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NOTE

An Efficient Synthesis of 1-[^{13}C]-Bromobenzene

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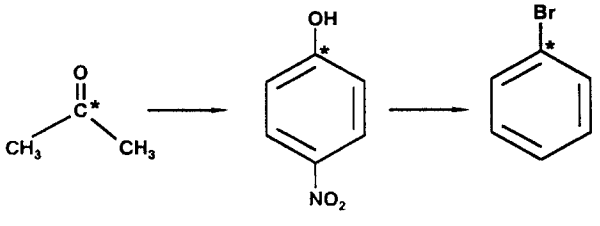
Summary

Various routes to functionalized benzenes labelled in position 1 were compared. 1-[^{13}C]-Bromobenzene has been synthesized in 7 steps with an overall yield of 5.4% from [^{13}C]-$BaCO_3$, by optimizing the direct transformation of *p*-nitrophenol into bromobenzene.

Key words: Carbon-13, [1-^{13}C]-Bromobenzene, Benzene Ring Labelling

Introduction

Despite the astonishing success of modern enantioselective and diastereoselective synthesis, the formation of simple ring labelled substituted benzenes still requires multistep procedures. During a solid state nmr project we were in need of considerable quantities of 1-[^{13}C] bromobenzene (1) for the preparation of [^{6}Li,^{13}C] phenyllithium. A literature survey reveals only three different routes to this compound. One possibility is to start from 2-[^{13}C] acetone[1] (2) which is condensed with nitromalonaldehyde[2] to form 1-[^{13}C] *p*-nitrophenol[3] (3). Conversion of 3 into 1 requires several steps.



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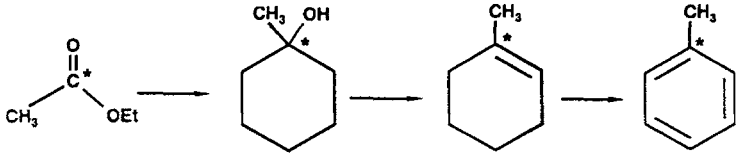
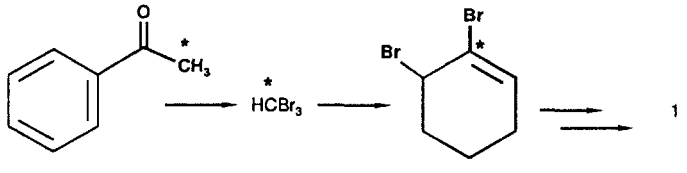
In a second procedure[4], the benzene ring is formed by dehydration and dehydrogenation of 1-hydroxymethylcyclohexane (5), obtained by addition of the bis-Grignard reagent of 1,5-dibromopentane to labelled ethylacetate (4). The difficulty of this pathway is the two step conversion of 5 to 1-[^{13}C] toluene (7), which, for small quantities of labelled material, is inconvenient. Four further steps are then required to convert 7 into 1.



4 5 6 7

With this background, a new sequence developed by Seebach[5] seemed to be very welcome. Here, 1-[^{13}C]-acetophenone (8), prepared in three steps from [^{13}C]-CH_3I serves as a source of bromoform (9), from which labelled dibromomethylenecarbene is generated. Reaction of this carbene with cyclopentene yields dibromocyclohexene (10), which, on further bromination with NBS and double dehydrobromination, should give easily the desired 1. However, in our hands, and as the authors admit[6], 1 obtained via this pathway displays severe label scrambling, which apparently occurs unavoidably in the last step. Therefore this synthesis cannot be used for an isotopically defined product 1.

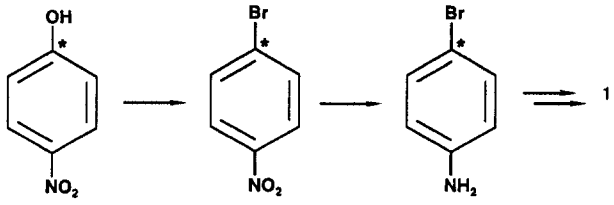


8 9 10

Results

We decided to attempt to optimize the first described procedure by reducing the number of steps required for the conversion of 3 to 1, and report here our synthesis of 1, which can now be accomplished in a total number of 7 steps in overall yield of 5.4% starting from [^{13}C]-$BaCO_3$.

[^{13}C]-CO_2, generated from [^{13}C]-$BaCO_3$ was reacted with methyl magnesium iodide to form, after exchange of the cation, lithiumacetate[7], which was converted into 2 by pyrolysis. After formation of 3 using known literature procedures[3], we optimized the direct transformation[8] of 3 into *p*-bromo-nitrobenzene (12), which was achieved by pyrolysis of the mixed tetraaryloxyphosphorous monobromide obtained from PCl_5, phenol and EtBr. 12 was reduced[9] to *p*-bromo-aniline (13) which was diazotized and transformed[10] into 1.



3 12 13

The direct conversion of 3 into 12 is essential for the success of the chosen route. Our procedure seems to provide the fastest access yet reported to selective ring labelled benzene derivatives in reasonable yield.

Acknowledgements

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Experimental

.Materials

[1-^{13}C]-$BaCO_3$ (98 % enriched) was purchased from Aldrich, Steinheim, Germany. NMR spectra were recorded on Bruker ARX-200, Bruker AC-300 or Bruker AM-400 spectrometers. EI-(electron-ionisation) mass spectra were obtained on a Varian CH7 mass spectrometer. For preparative gas chromatography an Aerograph A 90-P3 was used.

[1-^{13}C]-Lithiumacetate and [2-^{13}C]-acetone (2) were prepared according to the literature[7,1] in 90% and 97% yields respectively.

[1-^{13}C]-*p*-Nitro-phenol (3)

A mixture of (2) (1.30 g, 22 mmol) and nitromalondialdehyde (19.00 g, 5.5 equiv.) with 5 ml 25 % NaOH in 100 ml H_2O was allowed to stand for four days at room temperature. The deep red solution was then neutralized with dry-ice and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and the solvent was removed. The reaction was carried out two times. Additional (2) (1.13 g, 19.14 mmol) from [1-^{13}C]-Li_2CO_3 obtained by the prior pyrolysis, was also used in a third run. The combined yields of these reactions gave (3) as a light yellow solid in 52 % yield overall (4.14 g, 29.57 mmol).
^{1}H-NMR (Acetone-d_6, internal TMS = 0 ppm): = 6.97 (AA' part of AA',XX' system, *o*-2H, $^2J_{C,H}$ = 2.2 Hz, $^3J_{H,H}$ = 9.2 Hz), 8.08 (XX' part of AA'XX' system, *m*-2H, $^3J_{C,H}$ = 9.2 Hz, $^3J_{H,H}$ = 9.2 Hz).
^{13}C-NMR (Acetone-d_6, internal TMS = 0 ppm): = 116.42 (d, *o*-C, $^1J_{C,C}$ = 64.2 Hz), 126.74 (s, *m*-C), 141.7 (s, *p*-C), 164.19 (s, *ipso*-C).

[1-^{13}C]-*p*-Nitro-bromobenzene (12)

A mixture of PCl_5 (5.95 g, 1.0 equiv.) and phenol (8.06 g, 3.0 equiv.) was heated to 100 °C for 3 h under a nitrogen atmosphere. After cooling to room temperature, (3) (4.00 g, 28.56 mmol, 1.0 equiv.) was added and the mixture was heated again to 100 °C for 3 h. After cooling, 3.5 ml of bromoethane was added and the reaction was heated to gently

reflux the bromoethane for 2.5 h. Finally, the mixture was pyrolysed for 15 min. at 200 °C and crude (12) was distilled off under reduced pressure. Pure (12) was isolated after column-chromatography (silicagel, petrolether 40-60 / Et_2O 5:1) in 56 % yield (3.25 g, 16.08 mmol).
^{1}H-NMR ($CDCl_3$, internal TMS = 0 ppm): = 7.67 (AA' part of AA'XX' system, *o*-2H, $^3J_{H,H}$ = 9.0 Hz, $^2J_{C,H}$ = 3.0 Hz), 8.09 (XX' part of AA'XX' system, *m*-2H, $^3J_{H,H}$ = 8.9 Hz, $^3J_{C,H}$ = 10.7 Hz).
^{13}C-NMR ($CDCl_3$, internal TMS = 0 ppm): = 125.00 (s, *m*-C), 129.95 (s, *ipso*-C), 132.71 (d, *o*-C, $^1J_{C,C}$ = 63.7 Hz), {*p*-C not detected}.

[1-^{13}C]-*p*-Amino-bromobenzene (13)

A solution of (12) (3.25 g, 16.08 mmol) in 100 ml toluene was heated to reflux for 0.5 h. Activated iron (25 g iron-powder with 5 ml concentrated HCl) was then added as a catalyst and the well stirred suspension was heated to reflux again. Over a period of two hours, 10 ml of H_2O was added in small portions. The solution was cooled and filtered and the remaining iron-catalyst was extracted twice with toluene. The combined organic layers were concentrated to 20 ml and dried over $MgSO_4$. The desired product (13) was isolated as its hydrochoride by passing HCl-gas through the toluene solution. The resulting precipitate was filtered off and dried in vacuum. (13) was obtained in 82 % yield (2.75 g, 13.13 mmol).
^{1}H-NMR (D_2O, external TMS = 0 ppm): = 7.27 (AA' part of AA'XX' system, *m*-2H, $^3J_{H,H}$ = 8.7 Hz, $^3J_{C,H}$ = 10.5 Hz), 7.66 (XX' part of AA'XX' system, *o*-2H, $^3J_{H,H}$ = 8.7 Hz, $^2J_{C,H}$ = 3.4 Hz).
^{13}C-NMR (D_2O, external TMS = 0 ppm): = 122.34 (s, *ipso*-C), 124.78 (s, *p*-C), 129.32 (s, *m*-C), 133.21 (d, *o*-C, $^1J_{C,C}$ = 63.9 Hz).

[1-^{13}C]-*p*-Diazo-bromobenzene-tetrafluoroborate (14)

A solution of (13) (2.75 g, 13.13 mmol) in 8 ml H_2O and 6g 50 % HBF_4 was cooled to 0 °C and $NaNO_2$ (1.03 g, 1.15 equiv.) dissolved in a small amount of H_2O was added dropwise. The reaction mixture was stirred for an additional hour at 0 °C, and the resulting diazonium-salt was filtered off and washed with cold MeOH and Et_2O. The isolated (14) was dried for a short time and used immediately for the following reaction. (14) was obtained in 80 % yield (2.83 g, 10.37 mmol).
^{1}H-NMR (Acetone-d_6, internal TMS = 0 ppm): = 8.18 (AA' part of AA'XX' system, *o*-2H, $^3J_{H,H}$ = 9.2 Hz, $^2J_{C,H}$ = 2.8 Hz), 8.64 (XX' part of AA'XX' system, *m*-2H, $^3J_{H,H}$ = 9.2 Hz, $^3J_{C,H}$ = 10.3 Hz).
^{13}C-NMR(Acetone-d_6, internal TMS = 0 ppm): = 135.15 (d, *o*-C, $^1J_{C,C}$ = 76.5 Hz), 138.02 (s, *ipso*-C), 148.55 (s, *m*-C), {*p*-C not detected}.

[1-^{13}C]-Bromobenzene (1)

A suspension of (14) (2.83 g, 10.37 mmol) in 80 ml $CHCl_3$ was cooled to 0 °C and 50 % H_3PO_2 (8.36 g) was added. To the well stirred suspension, a few mg of Cu_2O were added in one portion. The reaction mixture was stirred for 1 h and neutralised with saturated Na_2CO_3 solution to pH 8. The layers were separated and the aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Pure (1) was isolated by preparative gas-chromatography (apiezon, 140 °C) in 61 % yield (1.00 g, 6.33 mmol).
^{1}H-NMR ($CDCl_3$, internal TMS = 0 ppm): = 7.35 - 7.09 (m, 3H, *m*- and *p*-H), 7.37 - 7.48 (m, 2H, *o*-H).

^{13}C-NMR ($CDCl_3$, internal TMS = 0 ppm): = 122.49 (s, *ipso*-C), 126.86 (d, *p*-C, $^3J_{C,C}$ = 10.7 Hz), 130. 02 (d, *m*-C, $^2J_{C,C}$ = 1.7 Hz), 131.54 (d, *o*-C, $^1J_{C,C}$ = 63.9 Hz).
The enrichment had a total value of 95 % and was determined by MS and by a ^{13}C inverse gated decoupling NMR spectrum.
MS (EI, 70 eV): 159 (59.65 %, M^+ [$^{81}Br^{13}C1^{12}C_5H_5^+$]), 157 (62.40 %, M^+ [$^{79}Br^{13}C1^{12}C_5H_5^+$]), 78 (100 %, [$^{13}C1^{12}C_5H_5^+$]), 51 (26.65 %, [$C_4H_3^+$]).

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