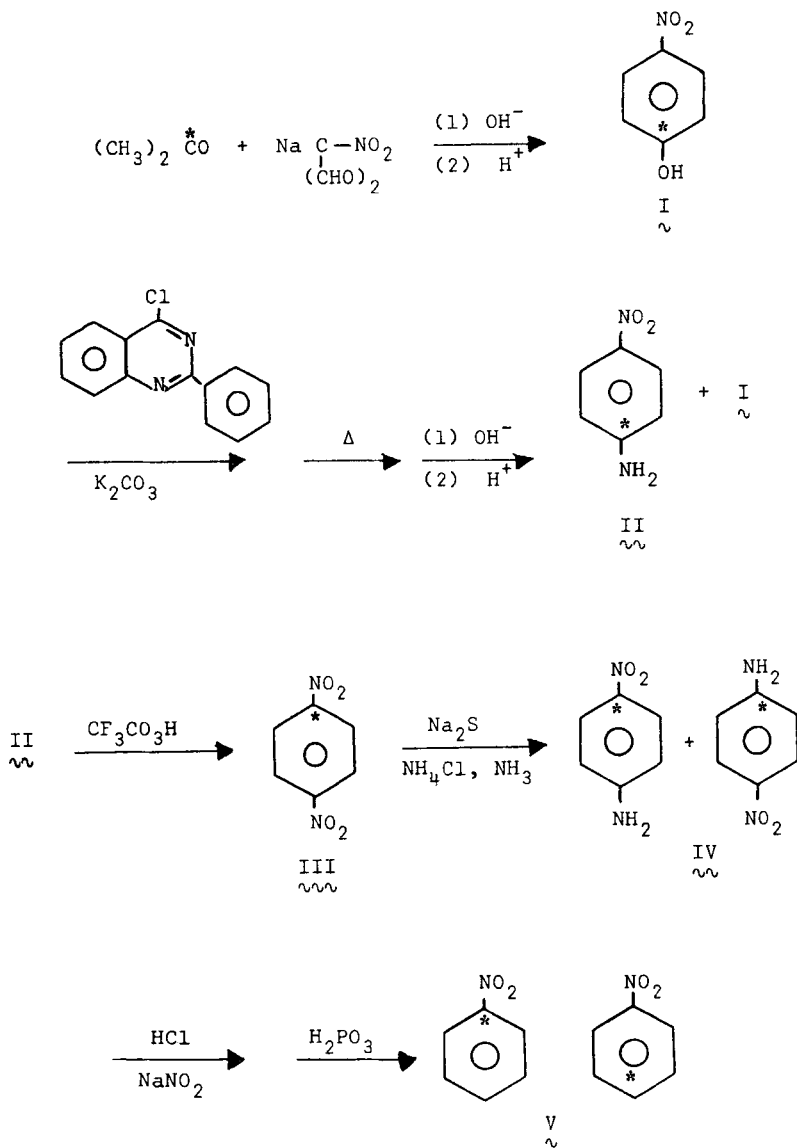# SYNTHESIS OF CARBON–13 ENRICHED NITROBENZENE

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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 spectroscopy[1] caused us to undertake the preparation of nitrobenzene-1-^{13}C. The efficiency of this preparation is greatly increased if one can utilize[2] 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 1. 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.

$(CH_3)_2 \overset{*}{C}O$ + $Na \underset{(CHO)_2}{\overset{|}{C}-NO_2}$ $\xrightarrow[\text{(2) H}^+]{\text{(1) OH}^-}$

I

$\xrightarrow{K_2CO_3}$ $\xrightarrow{\Delta}$ $\xrightarrow[\text{(2) H}^+]{\text{(1) OH}^-}$ + I

II

II $\xrightarrow{CF_3CO_3H}$ III $\xrightarrow[\text{NH}_4\text{Cl, NH}_3]{\text{Na}_2\text{S}}$ + IV

$\xrightarrow[\text{NaNO}_2]{\text{HCl}}$ $\xrightarrow{H_2PO_3}$ V

Scheme I

The label is incorporated into the aromatic ring via pre-
paration of 4-nitrophenol-1-^{13}C (I) through condensation of
acetone-2-^{13}C with sodium nitromalonaldehyde monohydrate.[3]
Utilizing the procedure of Hill[4] and Jones and Kenner[5] 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 com-
pletion 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-^{13}C (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 Waters[7] that even sodium borohydride
can reduce aromatic nitro compounds, we chose anhydrous potas-
sium carbonate[8] 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 decom-
position 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 coworkers[9] 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 mix-
ture 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 hy-
drolysis were separated by chromatography on an alumina column.
The fact that the maximum yield obtained remained[10] about 40%
and increased pyrolysis temperature and/or increased time at
elevated temperature failed to drive the reaction further sug-
gested 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 Scherrer[6] pro-
cedure 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 re-
covered 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-^{13}C (III) by the
method of Emmons[11] gave III in 84.2% yield. Reduction of III by
the method described by Hartman and Silloway[12] gave 4-nitroani-
line-1-^{13}C and 4-nitroaniline-4-^{13}C 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 hypophos-
phorus acid produced the equimolar mixture of nitrobenzene-1-^{13}C
and nitrobenzene-4-^{13}C (V) which we desired. The method of
Ruddy and Starky[13] 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 mono-
hydrate (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 concen-
trating 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 tem-
perature from exceeding 30°. A brown solid was removed by fil-
tration 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 pre-
cipitate, 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-[13]C (II). To 250 ml spectro grade acetone
which was dried over Linde 4A molecular sieves and deaerated with
nitrogen[17] 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 reflexed 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 insepction 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 reflexed 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 water[19] 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 acid[11] 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 Hartman[12] 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). Diazotization[13] 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 $\underset{\sim}{V}$ was effected by

preparative gas chromatography (5% carbowax on Chromosorb-P,

180°) with 96 mg collected (53%).

REFERENCES

1. R.G. Parrish, Grace Swartz Hall, and W.M. Gulick, Jr., Mol.
    Phys. 1973, 26, 1121; Carol Miller and W.M. Gulick, Jr.,
    ibid., 1974, 27, 1185; W.M. Gulick, Jr., V.J. King, and
    Carol Miller, ibid; in press.

2. Grace L. Swartz and Wilson M. Gulick, Jr., Mol. Phys., in
    press: We describe the carbon-13 interactions studied in the
    nitrobenzene anion radical obtained on reduction of the en-
    riched material.

3. Paul E. Fanta, Org. Syn. Col. Vol. 1963, 4, 844; Org. Syn.,
    1952, 32, 95.

4. H.B. Hill and J. Torrey, Jr., Am. Chem. J., 1899, 22, 89;
    H.B. Hill, Am. Chem. J., 1900, 23, 1.

5. E. Jones and J. Kenner, J. Chem. Soc., 1931, 1842.

6. R.A. Scherrer and H.R. Beatty, J. Org. Chem., 1972, 37, 1681.

7. M.G. Swanwick and W.A. Waters, J. Chem. Soc., D, 1970, 63.

8. R.B. Conrow and S. Bernstein, Steroids, 1968, 11, 151.

9. D.F. Morrow and M.E. Butler, J. Org. Chem., 1964, 29, 1893.

10. A yield of 66% was apparently obtained on one occasion only
    and is regarded as an artifact since it could not be reproduced.

11. A.S. Pagano and W.D. Emmons, Org. Syn., 1969, 49, 47; W.D.
    Emmons, J. Am. Chem. Soc., 1954, 76, 3470.

12. W.W. Hartman and H.L. Silloway, Org. Syn. Col. Vol., 1955,
    3, 82.

13. A.W. Ruddy and E.B. Starkey, Org. Syn. Col. Vol., 1955, 3, 665.

14. N. Kornblum, Org. Syn. Col. Vol., 1955, 3, 295.

15. This confirmed our suspicions that previous successful reac-
    tions occurred during work-up following addition of strong
    base to the reaction mixture.

16. Yield calculated based on 0.88 g acetone remaining in reac-
    tion mixture after work up of preliminary aliquot.

17. Considering the possibility of free radical decomposition
     products as proposed by Scherrer[6], 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.