

Preparation of 1-¹³C Enriched Benzonitrile, *Mono*-¹³C Enriched Benzene, and a Mixture of *Mono*-¹³C Enriched Benzonitriles

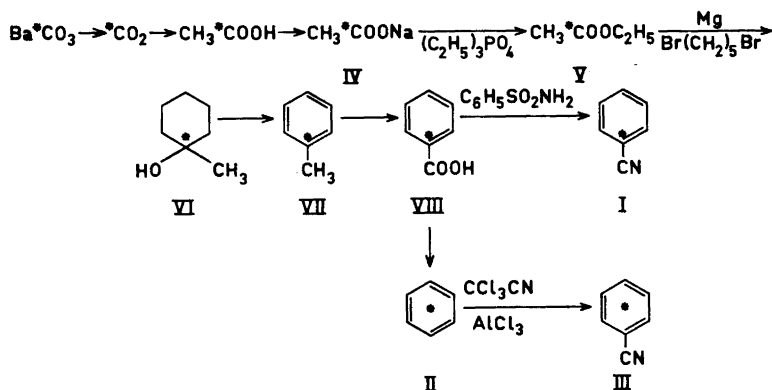
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Preparations of 55 % ¹³C-enriched CH₃¹³COONa (yield 87 %), CH₃¹³COOC₂H₅ (85 %), 1-methyl-[1-¹³C]cyclohexanol-1 (76 %), 1-methyl-[1-¹³C]benzene (85 %), [1-¹³C]benzoic acid (76 %), [1-¹³C]benzonitrile (62 %), *mono*-¹³C benzene (95 %), and a mixture of *mono*-¹³C enriched benzonitriles (38 %) are described. The purity has been checked gaschromatographically (where ever feasible) and spectroscopically.

The present work was undertaken in order to make available 1-¹³C enriched benzonitrile (I), *mono*-¹³C enriched benzene (II), and a mixture of *mono*-¹³C enriched benzonitriles (III), all for use in spectroscopic investigations and for later use in further preparative work.

The route followed was:



EXPERIMENTAL

*CH₃*COONa (IV)*. A Grignard solution was prepared from 240 mmole of CH₃I in 300 ml ether and an excess of magnesium. After dilution of the reaction mixture with 300 ml ether, 145 mmole of *CO₂ (from 29.55 g (150 mmole) Ba*CO₂ (55 % enriched) and conc. H₂SO₄) was introduced under cooling. After hydrolysis (200 ml H₂O), addition of 48 g (154 mmole) of Ag₂SO₄, cooling to 0°C, and addition of 50 ml half-concentrated H₂SO₄, steam-distillation of the product produced an aqueous solution of about 3 l, containing the available CH₃*COOH. After neutralization by 1 N NaOH, water was evaporated at 100°C, leaving (IV), which was finally dried on the vacuumline to constant weight, 10.75 g (130 mmole).

*CH₃*COOC₂H₅ (V)*. Slow distillation of 130 mmole of (IV) with 30 ml of triethylphosphate from a flask, immersed in an oil-bath (170°–210°C) produced a mixture of (V) and triethylphosphate. By distillation *in vacuo* at 0°C under stirring, fractions of (V) were collected until the vapor-pressure had decreased to 7 mm of mercury. Yield 9.71 g (110 mmole). The infrared spectrum (650–4000 cm⁻¹) showed that this sample was more than 99 % pure. Also, the proton magnetic resonance (PMR) spectrum at 60 Mc/s showed the presence of ¹³C (spin 1/2) in the *carbonyl* group with characteristic coupling to the CH₂ protons of the C₂H₅-group (3.1–3.2 c/s), no coupling to the CH₃ protons of the C₂H₅ group, but with a coupling of 6.9 c/s to the protons of the second, adjacent CH₂ group. From the PMR spectrum, the percentage of CH₃¹³COOC₂H₅ was seen to be 52. Within the experimental error this is consistent with the assumed percentage of 55 of the commercial Ba*CO₂ applied.

1-Methyl-[1-¹³C]cyclohexanol-1 (VI) was prepared as indicated in Ref.¹ 9.20 g (104 mmole) of (V) was converted to 8.95 g (79 mmole) of (VI). The final purification was carried out by means of a "preparative" gaschromatograph of conventional design (Perkin-Elmer 116E, column "C", length 2.7 m), treating 1 g at a time. A gaschromatogram of an analytical quantity (5 mg) showed the presence of an (unidentified) impurity of ca. 2 %.

1-Methyl-[1-¹³C] benzene (VII). In an evacuated system, 8.49 g (74 mmole) of (VI) was distilled into a perpendicular column containing a platinum catalyst (10 g H₂PtCl₄ (40 % Pt) reduced on 50 g of granulated coal). The column was electrically heated to 310°C. The totally dehydrated, but only partly dehydrogenated product was collected in a trap over 2–3 h. Weight 7.99 g. It consisted of an aqueous and an "organic" liquid phase. Gaschromatographic analysis (column "A", length 2 m) of the latter showed the presence of rapidly passing, unidentified components (0.4 %), cyclohexane (0.3 %), benzene (1.2 %), methylcyclohexane (9.1 %), (VII) in a yield of 88 %, and 0.6 % of slowly passing, unidentified components. The high yield makes it improbable that isomerization, spreading the ¹³C over the positions of the ring, has occurred. PMR-analysis confirmed this. If, namely, the CH₃-group had migrated during the formation of (VII), lines originating from ¹³C–H coupling would be observable. Such lines would be displaced 50–110 c/s with respect to the "ordinary" aromatic toluene protons. No such lines were observed. Instead, the expected coupling between 1-¹³C and the protons of the adjacent CH₂ group of (VII) showed up with a coupling constant of 5.9–6.0 c/s. From the intensity of the displaced CH₃-group lines the enrichment of (VII) was estimated to 55 %. The estimated quantity of (VII) in the mixture mentioned above was 5.8 g (63 mmole). For the present purpose (*vide infra*), separation from the impurities was unnecessary and not carried out.

[1-¹³C]benzoic acid (VIII). The above-mentioned sample of crude (VII) was heated under stirring and reflux on a steam-bath with a solution of 22 g KMnO₄ in 270 ml H₂O until the KMnO₄-colour disappeared (5 h). After acidification with conc. HCl and reduction of MnO₂ by gaseous SO₂ at room temperature the reaction mixture was cooled to 0°C which caused the main quantity of (VIII) to crystallize. After filtering, the mother-liquid was extracted 3 times by 50 ml of ether. The combined ethereal extracts were treated by 50 ml 2 N NaOH. Acidification of the separated aqueous layer and cooling, produced an additional amount of (VIII). After drying *in vacuo*, the total yield was 6.09 g, m.p. 122°–123°C (lit. 123°C). Combustion analyses showed the presence of about 3 % ashes, the yield of (VIII) is, therefore, 5.90 g (48 mmole). A KBr-disc spectrum of 1 mg in 30 mg KBr confirmed that the purity is > 95 %.

* The asterisk indicates the position enriched by ¹³C.

[1-¹³C]benzonitrile (I). 1.10 g of crude (VIII), containing 8.7 mmole of acid, was intimately mixed with 2.52 g benzenesulfonamide (16 mmole)³ and placed in a 50 ml cylindrical vessel, which was closed to the atmosphere by a CaCl₂-tube. The vessel, which was kept cold at the top by a stream of air, was immersed in a heated Wood's metal bath (220–225°C). Immediately after the melting of the reaction mixture magnetic stirring was started. After 2 h of heating at 220°C the temperature was increased to 300°C in the course of 15 min. After further 30 min of heating at 300°C, the reaction mixture was allowed to cool to room temperature. The cylindrical vessel was connected to a vacuum line and evacuated at –190°C. Then the temperature was raised to 0°C. A vapor-pressure of 25 mm of mercury (from benzene) was observed, internal magnetic stirring being applied. Fractions of these vapors were collected until the equilibrium vapor-pressure had dropped to 5–6 mm. Then the temperature of the vessel was raised to 25°C (vapor-pressure 25 mm). Fractions were again removed over a 36 h period until the pressure had fallen to 0.8 mm, the vapor-pressure of (I). (I) was distilled-off *in vacuo*. Yield 560 mg (5.4 mmole). The gaschromatogram showed the presence of only 0.3 % benzene. No infrared spectrum was taken, but the infrared spectrum of a sample, prepared in a test experiment using non-enriched material, was quite satisfactory. In a subsequent microwave investigation of the enriched sample (I) only lines from benzonitrile were observable. The relative intensity of the two microwave spectra corresponded to an approximate 1:1 ratio of the two components.

Mono-¹³C benzene (II). 1.83 g of crude (VIII), corresponding to 14.5 mmole of pure (VIII), was mixed with 0.3 g CuO and added to 10 ml quinoline. Decarboxylation was affected following Ref.⁴ The trap, in which the yield was collected, was connected to a vacuum line and evacuated at –80°C. After subsequent heating to room temperature benzene was distilled-off into a second trap, containing 2–3 g P₂O₅ which removed H₂O and a trace of quinoline. After 1 h, (II) was distilled-off. Weight 1.08 g (13.8 mmole). Judging from a gas chromatogram of (II), (column "A", length 2 m), purity was higher than 99.9 %.

Mixture of mono-¹³C enriched benzonitriles (III). Using a modification of Houben and Fischer's method⁵ 1.07 g of (II) (13.6 mmole) was mixed with 2.44 g (17 mmole) CCl₃CN, 5.5 g anhydrous AlCl₃, and 5.5 ml chlorobenzene in a 25 ml flask. Dry HCl was passed through, until all atmospheric air had been replaced after which a constant pressure of HCl from a bomb was maintained for 2 days, during which the reaction vessel was continuously shaken. After disruption of the bomb connection, the shaking was continued for 5 days. Following the instructions of Ref.⁵ very closely, we ended up by 9–10 g of a mixture of (III), chlorobenzene, ether etc. The vessel, containing the mixture, was connected to a vacuum line, cooled in liquid air, evacuated, and heated to 0°C. At this temperature a fraction (2.37 g) was removed, mainly consisting of ether and about 5 % chlorobenzene. After initial elevation of the temperature to 25°C and afterwards to 80°C, a second fraction (F) was collected, consisting of ether and the two aromatic components (5.30 g). A resinous remanence (about 1 g) was left. (F) was separated on a "preparative" gas chromatograph (column "C", length 2.7 m and use of O-rings covered with teflon to prevent diffusion). The yield of (III) was 600 mg. The purity of this sample was 98 % according to gas chromatographic analysis (column "A", length 2 m). The contaminations were H₂O and unidentified, volatile products from the reaction mixture and from decomposition from the stationary liquid phase of the gas chromatograph. A single distillation on the vacuum line under pressure control removed most of these impurities so that the purity of the final product was 99 % (gas chromatogram). Weight 540 mg (5.2 mmole). At a subsequent microwave examination the impression of high purity was confirmed.

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