preparation of Amidine from benzonitrile and amine

In a dry round bottom flask (50 ml) equipped with a magnetic stir bar was charged with NaH (480 mg, 60%, 1.2 equiv.). The flak was sealed with a rubber septum and 5 ml DMSO was added via a syringe. The resulting suspension was cooled with an ice-bath prior to the addition of the carbonitrile (10.0 mmol, 1.0 equiv.) and aniline (12.0 mmol, 1.1 equiv.). The mixture was kept at 0 oC for 30-40 min and then stirred for overnight (15 hr) at room temperature. The septum was removed, and ice-water (20 ml) was added with vigorous stirring. The aqueous layer was extracted with 20 ml ethyl acetate (EtOAc) of three times. The combined EtOAc was washed with water and then with brine. The combined organic layers (EtOAc) was dried over MgSO4, filtered and concentrated. The residue was recrystallized from alcohol to give white solid.

***N*-phenyl-4-methylbenzenecarboximidamide (3a):**
4-methylbenzonitrile (M. W= 117): 1.17g (10 mmol, 1.0 equiv.); Aniline (M.W = 93): 1.023 gm (11 mmol, 1.1 equiv); NaH: (480 mg, 60%, 1.2 equiv.); DMSO: 5 ml, 15 hrs.

Experimental data of 3a: White solid; yield: 65%; mp: 88-89°C. UV–Vis (MeCN): λ_{max} = 255.0 nm (Abs = 0.835). 1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 4.79 (br s, 2H), 7.00 (d, J = 8.4 Hz, 2H), 7.06-7.09 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H). 13C NMR (100 MHz, DMSO): δ = 21.4, 121.8, 122.9, 126.8, 129.2, 129.5, 132.9, 140.8, 149.7, 154.9.

***N*-Benzyl-4-(trifluoromethyl)benzenecarboximidamide (3b):**
Reaction conditions: 4- Trifluromethyl benzonitrile (M. W= 172): 1.72 gm (10 mmol. 1.0 equiv); Aniline (M.W = 93): 1.023 gm (11 mmol, 1.1 equiv); NaH:(480 mg, 60%, 1.2 equiv.), DMSO: 5 ml; room temperature, 15 hrs
Experimental data of 3b: White solid; Yield: 89% (124 mg), mp: 100-101°C. UV–Vis (MeCN): λ_{max} = 235.0 nm (Abs = 0.564); 1H NMR (400 MHz, DMSO): δ = 6.57 (br s, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 6.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 8.08 (s, 2H).

***N*-(o-tolyl)benzenecarboximidamide (3c):**
Reaction conditions: Benzonitrile (M. W= 103): 1.03 gm (10 mmol. 1.0 equiv); 2-Methylaniline (M.W = 107): 1.18 gm (11 mmol, 1.1 equiv); NaH:(480 mg, 60%, 1.2 equiv); DMSO: 5 ml, room temperature, 15 hrs.
Spectral data of 3c: Yield: 60% (63 mg), Color less solid; mp 105-107 °C. 1H NMR (400 MHz, DMSO): δ = 2.07 (s, 3H), 6.02 (br s, 2H), 6.73 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.42-7.50 (m, 3H), 7.97-8.00 (m, 2H).

***N*-Benzylbenzenecarboximidamide (3d)**:
Reaction conditions: Benzonitrile (M. W= 103): 1.03 gm (10 mmol. 1.0 equiv); Benzylamine (M.W = 107): 1.18 gm (11 mmol, 1.1 equiv); NaH:(480 mg, 60%, 1.2 equiv.); DMSO: 5 ml, 15 hrs.

Spectral data of 3d: Yield: 78% (82 mg), White solid, mp 69-70 °C. 1H NMR (400 MHz, DMSO): δ= 4.36 (s, 2H), 6.53 (br s, 2H), 7.21 (d, J = 7.2 Hz, 1H), 7.30 (t, J = 8.0 Hz, 2H), 7.32-7.43 (m, 5H), 7.82-7.85 (m, 2H).

5. Conclusion

In summary, this work highlights the versatility and synthetic importance of amidines through a comprehensive review of established and contemporary methodologies for their preparation. Classical approaches, including the Pinner reaction, together with modern Lewis acid-, transition metal-, and heterogeneous catalyst-mediated protocols, demonstrate the broad applicability of amidine synthesis under diverse reaction conditions. Experimentally, substituted benzonitriles were successfully employed as precursors for the preparation of amidine derivatives through direct reaction with aniline under basic conditions. The isolated products were obtained as white solids and characterized by melting point determination and UV–visible spectroscopy, while comparison with literature spectral data supported their structural assignment. The results demonstrate that substituted aromatic nitriles serve as effective substrates for amidine synthesis and further emphasize the value of amidine scaffolds as versatile intermediates in organic synthesis and medicinal chemistry. Continued development of efficient, sustainable, and broadly applicable synthetic methodologies is expected to expand the utility of amidine derivatives in pharmaceuticals, catalysis, and functional materials.

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