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Synthesis of substituted aryl amidines from aminoacetonitriles

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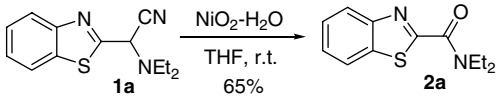
Abstract—Aryl aminoacetonitriles are oxidized by NiO_2–H_2O or MnO_2 in the presence of a wide range of NH_2-containing compounds to afford aryl amidines, presumably via iminium intermediates. A 'one-pot' procedure for the preparation of heteroaryl amidines from *N*-containing heteroaryl halides through a process comprising sequential S_NAr substitution and oxidation has also been developed.

Substituted aryl- and heteroaryl amidines are of interest as synthetic targets[1] and as structural elements with utility in drug design.[2] There is a dearth of simple and efficient methodologies for accessing highly substituted aryl amidines. Currently, the documented aryl amidine synthesis has been limited to the coupling of an amine with an imidoyl derivative[3] or the reaction with an iminium intermediate,[4] both of which usually originated from the corresponding amide. In this report, we would like to describe the scope of a mild and novel protocol to prepare *N*,*N*,*N*′-tri-substituted aryl- or heteroaryl amidines from 2-substituted aminoacetonitriles and NH_2-containing compounds that has been optimized into a practical and convenient one-pot procedure.

We have previously reported the formation of secondary amides via oxidation of an aminoacetonitrile derivative with NiO_2–H_2O under neutral conditions, as summarized in Scheme 1.[5] Several potential mechanistic pathways were proposed for this transformation in our initial communication and while the exact mechanism was not fully elucidated, a pathway involving a stabilized iminium cation, represented by **3** in Figure 1, was suggested. We hypothesized that if the iminium **3** was indeed an intermediate, it should be susceptible to interception by exogenous nucleophiles. Of particularly interest, the addition of an amine derivative provided the potential for a synthesis of substituted amidines. In order to examine this process, the *N*,*N*-diethylaminoacetonitrile **1a** was exposed to an excess of both NiO_2–H_2O and *n*-propylamine in THF at room temperature.



Scheme 1.

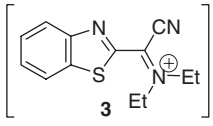


Figure 1.

As summarized in Scheme 2, the major product isolated was the amidine **4a**, obtained in 84% yield, as determined by LC–MS, with only small amounts of the amides **2a** (4%) and **5a** (8%) detectable. This confirmed that intermediate **3** could be trapped by a primary amine to form a *N*,*N*,*N*′-tri-substituted amidine and prompted a broader survey of reaction participants in order to define the scope and utility of the procedure.

Table 1 summarizes the results of these studies that demonstrate the generality of this process for the

Keywords: Aryl amidine; Heteroaryl amidine; Condensation–oxidation; Aminoacetonitrile; Nickel peroxide; Manganese oxide.
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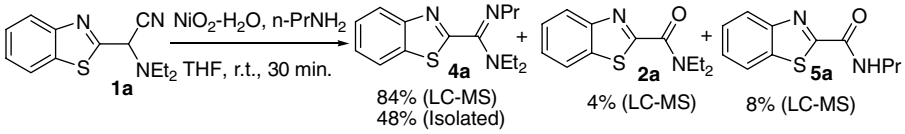
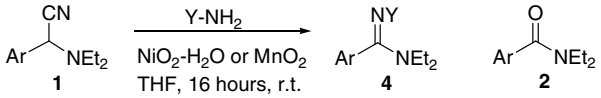


Scheme 2.

Table 1. The oxidation of heteroaryl aminoacetonitriles using NiO_2–H_2O or MnO_2 in the presence of amines to afford amidine derivatives



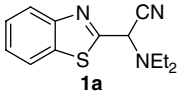
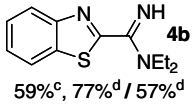
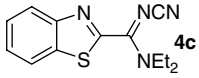
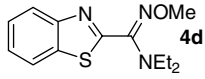
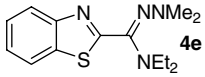
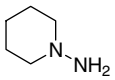
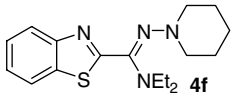
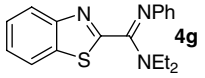
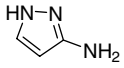
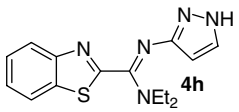
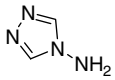
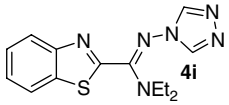
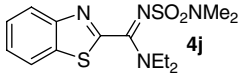
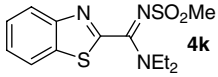
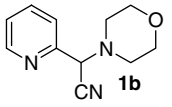
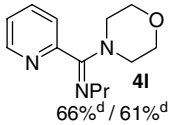
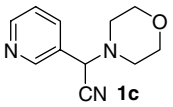
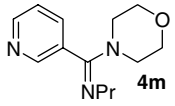
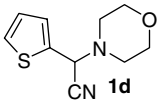
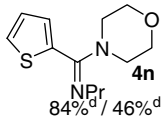
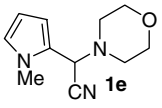
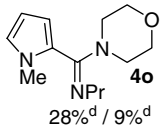
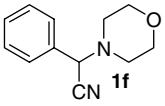
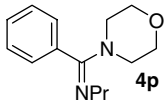
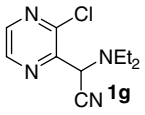
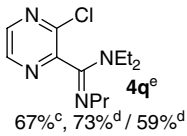
Entry	Y–NH_2	1	Product[a,b] yield by using NiO_2–H_2O/MnO_2
1	NH_4OH		 59%[c], 77%[d] / 57%[d]
2	NC–NH_2	**1a**	 64%[c], 51%[d] / 58%[d]
3	MeO–NH_2, HCl salt	**1a**	 12%[c], 15%[d] / 44%[d]
4	Me_2N–NH_2	**1a**	 35%[c], 46%[d] / 57%[d]
5		**1a**	 50%[d] / 54%[d]
6	Ph–NH_2	**1a**	 62%[c], 41%[d] / 25%[d]
7		**1a**	 38%[d] / 23%[d]
8		**1a**	 14%[d] / 16%[d]
9	Me_2NSO_2–NH_2	**1a**	 8%[d] / 12%[d]
10	$MeSO_2$–NH_2	**1a**	 18%[d] / 26%[c], 36%[d]

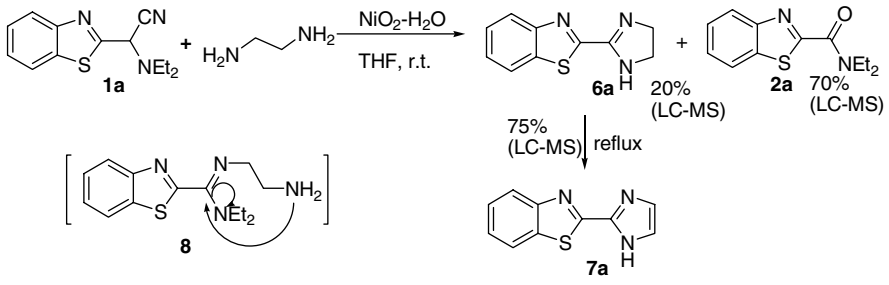
Table 1 (*continued*)

Entry	Y–NH_2	**1**	Product[a,b] yield by using NiO_2–H_2O/MnO_2
11	$PrNH_2$	 **1b**	 **4l** 66%[d] / 61%[d]
12	$PrNH_2$	 **1c**	 **4m** 97%[d] / 78%[d]
13	$PrNH_2$	 **1d**	 **4n** 84%[d] / 46%[d]
14	$PrNH_2$	 **1e**	 **4o** 28%[d] / 9%[d]
15	$PrNH_2$	 **1f**	 **4p** 70%[d] / 35%[d]
16	$PrNH_2$	 **1g**	 **4q**[e] 67%[c], 73%[d] / 59%[d]

[a] Other compounds in reaction mixture after 16 hours at room temperature included amide **2** and unreacted starting material **1**.
[b] Regiochemical structure was not determined.
[c] Isolated yield.
[d] LC–MS yield.
[e] Not degraded after 19 months.

preparation of novel aryl- and heteroaryl amidine derivatives of diverse structure using two different oxidants and a range of amine nucleophiles. As shown in Table 1, this procedure afforded products in low to good overall yields, as determined by LC–MS. Confirmation of the LC–MS yields was obtained for 1–2 product(s) (**4a/4q**, **4b**, **4c**, **4d**, **4e**, **4g** and **4k**) from each series ($ArC(=NR')NR_2$, $ArC(=NH)NR_2$, $ArC(=NCN)NR_2$, $ArC(=NOR')NR_2$, $ArC(=NNR'_2)NR_2$, $Ar(C=NAr')NR_2$ and $Ar(C=NSO_2R')NR_2$) by standard purification and isolation methods. The iminium intermediates **5**, generated by either NiO_2–H_2O or MnO_2,[6] were found to be quite reactive and could readily be captured by primary amines, anilines, heteroaromatic amines and sulfonamides. However, the yields of amidines varied and appeared to correlate with the nucleophilicity of the amine functionality. Consistent with this observation, acylated amines such as $EtCONH_2$, *t*-$BuOCONH_2$, $MeNHCONH_2$ and Me_2NCONH_2, being very weak nucleophiles were found to be unreactive partners (data not shown). It would be anticipated that the conjugate base would be more nucleophilic but these reagents are only weakly acidic with $pK_{a_{DMSO}}$ values of about 25[7a,b,i] and unlikely to form under the mild reaction conditions. In contrast, the more acidic cyanamide ($pK_{a_{DMSO}}$ 16.9, entry 2),[7a,b] sulfamide (entry 9) and methyl sulfonamide ($pK_{a_{DMSO}}$ 17.5, entry 10)[7a,b] presumably reacted via their more nucleophilic anionic forms after deprotonation since the $pK_{a_{DMSO}}$ of water is in the range 27–32.[7a,b,i] Primary amines,[7a,c,d,h] anilines,[7a,b,d,e,h,i] hydroxylamines[7a,d,h] and hydrazines[7a,d,f–h] were expected to react more readily due to their intrinsically higher nucleophilic nature, confirmed by the results shown in entries 1, 3–8, 11–16. While substituted hydrazines and hydroxylamines provided the corresponding amidine derivatives, neither hydrazine nor hydroxylamine afforded products, presumably due to the domination of dehydrogenation of these reagents resulting in the formation of N_2 and NO.

It is also apparent from Table 1 that NiO_2–H_2O and MnO_2 behaved in a similar manner, with both oxidants providing the desired products. However, the yield of product varies and appears to be dependent upon the identity of the individual reactants, with no overt reactivity trends apparent. These data suggest that both



Scheme 3. Imidazoline formation from aminoacetonitrile.

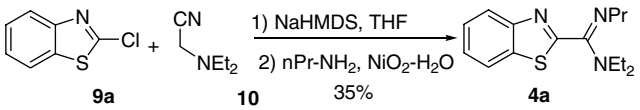
oxidants should be examined when applying this process to new substrates in order to identify the optimal conditions.

The scope of the reaction was extended to encompass bis-nucleophilic partners, leading to the production of heterocyclic amidines. For example, when ethylenediamine was employed as the nucleophile, the imidazoline **6a**[8] was produced in 20% yield, as determined by LC–MS (Scheme 3). This reaction presumably proceeds via an intramolecular displacement of the diethylamino moiety by the free primary amine in the newly-formed *N*,*N*,*N*′-tri-substituted amidine **8**. At elevated temperatures, the amidine **6a** underwent facile aromatization to furnish imidazole **7a**.[9]

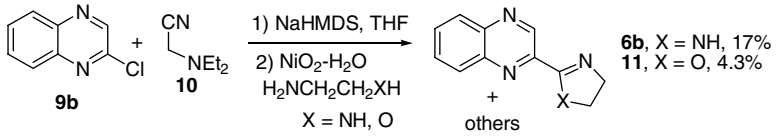
This process for amidine formation could be combined with the previously described S_NAr-oxidation protocol[5,10] to provide a convenient, single-pot process for the production of heteroaryl amidines from heteroaryl halides, as depicted in Schemes 4 and 5. In Scheme 4, the anion of *N*,*N*-diethylaminoacetonitrile **10**, prepared by deprotonation with NaHDMS in THF, was treated with 2-chlorobenzothiazole (**9a**) followed subsequently by exposure to NiO_2–H_2O in the presence of *n*-propyl amine to afford the benzothiazole amidine **4a** in an isolated yield of 35%.

Similarly, the employment of a bis-nucleophile such as ethylene diamine or 2-hydroxyethylamine instead of a simple primary amine led to the formation of the imidazoline **6a**[11] or oxazoline **11**, respectively, via the one-pot process that is summarized in (Scheme 5).[8,12]

In summary, the scope of a unique approach for the preparation of substituted aryl amidine derivatives and related heterocyclic amidines has been investigated. These conditions[13] allow for the construction of novel aryl amidines and related heterocyclic amidines effectively from the corresponding aryl aminoacetonitriles or heterocyclic halides in a procedure that is both convenient and rapid. The scope of substituted amidines that could potentially be synthesized via these processes suggest that this chemistry might be useful when attempting to balance or improve pharmacokinetic, pharmaceutic and safety parameters during a drug optimization campaign.[2] The extension of this methodology to the synthesis of hydrocarbon-based aromatic amides from aryl halides is under active investigation.



Scheme 4. One-pot amidine formation from heteroaryl halide.



Scheme 5. One-pot imidazoline and oxazoline formation from heteroaryl halide.

Acknowledgements

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Supplementary data

The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.04.142.

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13. The reaction and the subsequent work-up should be undertaken with care in a well ventilated hood due to the possibility of HCN liberation.