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[U-^{14}C]- and [$^{13}C_6$]-1,3-dibromobenzene; useful precursors with a rare substitution pattern in the synthesis of isotopologs

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A four-step procedure for the preparation of [U-^{14}C]-1,3-dibromobenzene and [$^{13}C_6$]-1,3-dibromobenzene, from the corresponding bromobenzene, has been developed in a 30% yield. The products were isolated in a high specific activity, 2.6 GBq/mmol, and highest possible ^{13}C incorporation.

Keywords: isotopically labelled synthesis; C-14; C-13; 1,3-dibromobenzene; ^{13}C; ^{14}C; *m*-dibromobenzene; stable labelled synthesis

Introduction

Isotopologs of 1,3-dibromobenzene[1] have been scarcely used over the years for the preparation of isotopically modified substances with a *meta* substitution pattern. To be able to prepare isotopologs of a candidate drug, a method was developed for the preparation of [U-^{14}C]- and [$^{13}C_6$]-1,3-dibromobenzene from [U-^{14}C]bromobenzene and [$^{13}C_6$]bromobenzene, respectively.

Experimental

General methods

All solvents used were analytical grade and commercially available. Anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon. ^{1}H spectra were recorded on a Bruker DRX600 NMR Spectrometer, ^{1}H spectra were referenced to TMS which was set to 0 ppm. Mass spectra were recorded on a gas chromatograph coupled mass spectrometer with electron impact ionization. Liquid scintillation analysis was performed on a PACKARD TRI-CARB 2900TR. Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F254) and UV-light (254 nm) visualized the spots. Flash column chromatography was performed on a Redisep^{TM} prepacked column.

[U-^{14}C]Nitrobromobenzene (3)

[U-^{14}C]Bromobenzene, **2**, (483 mg, 2.86 mmol, 7.4 GBq, 2.6 GBq/mmol) was mixed with nitric acid (2.2 mL, 31 mmol) and was cooled to 0°C. Sulfuric acid (150 µL, 2.8 mmol) was added, carefully, dropwise at 0°C four times, subsequently. The reaction mixture was taken slowly to 21°C. The reaction mixture was quenched with ice (10 g) and was extracted with diethyl ether, in three portions. The ethereal phase was dried over sodium sulfate, filtered and concentrated to give the title compound (891 mg, 73%). GC-MS *m/z* 201, 203, 205, 207, 209 (M^-).

[$^{13}C_6$]Nitrobromobenzene

[$^{13}C_6$]Nitrobromobenzene was prepared as for [U-^{14}C]nitrobromobenzene with similar yield. ^{13}C NMR (125.7 MHz, DMSO-d_6) δ ppm 146.8 (t), 134.7 (t), 132.8 (t), 129.3 (t), 112.8 (t). GC-MS *m/z* 207, 209 (M^-).

[U-^{14}C]Bromoaniline hydrochloride (4)

[U-^{14}C]Nitrobromobenzene, **3**, (891 mg, 2.08 mmol) was mixed with tin(II) chloride dihydrate (1.4 mg, 6.2 mmol) in ethyl acetate (5 mL). The mixture was heated to 78°C under nitrogen. Two extra portions of tin(II) chloride dihydrate (470 mg, 2.1 mmol) were added to complete the reduction. The reaction was concentrated. The residue was slurried in dichloromethane and filtered through silica (5 g), eluting with dichloromethane and dichloromethane/methanol 10/1. Hydrogen chloride in diethyl ether (8.33 mL, 8.33 mmol) was added. The mixture was concentrated to give [U-^{14}C]bromoaniline hydrochloride, **4**, (765 mg, ~100%). GC-MS *m/z* 169, 173, 175, 177, 179 (M^-).

[$^{13}C_6$]Bromoaniline hydrochloride

[$^{13}C_6$]Bromoaniline hydrochloride was prepared as for [U-^{14}C] bromoaniline hydrochloride with a similar yield. GC-MS *m/z* 177, 179 (M^-).

[U-^{14}C]Dibromoaniline hydrochloride (5) and [U-^{14}C]tribromoaniline hydrochloride (6)

[U-^{14}C]Bromoaniline hydrochloride, **4**, (458 mg, 2.08 mmol) was made basic with sodium hydroxide (10%, 4 mL) and was extracted

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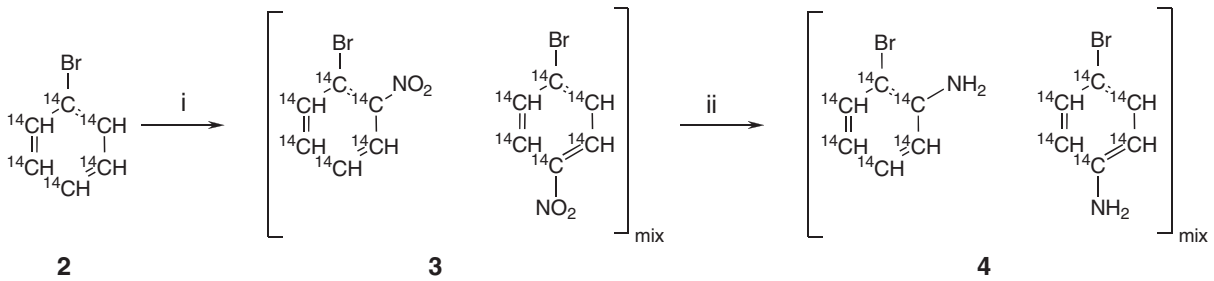
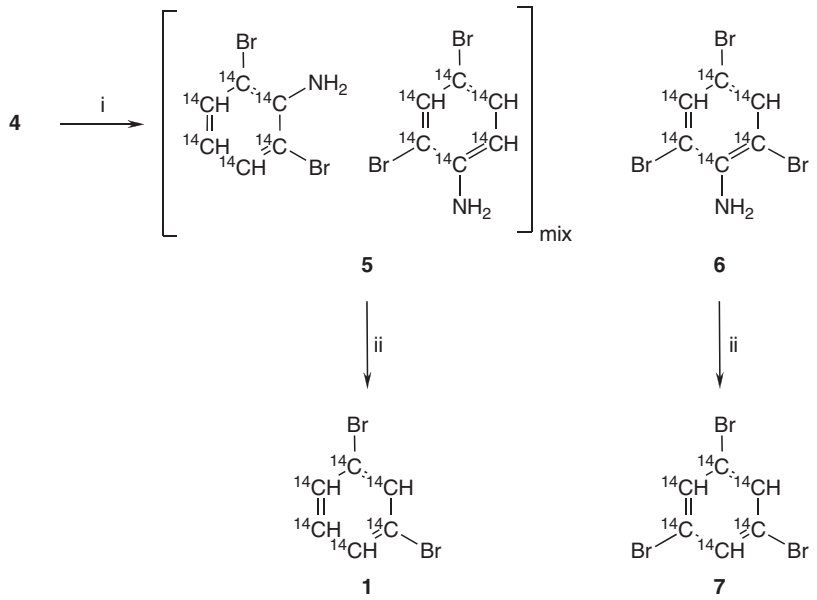


Scheme 1. (i) HNO_3/H_2SO_4, (ii) $SnCl_2$.



Scheme 2. (i) HMTAB, (ii) H_3PO_2, $NaNO_2$, Cu_2O.

with dichloromethane (10 mL) in four portions (phase separation by centrifuge). The organic phase was washed with water (3 mL) in three portions, was dried over sodium sulfate and was filtered. HMTAB [2] (478 mg, 1.0 mmol) was added portionwise (10 in all) until bromination was complete. The reaction mixture was filtered through silica (4 g) and was eluted with dichloromethane and dichloromethane/methanol 10/1. The eluate was carefully concentrated with a stream of nitrogen. The distillate was trapped in a dry-ice/ethanol cooled collector. The residue was chromatographed on silica (12 g) using heptane to heptane/ethyl acetate 4/1 ($R_f \sim 0.3$) as eluent. Pooled fractions were mixed with hydrogen chloride in dioxane (0.52 mL, 2.1 mmol). The mixture was concentrated to give [U-^{14}C]Dibromoaniline hydrochloride, **5**, (332 mg, 53%). GC-MS *m/z* 253–269 (M^-).

Fractions containing [U-^{14}C]tribromoaniline were pooled and hydrogen chloride in dioxane (0.52 mL, 2.1 mmol) was added. The mixture was concentrated to give [U-^{14}C]tribromoaniline hydrochloride, **6**, (175 mg, 22%). GC-MS *m/z* 327, 329, 331, 333, 335, 337 (M^-).

[$^{13}C_6$]Dibromoaniline hydrochloride and [$^{13}C_6$]tribromoaniline hydrochloride

[$^{13}C_6$]Dibromoaniline hydrochloride was prepared as for [U-^{14}C]dibromoaniline hydrochloride with a similar yield. GC-MS *m/z* 255, 257, 259 (M^-).

[$^{13}C_6$]Tribromoaniline hydrochloride was isolated with a similar yield. GC-MS *m/z* 333, 335, 337, 339 (M^-).

[U-^{14}C]-1,3-Dibromobenzene (1)

[U-^{14}C]Dibromoaniline hydrochloride, **5**, (332 mg, 1.11 mmol) was dissolved in hypophosphorous acid (4.46 mL, 44 mmol) and was cooled to 0°C. Sodium nitrite (191 mg, 2.77 mmol), dissolved in water (1 mL), was added. Dichloromethane (5 mL) and then copper(I) oxide (3 mg, 0.02 mmol) were added at 0°C. After 4 h the organic phase was separated and the water phase was extracted with dichloromethane (2 × 2 mL). The combined organic phase was dried over sodium sulfate, was filtered and concentrated. The product was bulb-to-bulb distilled at 60–70°C at 0.8 mbar on a kugelrohr apparatus to give 2.22 GBq [U-^{14}C]-1,3-dibromobenzene, **1**, (213 mg, 77%, S.A. 2.6 GBq/mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 7.31 (t, J = 8.04 Hz, 1H) 7.62 (dd, J = 7.97, 1.85 Hz, 2H) 7.85 (m, 1H). GC-MS *m/z* 234, 236, 238, 240, 242, 244 (M^-).

[$^{13}C_6$]-1,3-Dibromobenzene

[$^{13}C_6$]-1,3-Dibromobenzene was prepared as for [U-^{14}C]-1,3-dibromobenzene with a similar yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.43 (m, 1H), 7.72 (m, 1H), 7.92 (m, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 122.5 (m), 130.4 (m), 132.2 (m), 133.4 (m). GC-MS *m/z* 241, 243, 245 (M^-).

Results and discussions

By the nitration of bromobenzene **2** (Scheme 1), a mixture of nitro-bromobenzenes **3** was obtained. The mixture **3** was reduced with tin(II) chloride dihydrate in ethyl acetate to give the corresponding mixture of bromoanilines **4**. The mixture **4** was brominated with a bromine complex of hexamethylene tetraamine (HMTAB) (Scheme 2).[2] In order to a minimize dibromination, the reagent was added in small portions until the bromination was complete. A 2 to 1 mixture of di- and tribrominated aniline, **5** and **6,** was obtained, which could be separated chromatographically on silica. The products were isolated as hydrochloride salts to avoid evaporation in work-up and to have the material prepared for the diazotisative deamination. The dibromoaniline hydrochloride mixture **5** was dissolved in hypophosphorous acid and was diazotized with sodium nitrite. Following the addition of copper(I) oxide, the 1,3-dibromobenzene was extracted into dichloromethane upon formation. [U-^{14}C]-1,3-Dibromobenzene **1** was isolated by a final distillation, in 30% yield from [U-^{14}C]bromobenzene **2**, with retained specific activity, *i.e.* 2.6 GBq/mmol.

2,4,6-Tribromoaniline **6** was prepared in a similar way as for [U-^{14}C]-1,3-dibromobenzene **1**. [$^{13}C_6$]-1,3-Dibromobenzene was prepared in the same way from [$^{13}C_6$]bromobenzene with a similar total yield.

[U-^{14}C]-1,3-Dibromobenzene **1** was used for the preparation of [U-^{14}C]-labeled candidate drug, placing the label in the core of the structure. 2,4,6-Tribromoaniline **6** could be used for the preparation of 1,3,5-tribromobenzene,[3] **7**, analogous to that above.

Conclusions

A good yielding method for the preparation of [U-^{14}C]-1,3-dibromobenzene **1**, with high specific activity, and [$^{13}C_6$]-1,3-dibromobenzene has been developed.

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