A CONVENIENT SYNTHESIS OF ^{13}C-BROMOFORM AND ^{13}C-TETRABROMOMETHANE FROM ^{13}C-IODOMETHANE LABELLING THROUGH ^{13}:CBr_2

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SUMMARY

Phenyldithiane 3 is methylated with $^{13}CH_3I$ to give, through the thioacetal 4, labelled acetophenone (5). NaOBr-cleavage to the title compounds 1 and 2 (65 % and 76 %, respectively) and their use in the preparation of the dibromocyclopropane 6 and the dibromoolefin 7 are described.

Key-words: metallated 1.3-dithiane, hypobromide cleavage of $^{13}CH_3$-acetophenone, $^{13}CHBr_3$, $^{13}CBr_4$, dibromoolefination, $^{13}CBr_2$-addition to cyclohexene.

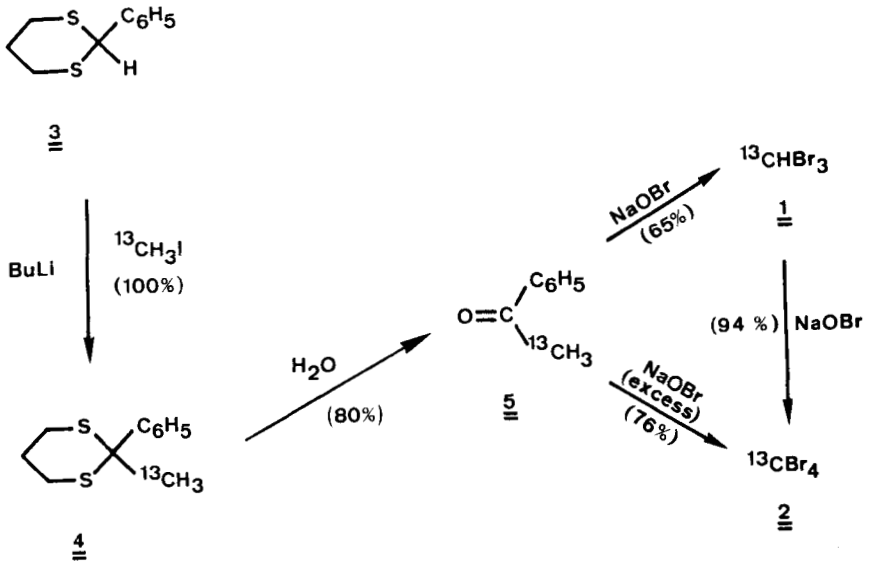
With the advent of ^{13}C-NMR spectroscopy ^{13}C-labelling has become a powerful tool in biochemical and other mechanistic work. In connection with our investigations of lithiocarbenoids, we needed $^{13}CHBr_3$ and $^{13}CBr_4$ for NMR studies. Since dibro-

0362-4803/80/0217-0279$01.00

Received April 3, 1979
Revised April 26, 1979

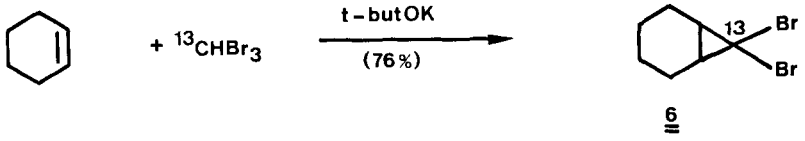
mocyclopropanes and dibromoolefins are versatile synthetic intermediates (see comments and ref. below), we would like to communicate here our reliable, simple and efficient procedure for the conversion of ^{13}C-iodomethane to $^{13}CHBr_3$[1] (1) and $^{13}CBr_4$ (2).

The synthesis is analogous to our previous route to deuteriobenzaldehyde[2]. Phenyldithiane 3 is methylated with $^{13}CH_3I$[3] to methylphenyldithiane 4 through its lithioderivative. Hydrolysis yields acetophenone (5)[4]. On large scale, the



neutral HgO/$HgCl_2$ hydrolysis 4 → 5 turned out to be superior to the less expensive chloramine-T-procedure[5]. The subsequent haloform cleavage is the crucial step requiring inverse addition of a NaOBr solution to acetophenone with cooling in order to prevent formation of too much CBr_4 which can easily be rendered the main product. Under optimum conditions, 65 % of bromoform are isolated along with 10 % of carbontetrabromide; this is separated as a higher boiling fraction (see experimental section).

As examples of incorporation of the CBr_2 unit into organic molecules we describe the preparations of 7-^{13}C-dibromonorcarane 6 and 4-t-butyl-^{13}C-dibromomethylenecyclohexane 7. Of the available procedures for carrying out the reactions (1)[6] and (2)[7] leading to these products from cyclohexene and 4-t-butylcyclohexanone those by Doering[6a] and Posner[7a], respectively, used the precious labelled bromides most economically. Application of reactions (1) and (2)

(1) 

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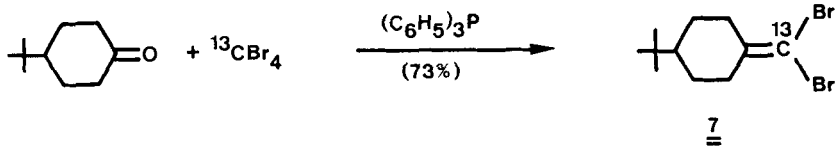
(2) 

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to other substrates[6,7] and further conversions of dibromides of type 6 and 7 can lead to a multitute of labelled structures[8,9].

EXPERIMENTAL SECTION

General remarks: melting points are uncorrected and were determined on a Tottoli melting point apparatus (Büchi) with 50°-range-thermometers (0.2° units). ^1H-NMR spectra: Varian EM 390 or HA 100. ^{13}C-NMR spectra: Varian CFT 20 or XL 100. Chemical shifts δ (ppm) are referred to tetramethylsilane as an internal standard.

2-(^{13}C-Methyl)-2-phenyl-1,3-dithian (4)

To a magnetically stirred solution of 13.9 g (71 mmol) of 2-phenyl-1.3-dithiane 3[2] in 120 ml of THF 47 ml (71 mmol) of an n-butyllithium solution in hexane

were added within 20 min by means of a syringe through a serum cap at - 78° C under argon. The solution was stirred at that temperature for one hour, whereupon 10.0 g (70 mmol) of neat $^{13}CH_3I$[3] were added slowly in the same manner. After 14 h at - 30° C (freezer), the stirred reaction mixture was allowed to warm up to room temperature, 50 ml of dilute HCl and 200 ml of water were added and the aqueous phase was extracted three times with 100 ml each of CH_2Cl_2/pentane (1:1). The combined organic layers were washed twice with 150 ml of water and dried over $MgSO_4$. After evaporation of the solvents, 15.0 g (100 %) of crude pale yellow dithiane 4 remained which solidified on standing. 100 mg of 4 were recrystallized from methanol to give colorless crystals, mp 34° C.

$C_{11}H_{14}S_2$ (210.4) Calc. C 62.84 H 6.71

found C 62.79 H 6.73.

^{1}H-NMR ($CDCl_3$): 1.76 (d, J = 129 Hz, $^{13}CH_3$), 1.78 - 2.04 (m, 2 H, 5-dithiane-CH_2), 2.68 (pseudo-q, 4 H, α-S-CH_2), 7.10 - 7.45 (m, 3 H, arom.), 7.80 - 8.00 (m, 2 H, arom.).

^{13}C-NMR ($CDCl_3$): 24.61 (12, C-5-dithiane), 28.00 (14, α-S-C-dithiane), 32.67 (1000, $^{13}CH_3$), 55.73 (d, J = 36 Hz, 1, C-2-dithiane), 126.95 (10, C-arom.), 127.69 (14, C-arom.), 132.45 (18, C-arom.).

$^{13}CH_3$-Acetophenone (5)

14.9 g (71 mmol) of crude dithiane 4 were dissolved in 450 ml of methanol/water (95:5) and after addition of 28.0 g (97 mmol) of $HgCl_2$ (solution in 100 ml of methanol/water, 95:5) and 11.0 g (51 mmol) of red HgO, the mixture was refluxed for 3 h. The white precipitate was suction filtered and the filter cake was carefully extracted twice with 100 ml of CH_2Cl_2 each. The clear solution was concentrated to 100 ml by distillation through a 20 cm Vigreux-column. After shaking with 400 ml of a 25 % NH_4OAc-solution and extracting the aqueous phase three times with 100 ml of CH_2Cl_2/pentane (1:1), the combined organic layers were washed with 300 ml of saturated NaCl solution and dried over Na_2SO_4. Dis-

tillation afforded 6.7 g (80 %) of labelled acetophenone 5 (bp = 76° C/14 Torr), (bp = 88.5° C/16 Torr, ref.[12]).

^{1}H-NMR ($CDCl_3$): 2.48 (d, J = 126 Hz, $^{13}CH_3$), 7.20 - 7.60 (m, 3 H, arom.), 7.70 - 8.00 (m, 2 H, arom.).

^{13}C-NMR ($CDCl_3$): 26.35 (9999, $^{13}CH_3$), 128.13 (373, arom. C), 128.42 (297, arom. C), 132.89 (216, arom. C), 197.29 (d, J = 43 Hz, 4, C=O).

Reaction of 5 with NaOBr

a) Bromoform (1), $^{13}CHBr_3$

With ice-cooling a NaOBr solution was prepared from 21.6 g (540 mmol) of NaOH, 105 ml of water and 8.3 ml (25.9 g, 162 mmol) of Br_2. The cold solution (max. 5° C) was added within 20 min to 6.5 g (54 mmol) of vigorously stirred and ice cooled acetophenone (5). A slightly yellow solution resulted while the temperature in the reaction vessel rose from 6° to 11° C. The cooling bath was removed and the solution was allowed to warm to room temperature within one hour. A colorless emulsion resulted. In a separatory funnel 10.2 g of product were obtained. The aqueous layer was extracted three times each with 30 ml of ether. The combined organic layers were washed once with $Na_2S_2O_6$ solution (1 g in 150 ml of water) and once with saturated NaCl solution, and dried over $MgSO_4$. After concentration of the solution by distillation through a 20 cm Vigreux-column 8.9 g (65 %) of $^{13}CHBr_3$ (1) were obtained by distillation, bp = 46° C/14 Torr. (bp = 46° C/14 Torr, ref.[13]).

As a higher boiling fraction (bp = 50 - 70° C/14 Torr), 1.8 g (10 %) of $^{13}CBr_4$ (2) could be isolated.

1: ^{1}H-NMR ($CDCl_3$): 6.80 (d, J = 204 Hz).

^{13}C-NMR ($CDCl_3$): 9.67.

2: ^{13}C-NMR ($CDCl_3$): - 29.81.

b) $^{13}CBr_4$ (2)

From $^{13}CHBr_3$ (1)[14]: in an Erlenmeyer flask 4.0 g (15.7 mmol) of 1 were added at room temperature to a stirred NaOBr solution, prepared from 2.54 g (63.5 mmol) of NaOH, 20 ml of water and 1.3 ml (4.1 g, 25.5 mmol) of Br_2. Stirring was continued until all of the bromoform had been transformed to a white solid (ca. 5 h). The product was isolated by the extraction procedure described in a). After removal of the solvent the white crystals were purified by sublimation (80° C/14 Torr) to yield 4.9 g (94 %) of $^{13}CBr_4$ (2), mp 91 - 92° C (mp 92 - 93° C, ref.[14]).

^{13}C-NMR ($CDCl_3$): - 29.81.

From $^{13}CH_3$-acetophenone (5): 3.5 g (29 mmol) of 5 were slowly added dropwise to an ice-cooled NaOBr-solution prepared from 14.0 g (350 mmol) of NaOH, 100 ml of water and 7.2 ml (22.6 g, 140 mmol) of Br_2. After removing the cooling bath the emulsion was stirred until all of the intermediate bromoform had turned into solid $^{13}CBr_4$ (2) (ca. 2 h). Usual work-up and purification as described above furnished 7.3 g (76 %) of $^{13}CBr_4$, mp 91 - 92° C.

^{13}C-NMR ($CDCl_3$): - 29.81.

Preparation of two geminal dibromo-^{13}C-derivatives

a) 7-^{13}C-7,7-Dibromo-bicyclo[4.1.0]heptane (6)

8.6 g (34 mmol) of 1 were added within 5 min to a magnetically stirred, ice cooled mixture of 5.5 g (49 mmol) of potassium tert. butoxide, 35 ml (27.2 g, 332 mmol) of cyclohexene, and 40 ml of tert-butanol. The reaction mixture was allowed to warm to room temperature within 20 min and was poured onto 300 ml of ice water. The organic layer was separated, the aqueous layer extracted three times each with 40 ml of pentane, the combined organic phases were washed twice with 100 ml of saturated NaCl solution and dried over $MgSO_4$. Distillation affor-

ded 6.6 g (76 %) of 6, bp = 102° C/8 Torr (bp = 100° C/8 Torr, ref.[6a]). ^{13}C-NMR ($CDCl_3$): 20.04 (35, C-3, C-4), 20.57 (d, J = 2.3 Hz, 22, C-2, C-5), 26.91 (d, J = 13.5 Hz, 12, C-1, C-6), 40.06 (1000, C-7). The assignment of C^2, and C^3 are reversed as compared to those made by Saito et al.[15]). We assigned the signal at 20.57 ppm to C^2 and C^5, because it shows coupling with $^{13}C^7$, while the signal at 20.04 ppm does not and should therefore belong to C^3 and C^4.

b) 4-tert-Butyl-1-(dibromo-^{13}C-methylene)-cyclohexane (7)

A solution of 0.41 g (2.6 mmol) of 4-tert-butyl-1-cyclohexanone, 3.52 g (13.5 mmol) of triphenylphosphine and 2.22 g (6.7 mmol) of $^{13}CBr_4$ (2) in 150 ml of dry benzene was refluxed for 17 h. After filtration, the solvent was evaporated and the residue was extracted with 50 ml of warm hexane; after repetition of this procedure, the product was purified by sublimation (90° C/14 Torr) to give 0.60g (73 %) of 7 as a colorless volatile solid, mp = 72° C (mp = 72 - 73° C, ref.[16]). ^{13}C-NMR ($CDCl_3$): 27.16 (22), 27.52 (330, CH_3), 32.19 (76), 34.55 (129), 47.34 (95, C-4), 81.56 (2810, $=CBr_2$), 144.68 (d, J = 86 Hz, 20, C-1).

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