Reductive Monoalkylation of Aromatic Amines via Amidine Intermediates

Jianxing Zhang, Hui-Min Chang, Robert R. Kane*

Department of Chemistry and Biochemistry and the Center for Drug Discovery, Baylor University, Waco, TX 76798, USA
Fax (254)710-4628; E-mail: bob_kane@baylor.edu

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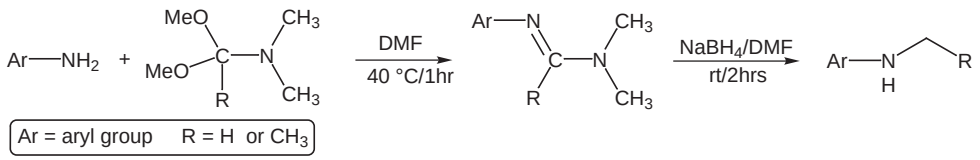
Abstract: The convenience and efficiency of using amidines as intermediates in the reductive monoalkylation of aromatic amines has been demonstrated. This monoalkylation can be performed as either a two-step synthesis or a one-pot procedure. Several examples are presented which clearly demonstrate the utility of this new method for the methylation or ethylation of aromatic amines, including unprotected nucleosides.

Key words: amidine, amine, monoalkylation, nucleoside, adenosine, cytidine

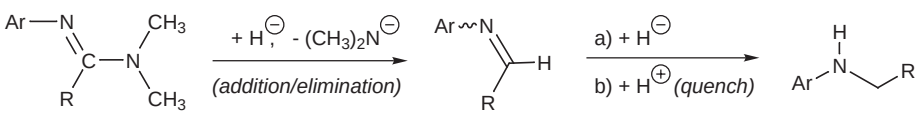
Our laboratory has an ongoing interest in methods for the selective *N*-6 monoalkylation of adenosine derivatives. The relatively limited methods in the literature for this alkylation include *N*-1 alkylation followed by the Dimroth rearrangement,[1] the alkylation of *N*-6-acylated adenosines using phase transfer catalysis followed by deacylation,[2] and the reduction of adenosine thioaminals.[3] We recently discovered that readily accessible *N*-6 amidine derivatives of adenosine[4] may be efficiently reduced to afford *N*-alkylated adenosines in good yield. In fact, this one- or two-pot procedure is a convenient, reasonably yielding, and relatively general method for the mono-methylation or ethylation of aromatic amines. The overall reaction sequence is shown in Scheme 1.[5]

The efficient conversion of aryl amines to amidine derivatives by treatment with the commercially available dimethyl acetals of dimethylformamide or dimethylacetamide is well known.[6] Amidines prepared in this manner or via other routes have been employed as synthetic intermediates[7] or as amine protecting groups, especially in nucleoside chemistry.[8] However, there have been very few reports in the literature describing the reduction of amidines. One manuscript describing the use of amidines as protecting groups reported the hydrogenolysis of several aliphatic amidines, affording *N*-methylated products in moderate yield.[9] This transformation presumably proceeds via the hydrolysis of a transiently formed geminal diamine,[10] which eliminated to form an imine which was subsequently hydrogenated. Meyers and Ten Hoeve also briefly noted the hydride reduction of an aliphatic amidine, which presumably reacted via a similar mechanism.[11] In an elegant study more closely related to the subject of this note, cyclic amidines, formed from the condensation of 1,2- and 1,3-diamines with aldehydes, were regioselectively reduced with DIBALH to yield mono-*N*-alkylated products in good yield.[12]

We have found that sodium borohydride in DMF reduces aryl amidines within 1 to 2 hours at room temperature to provide the alkylated aromatic amine as the major product. The regenerated starting amine accounts for the majority of the remaining mass balance. This reduction is unsuccessful in protic solvents (water, alcohols), and sodium cyanoborohydride, a reducing agent generally useful in reductive aminations,[13] did not reduce the amidines under a variety of conditions. We propose that the sodium borohydride reduction of aryl amidines proceeds by a two step process outlined in Scheme 2. The initial addition/elimination reveals an imine, which subsequently undergoes a second hydride addition to give the alkylated amine

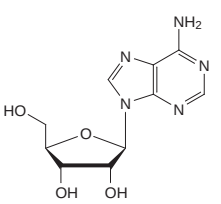
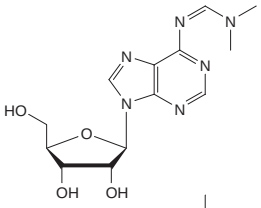
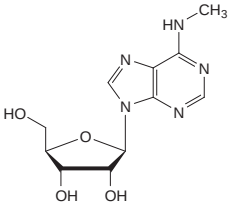
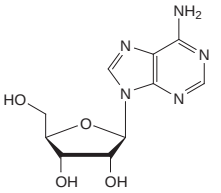
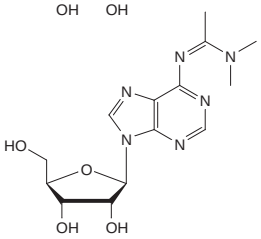
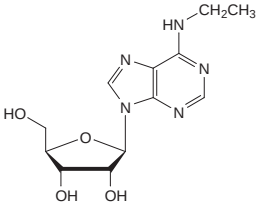
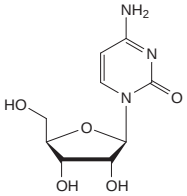
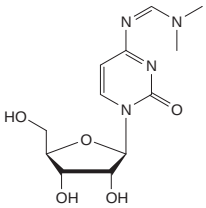
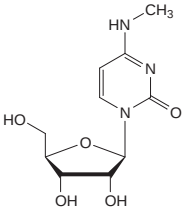
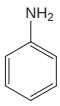
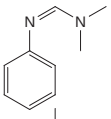
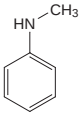
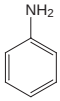
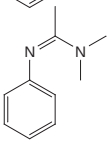
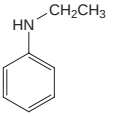
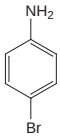
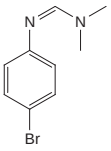
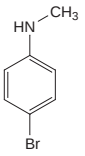
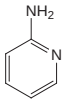
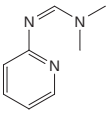
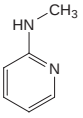


Scheme 1 Two-step reductive alkylation.



Scheme 2 Stepwise two-hydride reduction.

Table Reductive Alkylation of Aromatic Amines

Amine	Amidine Intermediate	Product	Yield
			a) 56% b) 63%
			b) 61%
			b) 71%
			a) 65%, b) 72%
			b) 73%
			b) 62%
			b) 68%

a) two-step approach; b) one-pot synthesis

after protonation. A hydrolytic mechanism as in reference 10 is less likely, as hydroxymethyl-substituted aryl amines are in equilibrium with the free amine and formaldehyde, rather than the imine.[14] It is clear that the alkylating species is not derived from the DMF solvent, as no *N*-ethylation is detected in reductions of formamidine derivatives.

In order to avoid the purification of labile amidine intermediates we also investigated the one-pot approach for this reductive alkylation. Indeed, the methylation or ethylation of aromatic amines can be readily accomplished by a one-pot process without isolation of the amidine intermediate. In this approach, amidine formation is allowed to proceed for one hour at 40 °C, after which the reaction mixtures are cooled to room temperature. Sodium borohydride is then added, and the reduction allowed to proceed for two hours at room temperature. Aqueous quench again afforded the desired methylated or ethylated products in reasonable yield.[15]

Results for representative amine alkylation reactions are reported in the Table. The alkylated amines were purified by silica gel flash column chromatography and their struc-

tures verified by HPLC, ^{1}H-NMR, and ^{13}C-NMR. Reasonable yields of the monoalkylated products are generally observed using either the one- or two-pot approach,[16] although the yields of products via the one-pot approach are slightly higher due to losses during the isolation of the amidines. We are presently examining the application of this reaction to the formation of more complex alkylated amines.

Acknowledgement

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References and Notes

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(5) Two-step approach to 6-*N*-methyladenosine: Adenosine (267mg, 1 mmol), dried by coevaporation with pyridine, was dissolved in 2−3 mL anhydrous DMF and *N*,*N*−dimethylformamide dimethyl acetal (1mL, 5.5 mmol, 5.5 equiv) was added. The resulting solution was stirred under N_2 at 40 °C (bath temperature) for 1 hour. The solution was then evaporated to dryness under vacuum and the residue submitted to flash chromatography on silica gel with CH_2Cl_2−CH_3OH−NMe_3 (95:5:0.5) eluent. Fractions containing 6-*N*-(1-dimethylamino)methylidene) adenosine (213 mg, 0.66 mmol, 66%) were evaporated to dryness and then dissolved in 3 mL DMF in a 10 mL round bottom flask. Sodium borohydride (130 mg, 3.5 mmole, 5 eq) was added and the mixture stirred at room temperature for 2 hours. Saturated sodium bicarbonate was used to quench the reaction mixture, and the resulting solution was filtered and the precipitate washed with 100 mL methanol. After evaporation of the solvent under vacuum the residue was applied to flash LC (silica gel) with CH_2Cl_2-CH_3OH-NMe_3 (9:1:0.05). 6-*N*-Methyladenosine (156 mg, 0.56 mmol, 85%, 56% overall) was obtained as an amorphous white solid. For non-nucleosidic substrates dichloromethane was used to wash the precipitate in the final step.
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(14) Abrams, W. R.; Kallen, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7777-7789.
(15) One-pot approach to 6-*N*-methyladenosine: Adenosine (267 mg, 1 mmol), dried by coevaporation with pyridine, was dissolved in 2−3 mL anhydrous DMF and then *N*,*N*−dimethylformamide dimethyl acetal (1mL, 5.5 mmol, 5.5 eq.) was added. The resulting solution was stirred under N_2 at 40 °C (bath temperature) for 1 hour. After the reaction mixture cooled to room temperature, sodium borohydride (130 mg, 3.5 mmol, 3.5 eq) was added and the mixture stirred at room temperature for 2 hours. Saturated sodium bicarbonate was used to quench the reaction mixture, and the resulting suspension was filtered and the precipitate washed with 100 mL methanol. The mixture was concentrated and the residue applied to flash LC (silica gel) with CH_2Cl_2-CH_3OH-NMe_3 (9:1:0.05) as eluent. 6-*N*-methyladenosine (177 mg, 0.63 mmol, 63%) was obtained. For non-nucleosidic substrates dichloromethane was used in the final extraction.
(16) Overall yields are excellent (>90%) if corrected for recovered starting materials, which accounts for the majority of the missing mass balance.

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