SYNTHESIS OF POLYDEUTERATED BENZOTHIAZOLES VIA SUPERCRITICAL DEUTERATION OF ANILINES

Thomas Junk[1]*, W. James Catallo[2], and L. Dana Civils[2]

[1]Hazardous Waste Research Center and [2]Laboratory for Ecological Chemistry, SVM,

Louisiana State University, Baton Rouge, LA 70803 (U.S.A)

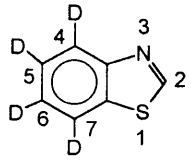
SUMMARY

2-[^{2}H]Benzothiazole, readily available according to the literature, was observed to undergo slow isotope exchange in water. This necessitated development of practical syntheses for benzothiazoles carrying deuterium labels in positions other than 2. [4,5,6,7-$^2H_4$]Benzothiazole and 4-[$^2H_3$]methyl[5,6,7-$^2H_3$]benzothiazole were prepared in good yields from [$^2H_7$]aniline and 2-[$^2H_9$]toluidine, which were obtained by novel rapid isotope exchange in supercritical deuterium oxide.

Key words: Deuterium labelling, supercritical isotope exchange, deuterated anilines, benzothiazole.

INTRODUCTION

Ongoing studies of the transformation of benzothiazole, a pollutant near sites of specific industrial activity (1) required the preparation of deuterated analogs of **1** and **2**. Initial experiments with 2-[^{2}H]benzothiazole, prepared according to the literature (2) resulted in a gradual loss of the deuterium label in water over several months.



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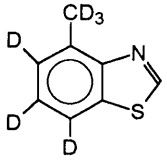

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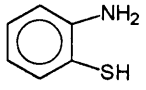

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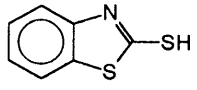

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CCC 0362–4803/97/080625–06$17.50
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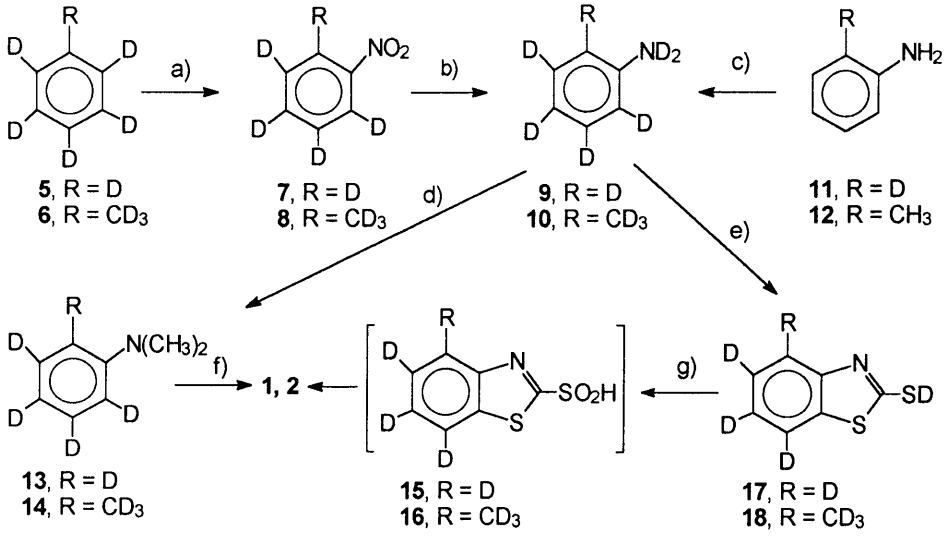
Received 26 August 1996
Revised 15 April 1997

In addition, the 2 positions of **1** and **2** are preferred sites of chemical transformations (3), thereby generating unlabelled transformation products. Several attempts to deuterate benzothiazole directly by Lewis acid catalyzed proton exchange under non-aqueous (4) and aqueous (5, 6) exchange conditions were unsuccessful. Both the High-Temperature-Dilute-Acid (HTDA) deuteration approach (7) and the attempted deuteration of benzothiazole with supercritical deuterium oxide under basic conditions (8) resulted in the generation of [$^2H_7$]aniline as the main organic product. The noble metal catalyzed exchange of **1** (9, 10) resulted in rapid catalyst poisoning, as expected. Attempts to deuterate **3** or **4** also were abandoned.

Of the various published synthetic pathways to benzothiazole and its alkylated homologs, only the treatment of N,N-dimethylaniline with sulfur (11) and the condensation of anilines with carbon disulfide and sulfur to **4** (12), followed by partial desulfurization were considered suitable options for the preparation of deuterated analogs. The preparation of the required deuterated anilines either by nitration and reduction of commercial perdeuterated aromatic precursors or by post-synthetic isotope exchange was investigated. All conversions are summarized in Scheme 1.



Scheme 1 Pathways to deuterated benzothiazoles. a) H_2SO_4/HNO_3, b) D_2/Pd, c) D_2O_{sc}, NaOD, d) CH_3I, e) S_8/CS_2, f) S_8, reflux, g) H_2O_2, HCl

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DISCUSSION

The nitration of [$^2H_6$]benzene or [$^2H_8$]toluene with H_2SO_4/HNO_3 produced isotopically pure products, but subsequent reduction with tin shot or hydrogen/palladium resulted in partial losses of the aromatic labels. This was avoided by reduction with deuterium/palladium in methan[^{2}H]ol. The deuteration of aromatic amines by the HDTA method is well established (13), but can be time–consuming. Subsequently, **9** and **10** were prepared from **11** and **12** by supercritical isotope exchange under basic conditions (8), a procedure which was found to be far superior to both HTDA method and *de novo* synthesis. Isotopic equilibration was complete within several hours, and extended to substrate methyl moieties known to remain unchanged during HTDA treatment. This method appears to be applicable to the preparation of perdeuterated alkylated anilines in general.

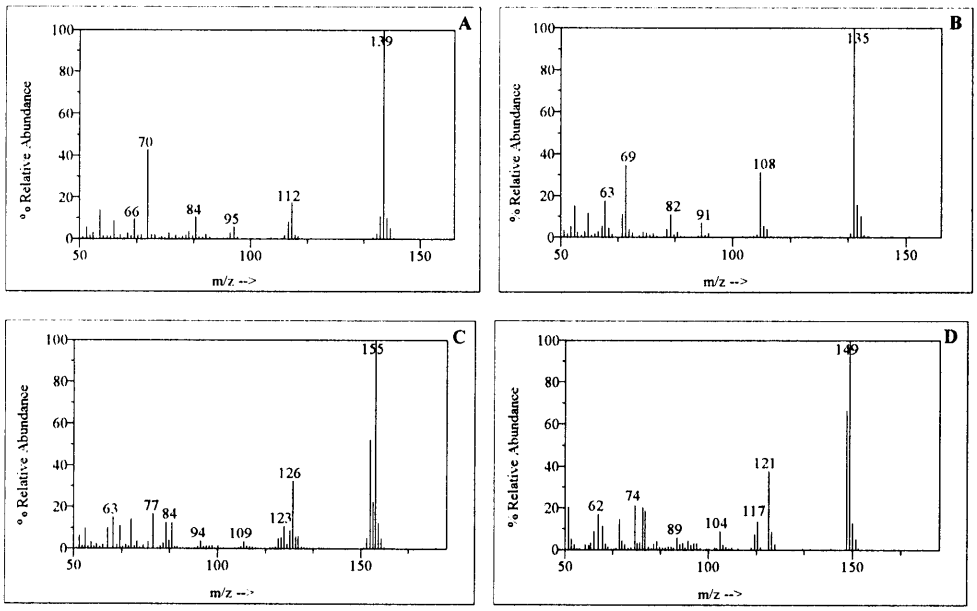

Figure 1 Mass spectra of [4,5,6,7-d_4]benzothiazole and 4-[$^2H_3$]methyl[5,6,7-$^2H_3$]benzothiazole (C), compared with reference spectra of non–labelled analogs (B and D). GC inlet, EI, 30 eV.

The preparation of N,N-dimethyl[$^2H_5$]aniline **13** has been described in the literature (14), but the subsequent cyclization of **13** to **1** by heating with sulfur was found to be unsatisfactory in terms of product yield and purity. In contrast, the treatment of **9** or **10** with carbon disulfide/sulfur (12) produced **17** and **18** in good yields. It is important to note that exchangeable protons (introduced

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during workup or handling of **9** or **10** in moist air) partially equilibrate during cyclization. Consequently, deuterated anilines have to be handled in a dry box if isotopic purities in excess of the ones reported in this study (>92/93%) are required of the final products.

Of several methods reported for the oxidation of **4** to benzothiazole, three (15, 16, 17) were tested. In practice, an adaptation of Cech's method (17, oxidation under acidic conditions with excess hydrogen peroxide) was best suited to prepare **1** and **2** in consistent yields. Mass spectra of **1** and **2** are shown in Fig. 1.

EXPERIMENTAL

Materials and methods. The published procedure for preparing [$^2H_5$]nitrobenzene (18) was extended to 2-[$^2H_7$]nitrotoluene, and these intermediates reduced to the amines with D_2/Pd. N,N-dimethyl[$^2H_5$]aniline was prepared by adapting a procedure given for the preparation of N,N-bis([$^2H_3{}^{13}C$]methyl)aniline (14), followed by cyclization with sulfur as reported (11). Other chemicals employed in this study were purchased from Aldrich Chemical Co. and used as received. Supercritical isotope exchange was performed in a 50 mL Hastelloy–C22 autoclave with metal gasketing (8) at approximately 600 bar pressure. **CAUTION: 316SS autoclaves suffer extreme corrosion under these conditions and are not suitable.** Melting points were measured on a Meltemp II melting point apparatus. GC/MS analyses were performed a Shimadzu GC17A gas chromatograph with QP5000 mass spectrometer, equipped with a 30 m × 0.28 mm × 0.2 μm DB–5 column. NMR spectra were recorded on a Bruker AC-200 spectrometer. Chemical and isotopic purities were evaluated by GC/MS and NMR, as appropriate.

[$^2H_7$]Aniline **9** and 2-[$^2H_9$]toluidine **10** by supercritical deuterium exchange. A 50 mL autoclave was charged with 6.0 g aniline (6.0 g 2-toluidine), 20 g deuterium oxide, and 0.1 g sodium deuteroxide solution 40%, purged with nitrogen, then placed in a preheated furnace. **CAUTION**: **Very high pressure.** After heating to 400±10° for 12 hrs, the autoclave was allowed to cool. The products were separated from aqueous phases, the remaining aqueous phases extracted with diethyl ether, and the combined organic phases returned for further treatment until the desired isotopic purities (>95%) were achieved. Yield, 5.03 g or 78% [$^2H_7$]aniline (5.35 g or 82% 2-[$^2H_9$]toluidine).

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2-Mercapto[$^2H_4$]benzothiazole **17** and 2-mercapto-4-[$^2H_3$]methyl[$^2H_3$]benzothiazole **18**.

CAUTION: **High pressure and malodorous byproducts.** A 15 mL Teflon lined bomb (19) was charged with 4.6 g (46 mmol) [$^2H_7$]aniline **9** (5.35 g or 46 mmol 2-[$^2H_9$]toluidine **10**), 3.8 g (50 mmol) carbon disulfide, and 3.2 g (100 mmol) sulfur. The bomb was heated to 250±5° for 4 hrs. After cooling, the remaining semisolid was dissolved in 8.5 g (212 mmol) sodium hydroxide and 100 mL water, decanted from a tarry residue, and the product precipitated by addition of excess acetic acid. After standing for 15 min solid material was collected by filtration. One recrystallization from glacial acetic acid furnished products that were sufficiently pure for further use. Yield, 4.2 g (53%) 2-mercapto[$^2H_4$]benzothiazole (3.5 g or 40.6% 2-mercapto-4-[$^2H_3$]methyl[5,6,7-$^2H_3$]benzothiazole).

[4,5,6,7-$^2H_4$]Benzothiazole **1** and 4-[$^2H_3$]methyl[5,6,7-$^2H_3$]benzothiazole **2**. A round bottom flask equipped with magnetic stirring and a Dean–Stark trap was charged with 4.1 g (24 mmol) 2-mercapto[$^2H_4$]benzothiazole **17** and 17.6 mL 36% hydrochloric acid. Oxidation was achieved by slow addition of 9.8 mL (147 mmol) 30% hydrogen peroxide at temperatures below 70°. The mixture subsequently was heated to 80° for 1 hr, neutralized with sodium carbonate (**foaming**), and the product steam distilled from the reaction mixture into the trap. Redistillation afforded pure material. Yield, 1.80 g (54%) [4,5,6,7-$^2H_4$]benzothiazole, isotopic purity >93%. By analogy, 3.50 g of **18** were converted to 1.50 g or 52% 4-[$^2H_3$]methyl[5,6,7-$^2H_3$]benzothiazole, isotopic purity >92%, by treatment with 15 mL 36% hydrochloric acid and 9.8 mL 30% hydrogen peroxide. ^{13}C NMR data for **1**: 121.5, C–D [$^1J(^2H–^{13}C)$ = 4.6 Hz]; 123.3, C–D [$^1J(^2H–^{13}C)$ = 4.6 Hz]; 123.6, C–D [$^1J(^2H–^{13}C)$ = 4.6 Hz]; 125.4, C–D [$^1J(^2H–^{13}C)$ = 4.6 Hz]; 133.5, C; 153.1, C; 153.8, C–H [$^1J(^1H–^{13}C)$ = 211.3 Hz].

ACKNOWLEDGMENT

We wish to thank the U.S. Minerals Management Service for supporting this and much related research. We thank Dr. Xiao (Katherine) Wu for her assistance in obtaining NMR spectra.

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