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Synthesis of *N*-substituted aryl amidines by strong base activation of amines

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ABSTRACT

We describe an efficient method for the direct preparation of *N*-substituted aryl amidines from nitriles and primary amines. The protocol employs activation of amines by a strong base and provides greater access to a pharmaceutically relevant functional group. This synthetic approach tolerates deactivated nitriles, nitriles with competing substitution sites, and aryl amines.

Introduction

Amidines are a class of pharmaceutically relevant small molecules, in addition to being important building blocks for organic chemical synthesis and having a number of applications in materials chemistry.[1–13] Benzamidine, the simplest aryl amidine, is a competitive, specific inhibitor of trypsin. Its derivatives act as antimicrobial and antiparasitic agents and have been used for the treatment of a variety of diseases, including pneumocystis pneumonia, antimony-resistant leishmaniasis, and human African trypanosomiasis.[14–20] Amidines are known to bind nucleic acids; such action is crucial to their mechanism of action in some disease models.[21–24] This property has been known for some time, and modulation of long, amidine-containing compounds has been proposed for sequence-specific targeting of both RNA and DNA.[25] In addition to being evaluated for anti-inflammatory, analgesic, and anti-cancer properties, amidine-containing moieties continue to be important in the search for treatments against Alzheimer's disease, malaria, and myotonic dystrophy type 1 (DM1).[16,26–31]

Recently, investigations of pentamidine (**1**, Fig. 1) and related analogs revealed that *N*-substituted aryl bis-amidines may be especially relevant to the development of effective therapeutics against myotonic dystrophy type 1, as a recent study identified the triaminotriazine-containing bis-amidine derivative **2** as a lead.[22,31] These findings, in conjunction with preceding literature on amidines, point to the importance of *N*-substituted amidines in pharmaceutical chemistry.

Several amidine-containing moieties possess important pharmaceutical properties in their own right. Tetrahydropyrimidine derivatives (e.g., **3**) display specific m1 receptor agonist activity and can act as neuromuscular blocking agents.[27,32,33] Benzimidazole derivatives have been investigated for their anthelminthic and antifungal activity; a new class of benzimidazole derivatives (e.g., **4**) has been identified as antimalarial lead compounds.[29,34–36] Both motifs can be considered *N*-substituted amidines. This pharmaceutical salience is the impetus for studying new examples of *N*-substituted amidines and examining methods for amidine synthesis.

Creation of new *N*-substituted amidines for study necessitates functionalization of the amidine group. Direct addition of nitriles and amines to form amidines is not possible; several strategies have been described to overcome this synthetic obstacle.[37–44] All possess limitations for use in *N*-substituted amidine synthesis, including poor synthetic efficiency, time and material economy, or starting material compatibility. Methods employing transition elements or metals have an added disadvantage when considering environmental impact.[40–42]

Preparation of unsubstituted amidines under basic conditions has been described, but the approach is not well studied.[16,45,46] Creation of a nucleophile by strong base activation of an amine presents the possibility of preparing a wider range of *N*-substituted

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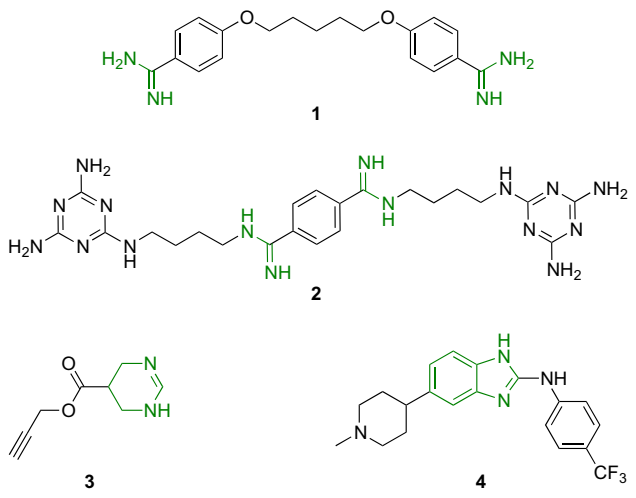


Figure 1. Amidines and amidine-containing moieties continue to be pharmaceutically relevant in studies of DM1, Alzheimer's disease, and malaria.

amidines in less synthetic steps and without the use of transition elements or metals. Khanna et al. reported the use of strong bases to activate an aniline derivative;[47] however, the method's compatibility with a range of starting materials, chemoselectivity, and synthetic efficiency are in general not well known. Here, we outline a simple protocol for preparing *N*-substituted aryl amidines under basic conditions and use it to synthesize a series of representative amidine targets in an effort to delineate these important properties. We further demonstrate that bisamidines and larger, amidine-containing moieties such as tetrahydropyrimidines and benzimidazoles are accessible via this method.

Results and discussion

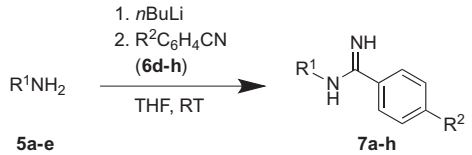
Molecules were chosen to demonstrate the feasibility of creating a functionalized amidine group that can be incorporated into the synthesis of pharmaceutically-relevant, amidine-containing moieties. To this end, the first series of targets examined amidine accessibility using a range of amines and nitriles (Table 1). At room temperature, primary amines (**5a**–**d**) were deprotonated with *n*-BuLi before addition of benzonitrile (**6d**); subsequent acidic work up and column purification afforded the desired amidines (**7a**–**d**) in good yields (60–80%) as their HCl salts. This approach was conducive to amidine preparation even with less reactive aryl amines (**5a**–**b**). Yields via this method exceeded those typical of the Pinner synthesis, and even some methods utilizing transition elements or metal catalysis. Mono-substituted aryl amidines (**7a**–**h**) are readily accessible, further overcoming limitations of synthesis via transition elements and/or metals.[40,41]

Under the same conditions, a series of aryl nitriles (**6e**–**h**) were added to the anion of 3-phenylpropylamine (**5e**). The products (**7e**–**h**) were obtained in substantive yields (40–60%), with deactivated nitriles (**6e**–**f**) giving comparable amounts of amidine to activated nitriles (**6g**–**h**). Though these yields are not markedly better than other established routes of preparation via acidic conditions, the array of compatibility with nitriles is noteworthy. Additionally, amidine formation by this method proceeds readily despite the presence of a competing nucleophilic aromatic substitution site on the nitrile (entry **g**). Mono-substituted amidines (**7e**–**h**) remain readily accessible, a feature of our protocol that overcomes limitations of amidine synthesis via lanthanide (III) triflates.[40,41]

Having explored the use of primary monoamines and mono-amidine formation using a primary diamine, we sought to apply this protocol to the creation of bis-amidines. For this purpose, we examined a series of diamines as substrates and generated the corresponding amidines, including one with a core reminiscent of the pharmaceutically-relevant structure (**2**) described by Wong et al. (Table 2).[31]

Serial amidine formation is possible via the method described, as two rounds of deprotonation and subsequent benzonitrile addition give the respective bis-amidine for both alkyl and aryl amines. The use of 1,4-phenylenediamine (**8a**) affords the para-bis-amidine (**9a**) in high yield (87%); however, use of 1,2-phenylenediamine yielded a mixture of the desired bis-amidine **9c** and minor

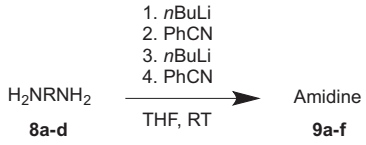
Table 1
Amidines prepared directly via addition of nitriles to activated amines

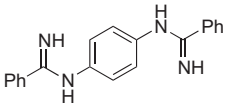
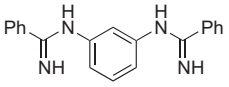
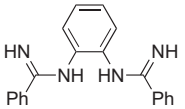
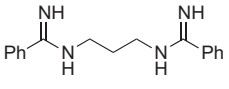
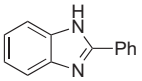
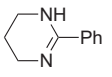


Entry	R^1	R^2	Yield[a] (%)
a	*p*-NH_2Ph	H	62
b	Ph	H	69
c	CH_2Ph	H	77
d	$(CH_2)_4$Ph	H	81
e	$(CH_2)_3$Ph	OMe	44
f	$(CH_2)_3$Ph	Me	52
g	$(CH_2)_3$Ph	F	58
h	$(CH_2)_3$Ph	CF_3	50

[a] Isolated as the HCl salt.

Table 2
Bis-amidines and cyclic amidines are accessible via the same method



Entry	R	Product **9**	Yield (%)
a	*p*-C_6H_4		87[a]
b	*m*-C_6H_4		32[a]
c	*o*-C_6H_4		34[a]
d	$(CH_2)_3$		50[a]
e	*o*-C_6H_4		32[a,b]
f	$(CH_2)_3$		60[a,b]

[a] Isolated as the HCl salt.
[b] Step 4 omitted.

amounts of benzimidazole derivative **9e**, likely through the transamination mechanism described by Gupta et al.[48] Analogously, use of 1,3-diaminopropane (**8d**) yielded the desired bisamidine **9d** in addition to the cyclic tetrahydropyrimidine product **9f**. Both **9e** and **9f** could be prepared preferentially by omission of the second addition of PhCN. The yield via our method for such cyclic species is comparable to several literature methods for access of the same species.[29,34,36] Thus large, cyclic, amidine-containing moieties remain synthetically accessible by our protocol, which also provides sufficient control over bis-amidine formation to allow for asymmetric synthesis where desired (albeit with less efficiency in cases where intramolecular transamination occurs readily).

Conclusion

The salience of *N*-substituted amidines to pharmaceutical chemistry is well established, and their synthetic accessibility continues to be relevant to the search for cures against a large number of human diseases. This project describes and studies a simple approach to the preparation of *N*-substituted amidines as an alternative to methods utilizing nitrile activation by acidic conditions or electron withdrawal, transition elements, and/or metals. Importantly, the vast majority of amidine targets in this study were obtained in yields greater than 40%, often much greater, using 1:1 ratios of starting materials and reaction times of 24 h at room temperature. Throughout the study, the method was compatible with a wider range of starting materials than typically allowed by other synthetic approaches, and permitted access to hitherto undescribed amidine species (**7d**–**h**, **9d**) as well as previously described but poorly characterized amidine species (**9a**–**c**).[49] This protocol of amidine preparation by strong base activation of amines, as well as further exploration of the complimentary Khanna method,[47] should make accessible a range of new *N*-substituted amidines for study against a variety of human diseases.

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Supplementary data

Supplementary data (experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra of all amidines) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.029.

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