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Synthesis of Carboalkoxychloro- and Bromodiazirines

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Received May 10, 2004

Abstract: The first known 3*H*-diazirines bearing a carbonyl group and a halogen atom on C-3 have been prepared by a novel synthetic method. Carboalkoxychloro- and bromodiazirines **1a**−**d** are formed in up to 45% yields by reductive dechlorination of carboalkoxy-*N*,*N*,*N*′-trichloroformamidines **9a**,**b** using chloride or bromide ion. This method constitutes the first example of the use of *N*,*N*,*N*′-trichloroamidines as starting materials in organic synthesis.

While the literature contains a number of examples of 3*H*-diazirines[1] bearing halogen or ester groups, 3-carboalkoxy-3-halodiazirines (**1**) are a class of compounds that remains so far undescribed. In fact, no diazirines bearing both a carbonyl group and a halogen atom on the ring carbon have been synthesized. Diazirines **1** are valence isomers of the long known diazohaloacetates (**3**).[2] Both **1** and diazirines derived from **1** by the halogen exchange reaction[3] (e.g., **2**) may serve as new precursors for the generation of carboalkoxycarbenes[4] in solution and in argon matrix. Herein, we report the first successful preparation of carboalkoxychloro- and bromodiazirines **1a**−**d** using a novel synthetic method. The only practical method for the preparation of chloro- and bromodiazirines remains the Graham's oxidation of amidines[5] with excess of the corresponding hypohalite in aqueous DMSO in the presence of halide. The product is typically isolated by extraction into a nonpolar solvent or, if it is sufficiently volatile, by evaporation in vacuo.

Carbomethoxyformamidine (**6a**), a precursor for halodiazirines **1a** and **1c** in Graham's oxidation, was synthesized in good overall yield from methyl cyanoformate (**4a**) via the iminoester **5a** (Scheme 1). Treatment of **6a** with sodium hypochlorite or hypobromite under standard Graham's conditions followed by extraction with hexanes and ether failed to yield the corresponding diazirines.

We hypothesized that this result may be due to unfavorable partitioning of the product between aqueous DMSO and hexanes. Diazirines bearing a longer alkyl chain ester group are more soluble in nonpolar solvents and hence their extractive isolation may be possible. Carbobutoxyformamidine (**6b**), a precursor for halodiazirines **1b** and **1d**, initially proved difficult to synthesize (Scheme 1). Butyl cyanoformate (**4b**) was readily converted to the iminoester **5b** but the latter did not afford any amidine **6b** upon treatment with ammonium chloride. Unreacted **5b** was recovered when the reaction was carried out at room temperature. At elevated temperatures, mixtures of products were obtained. However, **6a** can be transesterified to **6b** with 1-butanol. The amidinium group of **6a** apparently enables acid catalysis for the transformation of the neighboring ester group. With a catalytic amount (5 mol %) of triethylamine, transesterification is completed within 24 h at room temperature. Triethylamine probably facilitates the proton transfer between the amidinium and ester groups. Unfortunately, attempted Graham's oxidation of the amidine **6b** failed to yield the corresponding diazirines. A mixture of products was obtained in low yield and 1-butanol was its major component. The ester moiety is apparently hydrolyzed under strongly basic reaction conditions. The above observations may account for the fact that no diazirines **1** have been reported thus far. Given the difficulties encountered in the preparation of the butyl ester **6b**, a slightly more hindered analogue of the methyl ester **6a**, it seemed unlikely to be able to reach an even more hindered ester (e.g., *tert*-butyl) that would have a greater chance to sustain the reaction conditions of Graham's oxidation. As expected, transesterification of **6a** with *tert*-butyl alcohol did not occur.

We attempted to take advantage of Moss' modification of Graham's reaction,[6] whereby halodiazirines **1a**−**d**

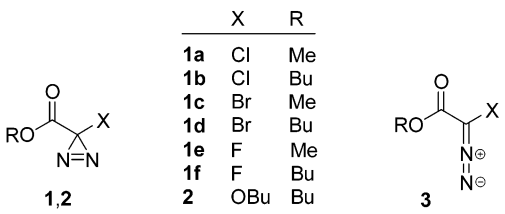
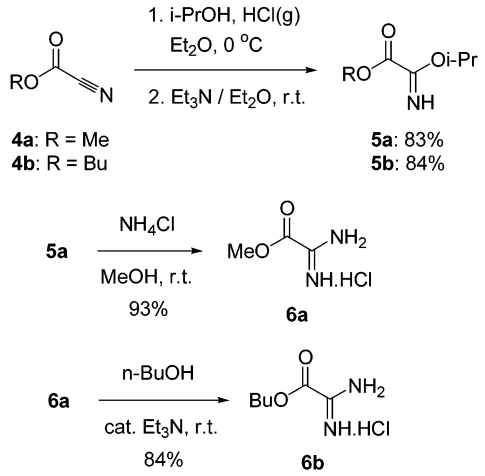


FIGURE 1.

SCHEME 1



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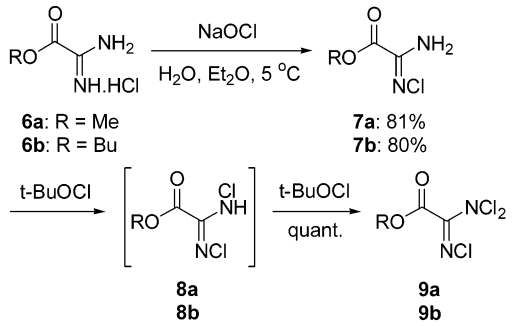
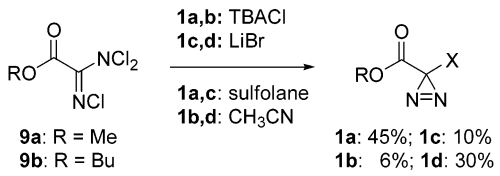
10.1021/jo040194r CCC: $27.50
Published on Web 09/22/2004

SCHEME 2



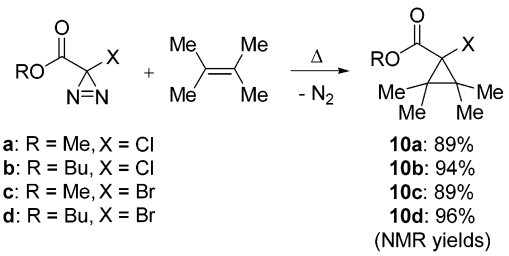
SCHEME 3



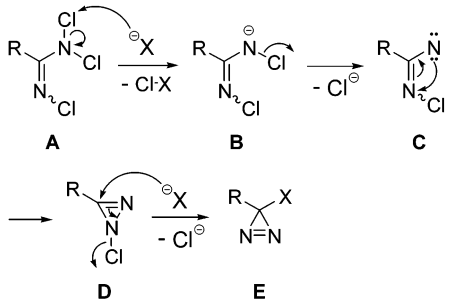
would be formed from the corresponding *N*,*N*′-dichloroamidines by using non-hydrolytic basic conditions (bulky base). Amidines **6** can be chlorinated in good yield with 1 equiv of sodium hypochlorite to afford the *N*-chloroamidines **7** (Scheme 2). The desired *N*,*N*′-dichloroamidines **8** are probably formed on further chlorination of **7** with 1 equiv of *tert*-butyl hypochlorite. However, the isolation of **8** is not possible due to their disproportionation[7] back to **7** and to the *N*,*N*,*N*′-trichloroamidines **9**. Treatment of **7** with an excess of *tert*-butyl hypochlorite affords **9** in quantitative yield. Only a few *N*,*N*,*N*′-trichloroamidines have been reported in the literature[8] and no reference pertains to their use as starting materials in organic synthesis. Despite the reported lability of some trichloroamidines,[8b] in our hands trichloroamidines **9**, prepared from crude (but pure by NMR) chloroamidines **7**, were stable in the dark for days at room temperature and for months at 0 °C. Interestingly, samples of **9** prepared from purified (crystalized from pentane/ether) **7** tended to start decomposing in weeks at 0 °C.

We have discovered that trichloroamidines **9** are reductively dechlorinated[9] to the halodiazirines **1a**−**d** with chloride or bromide ion under anhydrous conditions at room temperature (all yields are optimized). Chlorodiazirine **1a** can be prepared in 45% yield by treatment of **9a** with 5 equiv of tetrabutylammonium chloride (TBACl) in dry sulfolane (Scheme 3). The low vapor pressure of sulfolane allows for removal of the product from the reaction mixture under high vacuum. Virtually all chlorine, a presumed byproduct of the reaction, stays in solution (possibly associated with unreacted TBACl) and

SCHEME 4



SCHEME 5



is not vacuum-transferred along with the desired product. Bromodiazirine **1c** can be similarly prepared in 10% yield by the reduction of **9a** with 15 equiv of LiBr. The lower yield of **1c** compared to **1a** may be due to lower volatility of the former.

Reductive dechlorination of **9b** with 15 equiv of LiBr in dry acetonitrile followed by extraction with pentane resulted in 30% yield of bromodiazirine **1d**. Chlorodiazirine **1b** was obtained in only 6% yield upon reduction of **9b** with 5 equiv of TBACl in dry acetonitrile, extraction with pentane, and chromatographic separation from a mixture of products.

The diazirines **1a**−**d** have been characterized by their NMR, IR, and UV spectra. The chemical shifts of ^{13}C NMR signals of diazirine carbon (∼40 ppm for chlorodiazirines **1a**,**b**; ∼30 ppm for bromodiazirines **1c**,**d**) are similar to those reported for phenylhalodiazirines.[10] In IR spectra, the N=N stretching frequency is at 1615 (**1a**,**b**) or 1610 cm^{-1} (**1c**,**d**). The UV spectra show multiple weak absorptions (N=N n→π^*, $\epsilon \approx 10$) in the 294−335 nm region.

Acetonitrile solutions of the diazirines **1a**−**d** were stable in the dark at room temperature for at least days. Thermolysis of **1a**−**d** in tetramethylethylene afforded the corresponding cyclopropanecarboxylates **10**[11] (Scheme 4).

The proposed mechanism of the reductive dechlorination of *N*,*N*,*N*′-trichloroamidines **A** with halide ion is shown in Scheme 5. The key feature of the mechanism is the formation of the *N*,*N*′-dichloroamidine anion **B** in the first step.[6] The remaining events are identical with those of the Graham's reaction (formation of the imidoyl nitrene **C**, ring closure to the 1*H*-diazirine **D**, and S_N2' isomerization to the 3*H*-diazirine **E**).

With bromodiazirines **1c** and **1d** in hand, we attempted several bromide exchange reactions in DMF (extractive

(7) A similar disproportionation of *N*,*N*′-dichlorobenzamidine was described in ref 6.

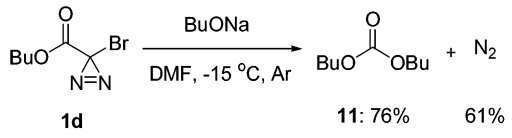
(8) (a) Coon, C. L.; Ross, D. L.; Hill, M. E. *Tetrahedron Lett.* **1966**, 3537. (b) Markovskii, L. N.; Pinchuk, A. M.; Khimchenko, T. V. *J. Org. Chem. USSR* (*Engl. Transl.*) **1969**, *5*, 1283. (c) Coon, C. L. Trichloroamidines, useful as chlorinating agents, bleaches, bactericides. U.S. Patent 3,526,664, September 1, 1970. (d) Coon, C. L. Polychlorobisamidines. U.S. Patent 3,673,252, June 27, 1972. (e) Davydov, A. V.; Kretov, A. E. *Zh. Vses. Khim. Ova. im. D. I. Mendeleeva* **1981**, *26*, 478.

(9) Reductive defluorination of tetrafluoroformamidine with 2 equiv of potassium iodide in acetonitrile was reported to yield difluorodiazirine. Rebertus, R. L.; Toren, P. E. *J. Org. Chem.* **1967**, *32*, 4045.

(10) Terpinski, J.; Denney, D. Z.; Beveridge, R.; Cox, D. P.; Moss, R. A. *Magn. Reson. Chem.* **1987**, *25*, 923.

(11) Cyclopropanecarboxylates **10a,c**: (a) Seyferth, D.; Woodruff, R. A.; Mueller, D. C.; Lambert, R. L. *J. Organomet. Chem.* **1972**, *43*, 55. (b) Mueller, C.; Stier, F.; Weyerstahl, P. *Chem. Ber.* **1977**, *110*, 124.

SCHEME 6



workup) or *N*-methylpyrrolidinone (NMP, evaporative workup). Treatment of **1c**,**d** with tetrabutylammonium fluoride at 0 °C led to decomposition and no fluorodiazirines **1e**,**f** were obtained. The reaction of **1d** with sodium butoxide in DMF at −15 °C under argon unexpectedly afforded dibutyl carbonate (**11**) in 76% yield (Scheme 6). Nitrogen gas liberated during the reaction was collected in 61% yield and was identified by mass spectrometric analysis (N_2 from air was rigorously excluded by carrying out all operations under argon—virtually no signals of air gases were observed in the mass spectra). On the basis of this observation, halodiazines **1a**−**d** may decompose by attack of hydroxide ion under Graham's oxidation conditions and hence cannot be isolated.

In summary, carboalkoxychloro- and bromodiazirines **1a**−**d** have been prepared by reductive dechlorination of the trichloroamidines **9** with TBACl or LiBr in dry sulfolane or acetonitrile. This novel method of preparation of halodiazirines constitutes the first documented example of synthetic use of *N*,*N*,*N*′-trichloroamidines. Further studies on the extension of this methodology to other halodiazirines as well as preparation of heterosubstituted carboalkoxydiazirines and matrix isolation of the corresponding carbenes are in progress.

Experimental Section

Caution! Neat diazirines are potentially shock sensitive and may violently decompose without warning. All operations with neat diazirines should be carried out behind a safety shield. However, we have never experienced any violent decomposition of the diazirines **1a**−**d**.

Methyl 2-Imino-2-isopropoxyacetate (5a). A mixture of 68 g (0.80 mol) of methyl cyanoformate (**4a**), 46 g (0.77 mol) of dry i-PrOH, and 700 mL of dry Et_2O was cooled to −5 °C with an ice-salt bath. Then, 117 g (3.2 mol) of dry HCl was slowly absorbed in the mixture with good stirring while maintaining the temperature below 10 °C. A white suspension formed. The reaction flask was sealed with septa and kept at 0 °C overnight. The contents of the flask solidified. Volatiles (HCl and Et_2O) were removed under water aspirator vacuum. The resulting white solid was washed in the reaction flask with 4 × 1000 mL of dry Et_2O and then dried in vacuo to yield 122 g (84%) of **5a**·HCl. ^{1}H NMR (CD_3CN) δ 12.20 (br s, 2H), 5.76 (sept, J = 6.1 Hz, 1H), 3.93 (s, 3H), 1.46 (d, J = 6.1 Hz, 6H); ^{13}C NMR (CD_3CN) δ 160.8, 156.8, 83.7, 55.7, 21.5.

To a suspension of 122 g (0.67 mol) of **5a**·HCl in 2500 mL of dry Et_2O was added a solution of 75 g (0.74 mol) of Et_3N in 300 mL of Et_2O. The mixture was stirred at room temperature for 4 h and filtered and the filtrate was concentrated under reduced pressure to afford 96 g (83% from **4a**) of **5a**, a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 8.77 (br s, 1H), 5.13 (sept, J = 6.2 Hz, 1H), 3.83 (s, 3H), 1.31 (d, J = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.9, 158.4, 70.5, 53.4, 21.2; IR (film) 3330, 1750, 1655 cm^{-1}; HRMS (CI+) *m*/*z* calcd for $C_6H_{12}NO_3$ $(M + H)^+$ 146.0817, found 146.0825.

Carbomethoxyformamidine Hydrochloride (6a). A mixture of 95.5 g (0.66 mol) of **5a**, 250 mL of MeOH, and 35.1 g (0.66 mol) of NH_4Cl was stirred at room temperature for 24 h. Most of the MeOH was removed under reduced pressure. To the concentrate was slowly added 600 mL of dry Et_2O with vigorous stirring. The product, a white solid, was filtered off, washed with dry Et_2O and dried in vacuo. Further concentration of the ethereal phase afforded another crop of product. The total yield of **6a** was 85.1 g (93%). Mp >260 °C (sealed capillary); ^{1}H NMR (DMSO-d_6) δ 9.85 (br s, 4H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 157.1, 154.5, 54.4; IR (KBr) 3180, 1780, 1695 cm^{-1}; MS (CI$^+$) *m*/*z* calcd for $C_3H_7N_2O_2$ $(M - Cl)^+$ 103.05, found 103.04.

Carbobutoxyformamidine Hydrochloride (6b). A mixture of 20.0 g (144 mmol) of **6a**, 800 mL of dry n-BuOH, and 0.85 g (8.4 mmol) of Et_3N was stirred at room temperature for 24 h. Most of the n-BuOH was removed at 30 °C (1×10^{-1} mmHg). To the concentrate was slowly added 300 mL of dry Et_2O with good stirring. The product, a white solid, was filtered off, washed with dry Et_2O, and dried in vacuo. This procedure afforded 22.9 g of **6b** containing ca. 6 mol % of Et_3N·HCl. The yield of **6b** after accounting for the latter impurity was 84%. Mp 114−116 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.77 (br s, 4H), 4.31 (t, J = 6.6 Hz, 2H), 1.68 (m, 2H), 1.40 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 156.6, 154.5, 67.6, 29.5, 18.2, 13.4; IR (KBr) 3150, 1770, 1710 cm^{-1}; HRMS (CI$^+$) *m*/*z* calcd for $C_6H_{13}N_2O_2$ $(M - Cl)^+$ 145.0977, found 145.0975.

Carbomethoxy-*N*-chloroformamidine (7a). A mixture of 15.0 g (108 mmol) of **6a** in 50 mL of water and 300 mL of Et_2O was cooled below 5 °C with an ice−water bath. Then, 143 g of ice-cold 5.25% Austin's commercial bleach (101 mmol of NaOCl) was added dropwise with vigorous stirring while maintaining the temperature below 10 °C. When the addition was completed, the mixture was stirred for another 5 min. Two layers were separated and the aqueous phase was extracted with 3 × 300 mL of Et_2O. Combined Et_2O phases were dried over $MgSO_4$ and concentrated under reduced pressure at room temperature to afford 12.0 g (81%) of **7a**, a white solid. Mp 72−74 °C (pentane/Et_2O); ^{1}H NMR ($CDCl_3$) δ 5.94 (br s, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 154.5, 53.8; IR (film) 3480, 3360, 1755, 1645 cm^{-1}; HRMS (CI$^+$) *m*/*z* calcd for $C_3H_5ClN_2O_2$ M^+ 136.0039, found 136.0039.

Carbobutoxy-*N*-chloroformamidine (7b). The above method for the preparation of **7a** was used with 11.0 g (58.0 mmol) of **6b** (containing 6 mol % of Et_3N·HCl) and 82.5 g of 5.25% bleach (58.2 mmol of NaOCl), affording 8.33 g (80%) of **7b**, a white solid. Mp 44 °C (pentane); ^{1}H NMR ($CDCl_3$) δ 5.94 (br s, 2H), 4.32 (t, J = 6.8 Hz, 2H), 1.74 (m, 2H), 1.42 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.3, 154.8, 67.4, 30.3, 18.9, 13.6; IR (KBr) 3490, 3350, 1740, 1635 cm^{-1}; HRMS (ES$^+$) *m*/*z* calcd for $C_6H_{11}ClN_2O_2Na$ $(M + Na)^+$ 201.0407, found 201.0414.

Carboalkoxy-*N*,*N*,*N*′-trichloroformamidines (9). A mixture of 50.0 mmol of the corresponding *N*-chloroamidine **7** and 81 g (0.75 mol) of t-BuOCl was stirred at room temperature in the dark for 24 h. Upon concentration under reduced pressure at room temperature, **9** were obtained in quantitative yield as yellow-orange liquids with a strong chlorine-like odor. **9a**: ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.3, 157.5, 54.0; IR (film) 1755, 1605 cm^{-1}; HRMS (CI$^+$) *m*/*z* calcd for $C_3H_4Cl_3N_2O_2$ $(M + H)^+$ 204.9337, found 204.9352. **9b**: ^{1}H NMR ($CDCl_3$) δ 4.42 (t, J = 6.6 Hz, 2H), 1.76 (m, 2H), 1.46 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.5, 157.2, 67.8, 30.2, 18.9, 13.5; IR (film) 1755, 1600 cm^{-1}; HRMS (CI$^+$) *m*/*z* calcd for $C_6H_{10}Cl_3N_2O_2$ $(M + H)^+$ 246.9807, found 246.9809.

3-Carbomethoxy-3-chlorodiazirine (1a). In a magnetically stirred 1000-mL round-bottomed flask, 18.0 g (64.8 mmol) of dry tetrabutylammonium chloride was dissolved in 80 mL of dry sulfolane. Then, 2.44 g (11.8 mmol) of **9a** in 25 mL of sulfolane was added dropwise over 10 min in the dark with vigorous stirring. When the addition was completed, the reaction flask was equipped with vacuum adapter connected to a U-trap evacuated by diffusion pump and cooled to −196 °C. The product was removed from the solution at room temperature under vacuum (5×10^{-4} mmHg) and collected in the U-trap. After 7 h the U-trap contained 1.03 g of turbid colorless liquid. The crude product was purified by fractional vacuum transfer (4×10^{-2} mmHg) into a trap cooled to −196 °C. The yield of **1a**, a clear colorless liquid, was 0.72 g (45%). ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 54.5, 41.1; IR (film) 1755, 1615 cm^{-1}; UV (pentane) λ_{max} 294 (sh, ϵ ∼6), 307 (sh, ϵ ∼13), 320 (ϵ ∼18), 333 (ϵ ∼14) nm.

3-Bromo-3-carbobutoxydiazirine (1d). To a solution of 20.0 g (0.23 mol) of dry LiBr in 340 mL of dry CH_3CN was added 3.80 g (15.4 mmol) of **9b** in 35 mL of CH_3CN dropwise over 15 min in the dark with vigorous stirring. When the addition was completed, the mixture was stirred for another 10 min and then was extracted with 5 × 400 mL of pentane. The combined pentane layers were concentrated under reduced pressure below 10 °C. This procedure afforded 1.07 g of pale yellow liquid, which was subsequently purified at room temperature by vacuum transfer (4×10^{-2} mmHg) into a U-trap cooled to −196 °C. The yield of **1d**, a colorless liquid with fruity odor, was 1.03 g (30%). ^{1}H NMR ($CDCl_3$) δ 4.22 (t, J = 6.6 Hz, 2H), 1.65 (m, 2H), 1.38 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.6, 68.2, 30.3, 30.0, 18.8, 13.5; IR (film) 1745, 1610 cm^{-1}; UV (pentane) λ_{max} 307 (sh, ϵ ∼15), 323 (ϵ ∼29), 335 (ϵ ∼32) nm.

Acknowledgment. Financial support was provided by NIH and the University of Pennsylvania Research Fund. T.M. gratefully acknowledges the Isabel and Alfred Bader Foundation for a graduate fellowship. We thank Drs. R. K. Kohli and J. Honovich for mass spectrometric analyses.

Supporting Information Available: Experimental and characterization data for compounds **1a**−**d**, **5**, **6**, **7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040194R