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HIGH-YIELD NITRATION OF BENZENE IN THE SYNTHESIS OF ^{15}N-LABELLED NITROBENZENE, ACETANILIDE, AND DIPHENYLAMINE

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SUMMARY

Labelled $H^{15}NO_3$ was used as the least-cost source of nitrogen label to prepare nitrobenzene by reaction of acetyl nitrate with excess benzene. This labelled product was subsequently converted to acetanilide-^{15}N and diphenylamine-^{15}N.

Key words: acetyl nitrate, nitrobenzene-^{15}N, acetanilide-^{15}N, and diphenylamine-^{15}N.

INTRODUCTION

The synthesis of diphenylamine-^{15}N from aniline-^{15}N in 82% yield has been reported (1). This route to this product has the disadvantage that it uses a relatively expensive starting material: on a per-mole basis, labelled nitrobenzene-^{15}N or aniline-^{15}N are currently available at three times the cost of $H^{15}NO_3$. Thus, a method for nitration of benzene in high yield based upon the nitric acid used could reduce the cost of monofunctional benzene derivatives labelled with ^{15}N by up to a factor of three. We report here such a procedure using acetyl nitrate for the nitration of excess benzene (2). Acetyl nitrate is unstable, and the pure substance is reported to explode under ill-defined conditions (3). We have encountered no problems with it when it is used promptly without prior distillation as a solution in excess acetic anhydride, in the temperature range 20-25°. We have used the same nitration procedure to convert 2,6-dinitrophenol into picric acid in 65% yield (not optimized).

The labelled nitrobenzene was reduced catalytically in benzene solution with hydrogen, the aniline produced extracted into dilute acid, and this aqueous solution

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acetylated directly by Fieser's procedure (4). Acetanilide was converted to diphenylamine by reaction with iodobenzene, under published conditions (5).

EXPERIMENTAL SECTION

Nitrobenzene-^{15}N: To 100 ml of acetic anhydride pre-cooled to 15° in a stirred 250 ml three-neck round bottom flask protected by a drying tube are added dropwise 8.0 ml (0.124 mole) of nitric acid-^{15}N (70% by volume in water, 99% $H^{15}NO_3$, from Prochem) at a rate controlled to maintain the temperature of the mixture at 20-24° C. (The temperature can rise very rapidly if the mixture heats above 30°.) This mixture was stirred at 20-23° for another 10 min, and then cooled to 0° C in an ice-salt bath. Reagent benzene (14 ml, 0.158 mole) containing two drops of concentrated sulfuric acid (reported (2) to accelerate the nitration) was added dropwise with the temperature held at 0°. This reaction mixture was stirred while it warmed to room temperature, and stirring continued for another 15 min. It was then poured onto crushed ice and the excess acetic anhydride allowed to decompose by standing overnight. It was extracted with CH_2Cl_2, and the organic layer washed successively with 10% aq NaOH, water, and saturated brine, and dried over sodium sulfate. Removal of solvents on the aspirator left a light yellow liquid which was used for the next step without further purification. Yield: 15.2 g, or 98% based upon the nitric acid used. Proton NMR identical to the published spectrum (6) of nitrobenzene, with a complex pattern of lines in the chemical shift range 7.5 to 8.3 ppm. The most intense line is at 7.63 ppm.

Acetanilide-^{15}N: The nitrobenzene (0.122 mole) was placed in a Parr shaker bottle together with 0.5 g Pd/C catalyst (10%) and 100 ml benzene, under hydrogen at 60 psi. The bottle was shaken at room temperature until the pressure remained constant; about 0.38 moles H_2 were consumed. The catalyst was filtered off and the benzene solution extracted with 300 ml of 0.5 $\underline{M}$ HCl solution (0.13 mole of HCl). To this extract of aniline was added 12.3 ml (0.130 mole) of acetic anhydride. A solution of 12.3 g (0.150 mole) of sodium acetate in 65 ml water was then added all at once (4). A suspension of crystals formed slowly on cooling; this was filtered off and dried. Yield: 14.1 g, or 85% from nitrobenzene-^{15}N.

Diphenylamine-^{15}N: Catalyst was prepared by heating 2 g Fernlock copper bronze with 0.5 g I_2 in a test tube so arranged that the iodine vapors distilled onto the copper. Acetanilide-^{15}N (10.0 g, 0.074 mol), together with iodobenzene (15.5 g, 0.076 mole), pre-dried powdered potassium carbonate (10.2 g, 0.074 mole), the catalyst, and 20 ml mixed xylenes were placed in a dry 250 ml round bottom flask equipped with a mechanical stirrer, air condenser, and thermometer. The mixture was refluxed vigorously so water produced slowly distilled through the air condenser for 48 h. The reaction mixture was then transferred to a beaker containing 300 ml hot water, stirred vigorously, and then cooled thoroughly. The solids (copper and salts, with ^{15}N-acetyldiphenylamine) were collected and refluxed with 100 ml ethanol containing 10 g KOH for 24 h. The hot solution was filtered to remove inorganic salts, and the filtrate cooled. Slow addition of water precipitated the diphenylamine, which was dried and purified by sublimation at 45°. The melting point was 51-52°, and the yield 11.5 g, or 91%. The overall yield was 76% from $H^{15}NO_3$, based upon the nitric acid label used.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.4, 127.5, 119.0, and 115.8 ppm (identical with unlabelled diphenylamine); $^{1}J(^{15}N\text{-}^{13}C) = 14.8$ Hz, $^{2}J(^{15}N\text{-}C\text{-}^{13}C) = 2.4$ Hz, $^{3}J(^{15}N\text{-}C\text{-}C\text{-}^{13}C) = 1.5$ Hz. None of these couplings are observed with the unlabelled compound.

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