

SYNTHESIS OF CARBON-13 ENRICHED NITROBENZENE

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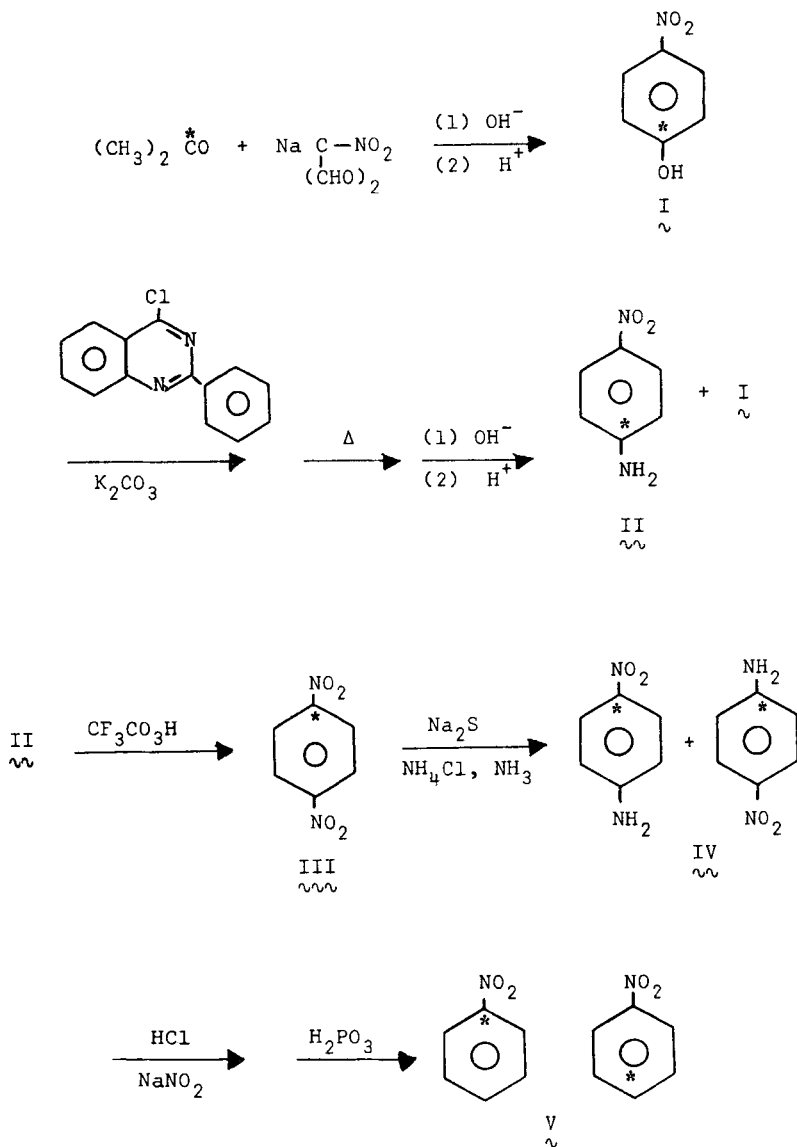
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SUMMARY

Synthesis of nitrobenzene enriched in ^{13}C at specific ring positions has been accomplished. The literature conditions for one of the reactions employed were found defective and are corrected. The nature of a second reaction is amplified and apparent thermodynamic control was discovered.

Stimulated by the fact that the information obtainable from experiments which use only the common isotopes in nature is often times now exhausted, isotopic enrichment is becoming increasingly common. Costs remain sufficiently high that efficient syntheses yield-optimized at the scale actually to be encountered, are required. Our continuing interest in the structure and solvation of nitroaromatic radical anions studied by electron spin resonance spectroscopy¹ caused us to undertake the preparation of nitrobenzene-1- ^{13}C . The efficiency of this preparation is greatly increased if one can utilize² a mixture of nitrobenzene-1- ^{13}C and nitrobenzene-4- ^{13}C .

We report here the synthesis of such a mixture which contains 22.5 mole-percent nitrobenzene-1- ^{13}C and an equivalent amount of nitrobenzene-4- ^{13}C . See Scheme I. In the course of our effort to yield-optimize each reaction in this sequence on the scale commensurate with our needs, we discovered that the extant literature is incorrect in one case and highly incomplete in a second case.



Scheme I

The label is incorporated into the aromatic ring via preparation of 4-nitrophenol-1-¹³C (I) through condensation of acetone-2-¹³C with sodium nitromalonaldehyde monohydrate.³ Utilizing the procedure of Hill⁴ and Jones and Kenner⁵ we obtained unpredictable and inconsistent yields in preliminary reactions. We elected, therefore, to work up the labeled reaction in more than one portion. An initial 12.5% aliquot gave only 13% yield and proved that the reaction does not, in fact, proceed to completion under the conditions described^{4,5} (mildly basic, cold, dilute, long standing). We discovered that instead the reaction runs rapidly in the cold (2 hours, 4-8°) in the presence of strong base and obtained a 74% yield for the remaining aliquot when the sodium hydroxide content of reaction mixture was increased to 16% by weight (4.1 M).

Conversion of I to 4-nitroaniline-1-¹³C (II) was effected using 4-chloro-2-phenylquinazoline. Several modifications of the procedure of Sherrer, et al.⁶ were introduced. In view of the report by Swanwick and Waters⁷ that even sodium borohydride can reduce aromatic nitro compounds, we chose anhydrous potassium carbonate⁸ instead of sodium hydride as the base to promote formation of the phenol-quinazoline adduct and found the reaction is essentially quantitative (95-98%) rather than 69%. As noted by Scherrer, et al.⁶, the nitro derivative often yields decomposition products on pyrolysis. In our hands, repeated attempts employing mineral oil or ethylene glycol media for the thermal rearrangement gave unacceptably poor yields of 4-nitroaniline. The highest yields (ca. 40%) were obtained when the rearrangement was carried out neat at 280-295°. The changes in the infrared spectrum of the mixture reported by Morrow and coworkers⁹ were observed; however, we found that beyond an apparent threshold conversion, this method proved unsuitable for following the

progress of the rearrangement reaction. Considering the mixture of compounds present, this failure is not surprising. We found instead a positive correlation between the extent of rearrangement and the visible appearance of the sample: clear, dark brown residues consistently gave the best yields.

Following the thermal rearrangement, the powdered material in aqueous methanol was subjected first to alkaline hydrolysis and then to acid hydrolysis. The solids obtained from the hydrolysis were separated by chromatography on an alumina column. The fact that the maximum yield obtained remained¹⁰ about 40% and increased pyrolysis temperature and/or increased time at elevated temperature failed to drive the reaction further suggested the possibility of thermodynamic control and thus the feasibility of recovering starting materials. Pursuing this possibility, a white, crystalline material which was obtained in substantial quantity from the chromatographic procedure was analyzed by mass spectrometry and identified as 4-methoxy-2-phenylquinazoline. We were, therefore, led to attempt recovery of 4-nitrophenol.

Following the two-stage hydrolysis of the Scherrer⁶ procedure and after extraction of 4-nitroaniline from aqueous base with ether, the aqueous phase was reacidified; further ether extraction recovered 4-nitrophenol. In the labeled reaction, the initial yield of II was 30.6% based on I taken, but 90% of the labeled material could be accounted for as both II and recovered I . Recycling I produced II in an overall yield of 69.2% based on the amount of I consumed.

Oxidation of II to 1,4-dinitrobenzene-1-¹³C (III) by the method of Emmons¹¹ gave III in 84.2% yield. Reduction of III by the method described by Hartman and Silloway¹² gave 4-nitroaniline-1-¹³C and 4-nitroaniline-4-¹³C as an equimolar mixture (IV).

Purification of IV on a fluorisil column resulted in a 79.5% yield. Diazotization of IV followed by reduction with hypophosphorus acid produced the equimolar mixture of nitrobenzene-1- ^{13}C and nitrobenzene-4- ^{13}C (V) which we desired. The method of Ruddy and Starky¹³ was used for the diazotization and the method described by Kornblum,¹⁴ suitably modified for small quantities of material, was employed for the reduction. Preparative gas chromatography obtained V in 53% yield.

EXPERIMENTAL

Solvents and various reagents were, except as specified, commercially available from common sources. As required, these materials were purified by established literature procedures. Infrared spectra were taken with a Perkin-Elmer 257 grating instrument and mass spectra were obtained using an AEI MS-902 with 70 eV ionizing energy. The gas chromatograph was a Perkin-Elmer Model 990 equipped with thermal conductivity detection. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

The procedure for preparation of sodium nitromalonaldehyde monohydrate is well documented.³ From 25 g of mucobromic acid (Aldrich) we obtained 4.9 g (32%) of purified product as pink crystals after recrystallization from 80% ethanol-water.

4-Nitrophenol-1- ^{13}C (I). Sodium nitromalonaldehyde monohydrate (3.31 g, 21.1 m mol) and sodium hydroxide (0.595 g, 14.8 m mol) were dissolved in 70 ml of water and cooled to 4° whereupon 0.50 g of acetone-2- ^{13}C (90 atom % ^{13}C , Merck Chemical Division, Merck, Sharpe, and Dohme, Ltd.) and an equivalent amount (0.64 ml) of spectro grade acetone (total 17.2 m mol) were added. After dilution with water to 200 ml, the reaction mixture was allowed to stand for five days at 2° and a 25 ml

aliquot (12.5% of the total by volume) was worked up by the literature method:^{4,5} The acidified mixture (12 M HCl) was extracted with ether and after drying, filtering and concentrating the ether layer, cold 50% NaOH solution was added to it. The solid thus obtained was filtered and then dissolved in the minimum volume of water. Acidification of this aqueous solution with 12 M HCl was followed by ether extraction; removal of the ether yielded 38 mg (13%) I.¹⁵

The remaining 175 ml of aqueous reaction mixture, after storage at 2° for a total of eight days, was transferred to an ice bath and 85 ml of cold 50% aqueous NaOH was added slowly such that the temperature of the reaction mixture was maintained in the 4-10° range. The mixture was stirred for two hours at 6° and then acidified with 12 M HCl using care to keep the temperature from exceeding 30°. A brown solid was removed by filtration and the reaction mixture was divided into two equal portions for convenience. Each portion of the acid solution was ether extracted (5 x 200 ml). The extracts were dried over sodium sulfate, filtered, and concentrated at reduced pressure to a dark yellow-brown residue. This residue was dissolved in the minimum volume of water and cooled; a yellow precipitate was obtained upon addition of cold, 50% aqueous NaOH. This precipitate, the sodium salt of I, was redissolved in a minimal amount of water, acidified, and extracted into ether. The ether solution was dried, filtered, and evaporated. The residue was purified by reduced pressure sublimation and dried in vacuo to afford crystalline light yellow I (1538 mg, 73.6%¹⁶) mp, 108-109.5°.

~~4-Nitroaniline-1~~¹³C (II). To 250 ml spectro grade acetone which was dried over Linde 4A molecular sieves and deaerated with nitrogen¹⁷ were added 1.58 g of I (11.4 m mol), 3.37 g of 4-chloro-2-phenylquinazoline ("AMexOL", Aldrich, 14.0 m mol), and 3.30 g

of anhydrous potassium carbonate (23.9 m mol). The mixture was refluxed under nitrogen for 27 hrs and then poured onto 225 g of ice and filtered on sintered glass to obtain the crude adduct as a pale yellow precipitate. Recrystallization of this precipitate (200 ml benzene) gave, after air drying, 3.74 g of the adduct of I (95.6%), mp 220-220.5°. The infrared spectrum of this material confirmed its identity.⁹ The adduct was divided into two portions each of which was carried through the reaction sequence described below to give II.

Thermolysis of 1.81 g of neat adduct in a nitrogen atmosphere was carried out at 285-295° using a Wood's metal bath. The material was heated for short periods of time, cooled, and examined by visual inspection and infrared spectroscopy (KBr disc). Thermolysis times as recorded from the time of liquification until removal from the heat were 4, 4, 7, 5, and 5 min, respectively (25 min total). The flask and contents were reduced to fine particles which were treated with 70 ml of 95 volume % deaerated methanol, 5.5 ml water and 5.5 g KOH. The mixture was refluxed under nitrogen for 1.5 hrs, acidified with 12 M HCl, and with the aid of 25 ml of deaerated methanol transferred to a clean flask through a narrow stem funnel.¹⁸ The acidified mixture was stirred at 51-52° for 30 min, transferred to an ice bath, and made basic by addition of saturated aqueous KOH. A yellow precipitate was obtained which was concentrated to mushy dryness on a rotary evaporator. This semi-solid was dissolved in 20 ml of water¹⁹ and the solution was extracted with ether (5 x 100 ml). The ether solution was dried, filtered, and evaporated in the usual way to obtain a yellow residue. Purification was effected by chromatography on an alumina column (hexane-ether eluent; product obtained with 80% ether) to afford 247 mg II, mp 145-146.5°. The aqueous solution was now made acidic

and extracted with ether (6 x 200 ml). This ether solution was dried and evaporated; purification of the resulting solid residue recovered 451 mg I , mp 111-112°.

The second portion, 1.90 g of adduct, was treated in a manner identical to that described above. This procedure gave 234 mg of II and recovered 481 mg of I . The recovered I (932 mg total) was recycled through the procedure to give 474 mg of II with recovery of 183 mg of I . In this way, consumption of 1.40 g of I produced 955 mg of II (69.2% overall).

~~1,4-Dinitrobenzene-1- ^{13}C~~ (III). Oxidation of II (932 mg, 6.75 m mol) with trifluoroperacetic acid¹¹ gave 955 mg of III (84.2%), mp 170-171.5°.

~~4-Nitroaniline-1- ^{13}C~~ , ~~4-nitroaniline-4- ^{13}C~~ mixture (IV). A slight modification of the procedure of Hartman¹² was applied to 563 mg of III (3.35 m mol). The combined reactants were stirred at 85° for one hr and then for 1.5 hrs more at room temperature. The mixture was extracted with copious quantities of ether (6 x 200 ml) which was reduced to ca. 75 ml and then washed with several portions of 10% HCl. The aqueous layer was made basic by addition of 50% NaOH and then extracted with ether (8 x 125 ml). The ether was dried and evaporated to yield crude IV which was fractionated by chromatography on florisil (25% ether hexane eluent). Fractions judged impure by their melting points were further purified by thin layer chromatography (silica gel G, methylene chloride eluent). The total yield was 368 mg of IV (79.5%), mp 144.5-145.5°.

~~Nitrobenzene-1- ^{13}C~~ , ~~Nitrobenzene-4- ^{13}C~~ mixture (V). Diazotization¹³ of IV (204 mg, 1.48 m mol) was followed by deamination.¹⁴ Cold hypophosphorus acid was added directly to the reaction mixture from the diazotization at ice temperature, stirred for 26 min and then stored at 2° for ca. 48 hrs. The

aqueous mixture was extracted with ether (5 x 50 ml) and the ether phase then was washed with 20% NaOH, dried, filtered, and concentrated by distillation. Separation of λ was effected by preparative gas chromatography (5% carbowax on Chromosorb-P, 180°) with 96 mg collected (53%).

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15. This confirmed our suspicions that previous successful reactions occurred during work-up following addition of strong base to the reaction mixture.
16. Yield calculated based on 0.88 g acetone remaining in reaction mixture after work up of preliminary aliquot.

17. Considering the possibility of free radical decomposition products as proposed by Scherrer⁶, as a precautionary measure solvents were deaerated and reactions run under a nitrogen atmosphere.
18. No paper was used in the funnel, thus allowing transfer of precipitate but removing glass fragments.
19. This aqueous solution acidified and ether extracted to recover I_2 .