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Novel Synthesis of Heterocyclic Aryl Amidines

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Abstract: We have developed a novel amidine synthesis that allows the preparation of heterocyclic amidines that were previously unknown and difficult to prepare by published methods. The route involves the lithiation of heterocycles by the action of *n*-BuLi followed by reaction with carbon disulfide and trapping with methyl iodide, yielding a dithioate ester. The latter, when heated in 20% methanolic ammonia at 80°C in a sealed tube provides the heterocyclic amidines directly, in good yield. The products are isolated by crystallization of the respective hydrochloride salts.
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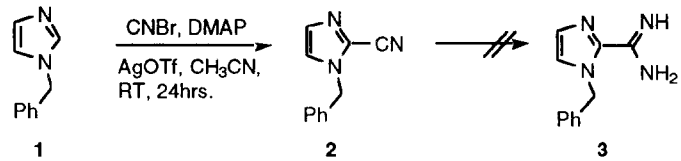
The classical method of preparing amidines is by the alcoholysis of nitriles in the presence of HCl, known as the Pinner synthesis,[1] and subsequent ammonolysis of the resultant imidate ester. The efficiency of this method is mitigated by the long reaction times required for the generation of the imidate salts. Alternatively, primary and secondary amides may be utilized as the starting, materials, since the imidate esters of these compounds may be generated by using Meerwein's salt, as well as the Pinner synthesis. Other methods for converting nitriles to amidines using copper (II) salts[2] and lanthanides[3] have also been reported. Garigipati[4] has recently reported that nitriles can be directly converted to amidines via reaction with the reagent derived from Me_3Al and NH_4Cl, a reagent which was originally reported by Weinreb[5] for the conversion of esters to primary amides.

In the course of our research, it became necessary to prepare heterocyclic amidine derivatives that contained nitrogen atoms in the ring (i.e. imidazole or thiazole). Our initial strategy commenced with 1-benzyl-2-cyano-imidazole, **2**, which was prepared from imidazole, **1**, by a modification of the procedure reported by McCarthy and coworkers.[6] Attempts to convert the nitrile, **2**, to the desired amidine, **3**, by the classical methods mentioned above were fruitless due to lack of reactivity, possibly as a result of the basicity of the imidazole nucleus. We then set out to find alternate ways to prepare these types of amidines.



1 **2** **3**

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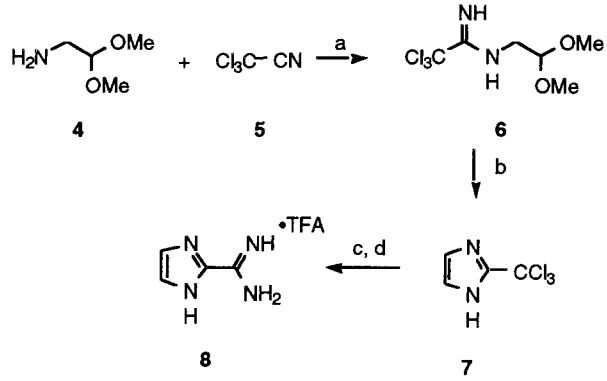
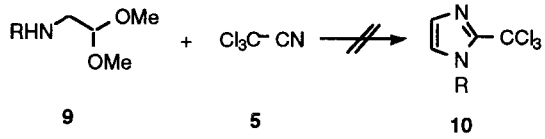
Holan and coworkers[7] have reported that 2-trihalomethylbenzazoles may be converted to the respective 2-amidino derivatives by treatment with ammonia. We then attempted to utilize this as a general route for the preparation of heterocyclic amidines. Nava and coworkers[8] reported the preparation of 2-trichloromethylimidazole, **7**, starting from trichloroacetonitrile, **5**, and aminoacetaldehyde dimethyl acetal, **4**, as illustrated below. The novel 2-amidino-imidazole, **8**, was prepared in this manner.

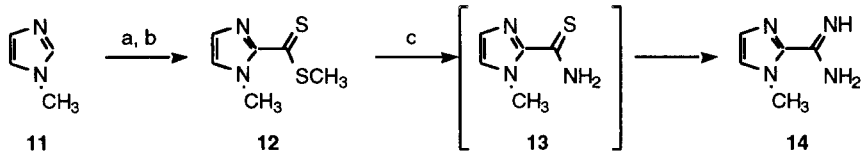


a) THF, -40°C to RT; b) TFA, 0°C to RT; c) 10%NH_3/EtOH, 85°C, 16hrs.; d) TFA

This synthetic methodology, however, was not generally useful since the initial reaction of trichloroacetonitrile with N-substituted aminoacetaldehyde dimethyl acetal **9** did not proceed to give the expected imidazole product **10**. In our hands, only unreacted starting materials were recovered even using extended reaction times. Also, attempts to alkylate the imidazole, **7**, were unsuccessful due to the apparent instability of this compound towards any base.[9]



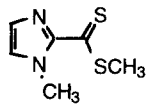
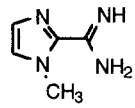
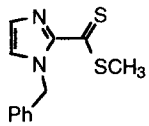
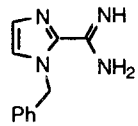
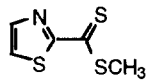
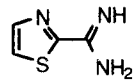
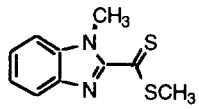
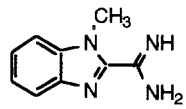
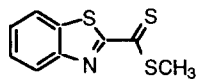
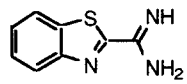
A recent paper by Brandsma,[10] reports the preparation of various dithioate esters by trapping of a lithiated heterocycle with carbon disulfide, followed by alkylation with methyl iodide, as illustrated below in the formation of **12**. Since the dithioates are in the desired oxidation state, we envisaged that this might be a useful intermediate for the preparation of amidines. The initial displacement of a methylthio group by ammonia to give an intermediate thioamide was expected to be facile. Since there is literature precedence for the conversion of N-BOC thioureas to N-BOC protected guanidines[11] and conversion of thioamides to amidines,[12] we expected that the *in situ* conversion of thioamides such as **13** could be possible. This would allow for an efficient two pot synthesis of amidines from heterocyles that would be quite general.



a) *n*-BuLi, CS_2, THF, -78°C; b) MeI, warm to RT; c) anhydrous ammonia

We prepared several dithioate esters illustrated in Table 1, using the procedure from Brandsma, and these were converted to the respective amidine derivatives by treatment with 20% anhydrous ammonia in MeOH in the presence of sodium methoxide.[13] In all cases the bright red color of the dithioate esters disappears after several minutes, indicating complete conversion to thioamide, as was confirmed by ^{1}H NMR and TLC analysis. Complete reaction to the desired amidines was achieved after overnight heating in all cases. In the absence of sodium methoxide, the reactions essentially stopped at the thioamide stage, yielding only modest yields of amidines (<10%).

Table 1: Conversion of dithioate esters to amidines with 20% NH_3/MeOH containing 3 eq. of NaOMe[14]

Entry	Dithioate	Product	Yield (%)
1			53
2			60
3			74
4			67
5			63

In conclusion, we have developed a synthetic method which provides access to heterocyclic amidines, which were previously inaccessible using known routes. The overall route is brief, requiring only two pots and can be performed in multigram scale. This strategy complements the other known methods of amidine

preparation, since it does not involve activation of a nitrile or amide with transition metal catalysts or other acids.

References and Notes:

1. Pinner, A. Die Iminoäther und ihre Derivate, Verlag R. Oppenheim, Berlin, **1892**.
2. For copper (I) mediated reactions see: Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*(40), 6395-6398.
3. For the use of lanthanides in the preparation of amidines see: Forsberg, J., et. al. *J. Org. Chem.* **1987**, *52*, 1017-1021.
4. Garigipati, R.S. *Tetrahedron Lett.* **1990**, *14*, 1969-1972.
5. Levin, J.; Turos, E.; Weinreb, S. *Syn. Comm.* **1982**, 12, 989-93.
6. Whitten, J.P.; McCarthy, J.R. and Matthews, D.P. *Synthesis* **1988**, pg 470. In our hands, the procedure reported in this paper only led to the 2-bromo analog. Addition of AgOTf to the mixture of CNBr and DMAP effectively removed the bromide from the reaction medium by precipitation and resulted in the production of the desired 2-cyano imidazole as the exclusive product.
7. Holan, G.; Samuel, E. *J. Chem. Soc. (C)*, **1967**, 25-29. Ennis, B.C.; Holan, G.; Samuel, E. *J. Chem. Soc. (C)* **1967**, 30-33.
8. Galeazzi, E.; Guzmán, A.; Nava, J.L. *J. Org. Chem.* **1995**, *60*, 1090-1092.
9. It is likely that base would catalyze the loss of a chloride from the 2-substituent, thus generating an exocyclic methylene derivative that would be highly reactive. This analysis is precendented by the work of Holan, et. al. as cited in reference 3.
10. Verkruijsse, H.D.; Brandsma, L. *J. Organomet. Chem.* **1987**, *332*, 95-98.
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12. Bernthsen and Demselber *Annalen* **1877**, *184*, 321. Bristow, N.W., Charlton, P.T., Peak, D.A., Short, W.F. *J. Chem. Soc.* **1954**, *616*, 623.
13. A typical procedure is as follows: The respective dithioate ester is added to a suspension of sodium methoxide (3 eq.) in 20% NH_3/MeOH (50 mls/gram of substrate) in a pressure tube (Ace Glass). After sealing the tube, the mixture is heated at 80°C for 24 hours. After cooling to room temperature, the tube is carefully opened and the solvent was evaporated *in vacuo*. The residue was transferred to a separatory funnel and partitioned between EtOAc and HCl(aq.). The combined aqueous layers were neutralized with sat. $NaHCO_3$ (aq.) and then extracted with EtOAc (3-5 times). The combined organic layers were dried (Na_2SO_4) and then evaporated *in vacuo*. The residue was dissolved in isopropanol (minimum amount required to dissolve free base 2-10 mls) and a solution of CH_3SO_3H (1eq.) in isopropanol (10 ml/gram) was added. The ppt of the products was collected by vacuum filtration and dried *in vacuo*.
14. All products were purified by crystallization of the CH_3SO_3H salts. Yields reported are for the purified salts of the products.