A Convenient Reductive Deamination (Hydrodeamination) of Aromatic Amines

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Reductive deamination (hydrodeamination) of aromatic amines can be conveniently carried out by amination of the corresponding arylamine methanesulfonamides using chloroamine under alkaline conditions. The intermediate aryl methanesulfonylhydrazines directly eliminate methanesulfinic acid, affording diazenes which extrude nitrogen affording the desired deaminated products. Both sulfonamide formation and reduction reactions occur in high yield and are compatible with a variety of functional groups.

Reductive removal of an amine group, hydrodeamination, is a very important transformation in organic chemistry. Reactions involving such reductive processes are particularly useful in aromatic chemistry because of the strong directing effects associated with amine substituents. Generally, reductive deamination is carried out on arylamines by diazotization of the amine function, affording the corresponding diazonium salt followed by reduction using hypophosphorous acid, sodium borohydride, or a variety of other reducing agents.[1] Alternative deamination procedures are very limited in the literature. One such method, the reductive deamination described by Nickon and Hill,[2] involves conversion of an amine into the corresponding sulfonamide derivative followed by amination to the corresponding sulfonylhydrazine. Under alkaline conditions, the sulfonylhydrazine undergoes an elimination reaction affording the corresponding sulfinate salt and an intermediate diazene which extrudes nitrogen affording the corresponding reduced product. The reaction generally worked well in the case of primary aliphatic amines, but only poorly on an aromatic amine substrate. We subsequently investigated the factors that influence the course of related hydrodeamination reactions on aliphatic amines.[3] In our continuing studies on functionalizing deamination reactions,[3−6] we later sought to expand these processes to reductions of primary amine groups directly attached to aromatic systems.

As in our previous studies, we investigated the effect of the sulfonamide substituent, the solvent, the aminating agent, and the base in carrying out the desired transformations.

Initial attempts to prepare the required monosulfonamide derivatives were hampered by the strong tendency of arylamines to undergo disubstitution in this reaction. This tendency was particularly pronounced when using aryl sulfonyl halides such as *p*-toluenesulfonyl chloride and 2-nitrobenzenesulfonyl chloride. Disubstitution occurred to a lesser extent when methanesulfonyl chloride was used in this reaction, probably due to the decreased acidity of the initially formed monosulfonamide relative to arylsulfonyl derivatives. The sulfonamide formation was generally best carried out in dichloromethane using pyridine as a base. Pure monosubstituted methanesulfonamides could be obtained efficiently and in high yield using alkaline extraction of the crude sulfonamide mixture followed by acidification (see Tables 1 and 2). Aside from the ready availability of many of the required methanesulfonamides in this reaction,[7,8] there is the corresponding advantage of increased atom economy in the reductive procedure relative to the corresponding arylsulfonyl derivatives.

Conversion of the methanesulfonamide to the corresponding methanesulfonylhydrazine was then investigated. We evaluated a number of different aminating agents in this reaction. Commercially available hydroxylamine *O*-sulfonic acid had been used in the initial studies by Nickon.[2] As we previously noted this reagent often proved to be unsatisfactory due to its limited solubility in organic solvents, particularly when the amine to be reduced was relatively hydrophobic.[3] This was generally the case for the aromatic molecules investigated. Both *O*-2,4-dinitrophenylhydroxylamine[9] and *O*-mesitylenesulfonylhydroxylamine[10] proved to be satisfactory in the transformations; however, the preparations of these compounds were relatively tedious. Safety hazards have also been noted in the case of the latter reagent. Removal of the aryl byproducts also made isolation of the sulfonylhydrazine intermediates, as well as the final deamination products, more complicated.

In our earlier work, we had investigated the use of chloroamine as an aminating agent.[3] Although this

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Table 1. Reductive Deamination of Simple Arylamines

$$ArNH_2 \xrightarrow[\text{pyridine}]{CH_3SO_2Cl} ArNHSO_2CH_3 \xrightarrow[\text{NH}_2Cl]{NaH} ArH$$

Ar	Sulfonamide % Yield (Ref.)	ArH % Yield	Ar	Sulfonamide % Yield (Ref.)	ArH % Yield
H₃C—⟨⟩—	96% [a]	87%	naphthalen-2-yl	88% [a]	85%
3,5-(H₃C)₂C₆H₃	91% [b]	88%	2-Cl-C₆H₄	62% [a]	53%
H₃CO—⟨⟩—	93% [a]	96%	2,4-Cl₂C₆H₃	43% [a]	75%
H₃CCH₂O—⟨⟩—	97% [a]	86%	2,6-(CH₃)₂C₆H₃	80% [b]	81%
naphthalen-1-yl	87% [a]	92%			

[a] Reference 7. [b] Reference 8.

reagent proved to be extremely effective in the amination reactions, the usual preparation of chloroamine was not convenient and potentially hazardous. In this procedure sodium hypochlorite is added to a cooled solution of aqueous ammonia, and the resulting gaseous chloroamine distilled at 40–45 °C under reduced pressure into a dry ice-cooled ether solution. Ethereal chloroamine could be obtained in about 30% yield.[11] An alternative less well-known published procedure for the preparation of chloroamine proved to be much more convenient.[12]

This procedure involves buffering the sodium hypochlorite–ammonia reaction with ammonium chloride, avoiding over-chlorination of the initially formed chloroamine which can be readily extracted in organic solvents. This reaction does not require distillation of the ether–chloroamine mixture and affords ethereal chloroamine in typical yields of greater than 90%. For the purposes of the deamination reaction, extraction with dichloromethane–ether mixtures led to lowered extraction of chloroamine from aqueous solution but the resulting chloroamine solution was easier to dry and proved to be very effective in subsequent amination reactions.

The monosulfonamides could be best converted to the desired *N*-aryl-*N*-sulfonylhydrazine intermediates at 0° C with excess chloroamine solution using dimethylformamide as a cosolvent and solid sodium hydride as a base. Although the desired sulfonylhydrazines can be isolated if desired, for reductive deamination the amination and subsequent elimination reactions are best carried out in situ using 2.0 equivalents of sodium hydride per mole of sulfonamide. Under these conditions, the initially formed sulfonylhydrazines rapidly eliminate methanesulfinic acid affording the corresponding diazenes, which subsequently extrude nitrogen affording the desired reduced products.

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$$ArNH_2 \xrightarrow[\text{pyridine}]{CH_3SO_2Cl} ArNHSO_2CH_3 \xrightarrow[\text{NH}_2Cl]{NaH} \underset{NH_2}{\overset{Ar}{\underset{|}{N}}}SO_2CH_3$$

$$ArH \xleftarrow{-N_2} \left[Ar-N=N-H \right] \xleftarrow[\text{- CH}_3SO_2H]{NaH,}$$

The required series of reactions—sulfonamide formation, amination, and elimination—occur satisfactorily both on simple arylamines (Table 1) and also on multifunctional molecules (Table 2). As seen in Table 1, particularly in the case of 2,6-dimethylaniline, the reaction works well even in extremely sterically hindered environments. Ketone, carboxylic acid, ester, and nitro functions do not interfere with the overall deamination process (Table 2). Only slight differences in workup, particularly in the initial monosulfonamide-forming procedure, led to high yields of isolated reduction products. Although no problems were noted in the case of methanesulfonamides containing the above-mentioned functional groups, substrates containing moderately acidic functional groups required slight modifications to the general procedure. As expected, *p*-aminobenzoic acid methanesulfonamide required excess NaH for the deamination, affording benzoic acid in 82% yield upon acidification, but the deaminations of arylamines containing amide and phenolic groups proved to be more complicated. The best conditions for the deamination of the methanesulfonamide of 4-aminophenol required the use of 3.0 equiv of NaH affording phenol in 82% yield. Use of 2.3 equiv of base afforded the product in 71% yield. The methanesulfonamide of 4-aminobenzamide afforded benzamide in 57% isolated yield when treated with excess chloroamine and 4.0 equiv of NaH. The yield of product fell to 50% when 3.0 equiv of base was used and to 38% with 2.0 equiv. The lowered yields of deamination product in the latter case are probably due to the nucleophilicity of the deprotonated amide function leading to reaction at this center with chloroamine. When benzamide itself was treated with NaH and chloroamine under the normal

Table 2. Reductive Deamination of Functionalized Arylamines

$$\text{ArNH}_2 \xrightarrow[\text{pyridine}]{\text{CH}_3\text{SO}_2\text{Cl}} \text{ArNHSO}_2\text{CH}_3 \xrightarrow[\text{NH}_2\text{Cl}]{\text{NaH}} \text{ArH}$$
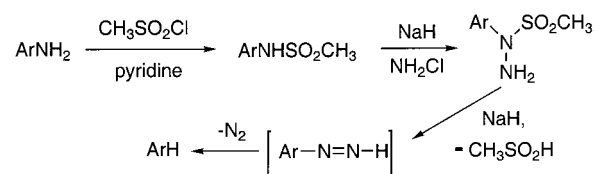
Ar	Sulfonamide % Yield (Ref.)	ArH % Yield
H₃C–C(O)–C₆H₄–	89% [a]	68%
H₃CO–C(O)–C₆H₄–	89% [a]	98%
HO–C(O)–C₆H₄–	74% [b]	82%
HO–C₆H₄–	81% [c]	98%
H₂N–C(O)–C₆H₄–	90% [d]	50%
O₂N–C₆H₄–	90% [e]	81%

[a] Reference 8. [b] Reference 15. [c] Reference 16. [d] This work. [e] Reference 17.

reaction conditions, benzamide could only be recovered in 62% yield.

The mild conditions necessary for the deamination sequence appear to be ideal for the reduction of complex arylamines.[13] The ready formation of the required intermediate methanesulfonylhydrazines using the procedures described here may lead to a greatly expanded utility for other functionalizing deamination reactions. Related work in these areas is currently in progress.

Experimental Section

[1]H spectra were recorded on a 300-MHz spectrometer. Infrared spectra were recorded using KBr or neat liquid samples. Mass spectrometric determinations, and purity assessments were carried out using GC–MS. Melting points are uncorrected. Elemental analyses were carried out by Desert Analytics, Tucson, AZ. Unless otherwise described, commercial reagents were used without further purification.

Chloroamine (Modification of the Procedure of Schmitz and Co-Workers).[12] Ammonium chloride (0.707 g, 13.2 mmol) was added to a 2.0 M aqueous ammonia solution (4.35 mL, 8.7 mmol), and the mixture was cooled in an ice bath. To this cooled mixture was added dropwise 5.25% (0.76 M) aqueous sodium hypochlorite (commercial bleach) (18.8 mL, 14.3 mmol) over 15 min and the mixture stirred an additional 15 min at 0 °C. The aqueous solution was extracted with a cold (0 °C) mixture of dichloromethane (12 mL) and ether (10 mL) and then with another portion of cold dichloromethane (12 mL). The combined organic extracts were dried with CaCl₂

at −10 °C for 30 min. An aliquot of the ethereal chloroamine solution could be iodometrically titrated using potassium iodide and sodium thiosulfate to accurately determine the chloroamine concentration in the organic solution (see Supporting Information). The typical yield of chloroamine in solution using this procedure was 5.0 mmol. **Note:** Although no problems were experienced in the preparation and handling of chloroamine using this procedure, it should be noted that only dilute solutions of chloroamine should be prepared. More concentrated solutions readily decompose potentially creating a safety hazard.[14] The preparation and reactions of chloroamine should also be carried out in a well-ventilated hood.

General Arylamine Hydrodeamination Procedure. Methanesulfonyl chloride (0.92 mL, 12 mmol) was added to a cooled 0 °C stirred solution of the arylamine (12 mmol) in pyridine (1.09 mL) and dichloromethane (35 mL), keeping the temperature below 10 °C. The mixture was allowed to come to room temperature overnight and then quenched with 6 N NaOH and enough water to dissolve the resulting solid. Phases were separated, and the aqueous phase was extracted with dichloromethane. The aqueous phase was cooled to 0° C and acidified with concentrated HCl. The resulting solid methanesulfonamide was filtered and dried under reduced pressure. The crude dried product was generally adequately pure for subsequent reactions.

The methanesulfonamide (3 mmol) in DMF (15 mL) was stirred and cooled to 0 °C under a positive nitrogen atmosphere. Sodium hydride (95%, 152 mg, 6 mmol) was added and the mixture stirred for an additional 2 h. The freshly prepared chloroamine solution (5 mmol) was added and the mixture stirred at 0° C for 4 h and allowed to come to room temperature with stirring overnight. The mixture was then poured into ice–water (50 mL) and extracted with hexanes (2 × 50 mL), and the combined hexane extracts were consecutively washed with 1 M HCl, 3 M NaOH, water, and saturated sodium chloride. Concentration afforded the desired reduction products in good to excellent yields as described in Tables 1 and 2. All products are known compounds with spectra and physical constants identical to those reported in the literature.

4-Methanesulfonamidobenzoic Acid. To a stirred cooled (0 °C) solution of 4-aminobenzoic acid (1.37 g, 10 mmol) in THF (35 mL) was added alternately in portions NaOH (1.7 M, 15 mL) and methanesulfonyl chloride (1.13 mL, 15 mmol), keeping the pH 9–11. The mixture was stirred 5 h at 0 °C and allowed to come to room temperature overnight. The mixture was cooled in an ice bath and slowly acidified to pH 2 with cold 1.0 M sulfuric acid. The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were washed with water and brine. Drying with MgSO₄ and concentration afforded the crude sulfonamide, 1.59 g (74% yield), mp 119−121 °C (lit.[15] mp 121−123 °C), which was of satisfactory purity for direct use in the deamination reaction.

Reduction of 4-Methanesulfonamidobenzoic Acid. 4-Methanesulfonamidobenzoic acid (430 mg, 2 mmol) stirred in DMF (15 mL) at 0 °C was treated with NaH (95%, 173 mg, 6.8 mmol), and stirring continued for 2h at 0 °C. Chloroamine solution (3.3 mmol) was added, keeping the temperature at 0 °C for 3 h and then allowing the mixture to come to room temperature overnight. The mixture was then acidified to pH 2 with 1 M HCl and extracted with dichloromethane (3 × 30 mL). Drying over sodium sulfate and concentration afforded benzoic acid, 200 mg, 82% yield, identical in all respects to authentic material.

Reduction of 4-Methanesulfonamidophenol. To a stirred cooled (0 °C) solution of 4-methanesulfonamidophenol[16] (561

(13) Although direct comparisons between the methods reported here and standard deamination methods described in the literature are possibly unreliable, the overall yields described in this work are comparable or superior to deaminations previously reported. (e.g., *p*-toluidine: yield, this work 84%, reported 77-83%;[18] 2-aminonaphthalene, this work 75%, reported 35-45%;[18] 4-aminobenzoic acid, this work 61%, reported 68%;[19] methyl 4-aminobenzoate, this work, 87%, reported 54%.[19])

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mg, 3.0 mmol) in acetonitrile (15 mL) and DMF (5 mL) under positive nitrogen pressure was added solid NaH (207 mg, 9.0 mmol, 3.0 equiv.). The mixture was stirred at 0 °C for 2 h, and the chloroamine solution (5 mmol) was added, keeping the mixture at 0 °C for 4 h and then allowing the reaction to come to room temperature overnight. The mixture was then poured into ice–water (50 mL), acidified to pH 2–3, and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water and then brine and dried with anhydrous sodium sulfate. Concentration afforded crystalline phenol (232 mg) identical in all respects with authentic material (82% yield). Use of 2.3 equiv of NaH afforded phenol in 71% isolated yield.

4-Methanesulfonamidobenzamide. Methanesulfonyl chloride (0.77 mL, 10 mmol) was added to a cooled 0 °C stirred solution of 4-aminobenzamide (1.36 g, 10 mmol) in pyridine (1.84 mL, 22 mmol) and dichloromethane (35 mL) keeping the temperature below 10 °C for 2 h. The mixture was allowed to come to room temperature overnight, and the resulting colorless crystals were filtered and recrystallized from 95% ethanol affording pure sulfonamide: 1.93 g, 90% yield; mp 228–230 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (s, 1H), 7.84 (d, 2H) ($J = 8$ Hz), 7.28 (s, 1H), 7.22 (d, 2H), 3.05 (s, 3H), 2.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 167.9, 141.8, 129.7, 129.6, 118.5, 40.3; IR (KBr) ν_{max} 3379, 3296, 3243, 1651, 1597 cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_3S$ (214.25): C, 44.84; H, 4.70; N, 13.08. Found: C, 44.84; H, 4.61; N, 12.82.

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Reduction of 4-Methanesulfonamidobenzamide. The crude sulfonamide (642 mg, 3 mmol) in acetonitrile (15 mL) and DMF (5 mL) under nitrogen was cooled at 0 °C, and NaH (288 mg, 12 mmol) was added. The mixture was stirred for 2 h, the chloroamine solution (5 mmol) added at 0 °C, and the mixture stirred for 5 h. The mixture was poured into water, neutralized, and extracted with CHCl$_3$ (3 × 30 mL). Drying over MgSO$_4$, concentration, and recrystallization from ethanol afforded benzamide, 423 mg, mp 126–128 °C, identical in all respects to authentic material in 57% yield. Under analogous conditions use of 3.0 and 2.0 equiv of NaH afforded pure benzamide in yields of 50 and 38%, respectively.

Supporting Information Available: Methods for the analysis of chloroamine solutions and sodium hypochlorite by indirect iodometric titration. Table of data characterizing the methanesulfonamides reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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