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A Convenient Conversion of Primary Amines into the Corresponding Halides -- Radical Promoted Halodeamination via N-Substituted-N-Tosylhydrazines

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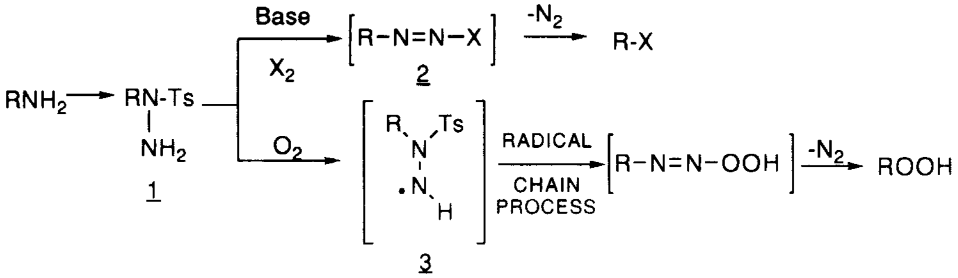
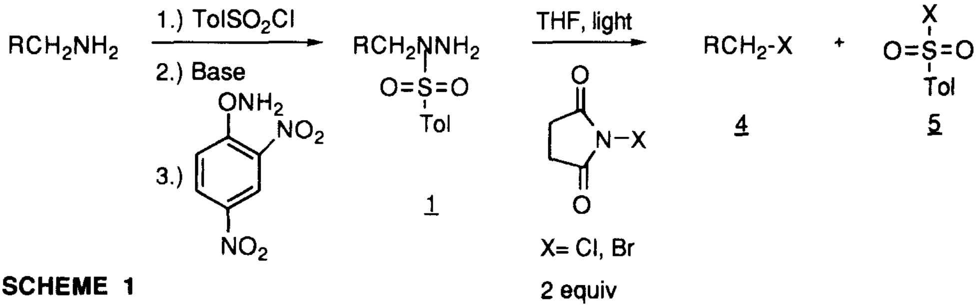
Abstract: Treatment of 1-substituted-1-tosylhydrazines with 2 equivalents of NCS or NBS in dry THF in presence of light affords the corresponding alkyl halides in good yields. This reaction presumably involves the initial formation of a stabilized hydrazyl radical which is halogenated in a radical chain process. Elimination of p-toluenesulfinic acid and extrusion of nitrogen leads to the corresponding alkyl halide. This route provides an improved method for halodeamination under neutral reaction conditions.

Replacement of a primary amine group with halogen is generally a difficult process, often involving complex reagents and vigorous reaction conditions.[1-4] We recently reported a base-promoted halodeamination reaction in which primary amines could be converted into the corresponding halides via the N-tosylhydrazine derivative **1**. This reaction presumably occurs via a halodiazene intermediate **2**.[5] While this halodeamination process can be carried in quite good yield at room temperature, the strongly basic reaction conditions may limit its synthetic utility in certain circumstances. In the course of our investigations into other reactions of N-substituted-N-tosylhydrazines, we found that these compounds could be converted in excellent yields into the corresponding alcohols and hydroperoxides.[6,7] The hydroxy- and hydroperoxydeamination reactions were observed to proceed by a radical mechanism involving a stabilized hydrazyl radical **3**. The transformations of 1-substituted-1-tosylhydrazines clearly can occur via two different mechanisms, radical or anionic, depending on the reaction conditions. Based on these observations, we investigated whether the halodeamination process could be carried out under milder radical chain conditions.

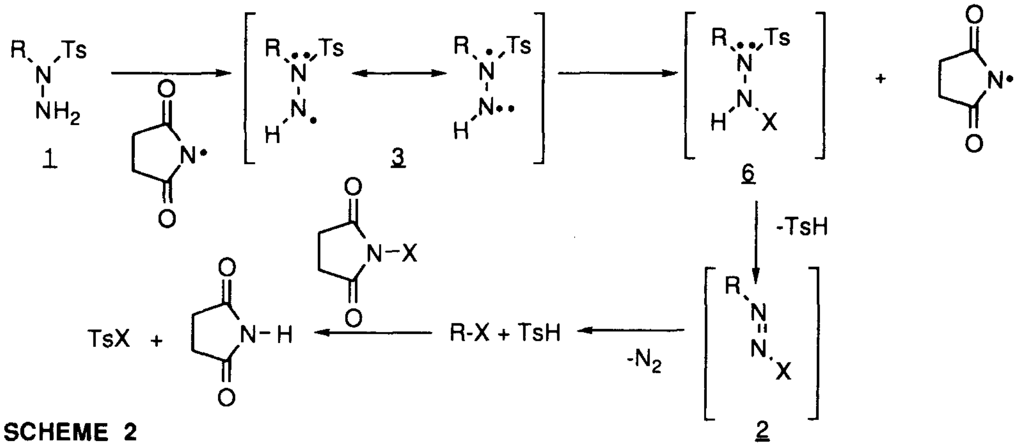


We observed that when N-substituted-N-tosylhydrazines were treated with N-chloro- or N-bromosuccinimides at room temperature the corresponding halides were obtained in good yield under extremely mild conditions. Preparation of the alkyl halides via this radical process involves conversion of the primary amines into the corresponding p-toluenesulfonamide, followed by amination to the N-substituted-N-tosylhydrazine **1**.[8] Treatment of the tosylhydrazine with 2 equiv of N-chloro or N-bromosuccinimide in dry THF under inert atmosphere afforded the corresponding alkyl halides **4** **(Scheme 1)** in good yields after flash chromatography on silica gel **(Table)**.[9,10] THF proved to be an ideal solvent for the reaction, presumably due to its lack of reactivity with the stabilized hydrazyl radical. The main by-products isolated from the reaction mixtures were the p-toluenesulfonyl halides, presumably formed by reaction of p-toluenesulfinic acid with the halogenating reagent.[11]



SCHEME 1

While the mechanism for this halodeamination reaction is not completely clear, a number of experiments suggest a stabilized hydrazyl radical is the key intermediate. Treatment of the tosylhydrazine with one equivalent of NaH in presence of NCS at 0ºC afforded the corresponding alkyl chlorides in only 7% yield, along with a variety of by-products. When the halodeamination reaction was attempted in $CHCl_3$ instead of dry THF only a complex mixture was obtained, suggesting that the choice of solvent plays an important role in the reaction. Subsequently it was also observed that the tosylhydrazines themselves react rapidly (15 min.) at room temperature with chloroform in the absence of NCS or NBS. Finally, when the reaction was done in absence of light, only 2% of the pure alkyl halide was obtained after 7 days at room temperature. These observations suggest the mechanism as described in **Scheme 2**.



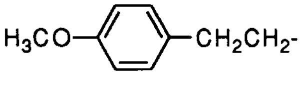
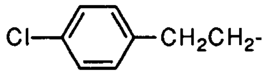
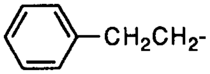
SCHEME 2

In this proposed reaction mechanism, photochemically generated succinimide radical abstracts a hydrogen atom from the N-substituted-N-tosylhydrazine **1** to afford the hydrazyl radical **3**. This species should be readily generated because of the resonance stabilization due to formation of a "three electron bond"[12] as well as by "captodative" stabilization.[13] Abstraction of the halogen would afford the N-halohydrazine intermediate **6** and regenerate the succinimide radical leading to a radical chain halogenation process. Elimination of p-toluenesulfinic acid would afford the N-halodiazene intermediate **7** which would extrude nitrogen to afford the corresponding halide. Halodiazene **7** had previously been proposed as an intermediate in the anionic halodeamination reaction.[5]

The radical dehydrohalogenation reactions presented here provide a mild and convenient route for the conversion of primary amines to the corresponding halides. Work is currently in progress to determine the scope and limitations of this novel synthetic method.[10]

TABLE. Preparation of alkyl halides via halodeamination

$$RN(NH_2)Tos \longrightarrow RX$$

R	R-X % Yield	
	Cl	Br
	82^a	86^a
	95^a	87^a
	57^b	67^b
$CH_3(CH_2)_{10}CH_2$-	68^b	65^b
$CH_3(CH_2)_{14}CH_2$-	88^a	68^b

a. Isolated optimized yields of pure products.
b. Isolated unoptimized yields of pure products.

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8. Amination using O-(2,4-dinitrophenyl)hydroxylamine proved to be more convenient than reactions using O-mesitylenesulfonylhydroxylamine.[5] [See: Sheradsky, T; Salemnick, G.; Nir, Z.,*Tetrahedron*, **1972**, *28*, 3833; Sheradsky, T. *Tetrahedron Lett..*, **1968**, 1909 ; Ilvespöö, A.O.; Marxer, A. *Helv. Chim. Acta*, **1963**, *46*, 2009.]
9. The typical radical halodeamination procedure is carried out as described for 1-chlorohexadecane: [A flask containing 1-tosyl-1-hexadecylhydrazine (0.463 g, 1.13 mmol) and NCS (0.302 g, 2.26 mmol) was thoroughly degassed by evacuation and flushing with argon. Freshly distilled dry THF (20 mL) was added via syringe, affording a homogeneous reaction mixture. Almost immediately a precipitate separated. The mixture was stirred for 16h under diffuse laboratory light. The mixture was poured into ice-water (50 mL), and extracted with hexanes (3 X 50 mL). The combined extracts were dried over anh. Na_2SO_4, and concentrated to afford a pasty solid. Flash chromatography on silica (hexanes) afforded pure 1-chloro-hexadecane as an oil (0.236 g, 88% yield), FTIR (neat) 2952, 2924, 2854, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (t, J=6.7 Hz, 2H), 1.81-1.73 (m, 2H), 1.26 (bs, 26H), 0.88 (t, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 45.2 (t, J=149 Hz), 32.7, 31.9, 29.7 (superimposed), 29.6 (superimposed), 29.5 (superimposed), 29.4 (superimposed), 28.9, 26.9, 22.7, 14.1]. This material was identical in all respects to authentic commercial 1-chlorohexadecane.
10. While the Table lists only the reactions of primary amines with nitrogen attached to a primary carbon, preliminary experiments show that the reaction also occurs at secondary carbon centers. Reactions starting with 2-aminooctane afford the corresponding chloro- and bromo- derivatives in unoptimized yields of 38% and 18% respectively. The low yields probably are a result of difficulties in purifying the unstable intermediate tosylhydrazines, with by-products inhibiting the radical process. Work is currently underway to improve the availability of pure tosylhydrazines from amines attached to secondary (and tertiary) carbons.
11. Treatment of p-toluenesulfinic acid with N-chlorosuccinimide under these halodeamination conditions affords toluenesulfonyl chloride in excellent yields.
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