SYNTHESIS OF 4-^{13}C AND 3,5-^{13}C LABELED ANILINE AS PRECURSOR OF ^{13}C - LABELED MONOSUBSTITUTED BENZENES

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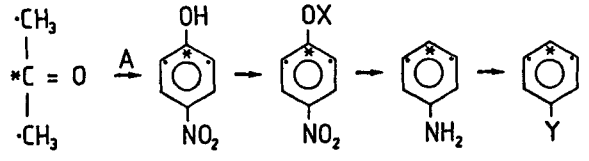
SUMMARY

Aniline (IV), specifically ^{13}C labeled in the 4- or in the 3,5-position (IVa and IVb), has been synthesized with 55% yield from ^{13}C labeled p-nitrophenol (II). The reduction of the NO_2 group and the removal of the OH group was performed in one step by reduction and hydrogenolytic cleavage of p-nitrophenol-methanesulfonate (III), prepared in 90% yield from (II). From (IV) a number of specifically ^{13}C labeled monosubstituted benzenes C_6H_5Y (Y = CN, Hal, NO_2) are easily accessible.

INTRODUCTION

Although aniline is a key molecule for the synthesis of a number of chemically and biologically important molecules, it is surprising that a convenient synthesis of aniline-4-^{13}C (IVa) and of aniline-3,5-$^{13}C_2$ (IVb), which

Scheme I



* Ia * IIa * IIIa * IVa * Va

· Ib · IIb · IIIb · IVb · Vb

*, · = ^{13}C, A = $NaC(NO_2)(CHO)_2$, X = mesylate, Y = CN, Hal, NO_2

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are useful for NMR studies of (IV) and its derivates, has not yet been reported to our knowledge. Ott[1] and Noel[2] have described a synthesis of uniformly ^{13}C labeled aniline, whereas Dickinson et al.[3] have synthesized aniline-1-^{13}C. In principle, IVa could have been obtained from nitrobenzene-4-^{13}C which was prepared by Swartz et al.[4] in a difficult five-step synthesis from p-nitrophenol-1-^{13}C (IIa). A synthesis of the latter starting off from acetone was proposed by Korte et al.[5] (first step in Scheme I). We report here an easy high yield two-step conversion of II to IV according to Scheme I.

RESULTS AND DISCUSSION

In order to find the optimum pathway for the conversion of II to IV we first tried the method of Vowinkel et al.[6] These authors converted the OH group into an O-CN group using gaseous BrCN, and then into the OX group, where X = N,N-diethylurea. The OX group was then removed under reducing conditions where also the NO_2 group is converted into an NH_2 group. We found, however, this procedure neither convenient nor efficient because of the three steps involved and because of non-satisfactory yields of IV when working with small quantities. Therefore, we focussed on the method of Clauß et al.[7] for reductive removal of phenolic OH groups via the corresponding mesylates. Although this procedure had not yet been applied to nitrophenols, we expected that III, where X = mesylate, could be converted to IV under reducing conditions in one step. In fact, we found that the conversion of II to IV via III can be easiliy achieved in a 55 % yield with X = mesylate. We tried also X = brosylate and tosylate, but obtained only 40 % yields. Depending on the position of the ^{13}C label in the starting compound acetone we obtain either IVb or IVa. IV can be easily converted into a number of different specifically ^{13}C labeled monosubstituted compounds (V) using known procedures, e.g. nitrobenzene by oxidation[9] of IV, and other compounds with Y = CN, Hal via the Sandmeyer- reaction.[10]

EXPERIMENTAL

p-Nitrophenol (II)

II was prepared according to the literature[5] from acetone-2-^{13}C and acetone-1,3-$^{13}C_2$ (90% enriched), purchased from Amersham Corp. England.

p-Nitrophenylmethansulfonate (III)

III was prepared according to the method of Saunders et al.[11] II (2.8 g, 20 mmol) was suspended in 1n NaOH (30 ml, 30 mmol). Methansulfonylchloride (2.3 g, 30 mmol) was added in small quantities. Crude III precipitated and was

filtered and washed with water. By repeated recrystallization from 90% ethyl alcohol we obtained colourless crystals (3.9 g, 90% yield).

Specifically ^{13}C labeled aniline (IV)

p-Nitrophenyl-1-^{13}C-methansulfonate (III) (3.9 g, 17.8 mmol) was dissolved in 30 ml methanol to which triethylamine (1.8 g, 17.8 mmol) and 5% palladium -on-carbon catalyst (0.6 g) was added. The dehydrogenation was performed in an autoclave using hydrogen pressure of 40 bar for 30 min, while the solution was stirred strongly. The solution was filtered and diluted with water. Potassium hydroxide was added to extract IV with ether. The ether and triethylamine were evaporated carefully at reduced pressure. The residue was destilled in a microstill at 10^{-1} bar (1.05 g, 55% yield from p-nitrophenol (II)). In order to check the chemical and isotopic purity of the product a sealed NMR sample of IVa in $CDCl_3$ was prepared on a vacuum line. The ^{1}H decoupled ^{13}C NMR spectrum at 75.47 MHz of this sample did not show any sign of a chemical impurity. The following ^{13}C signals were observed: 1. a doublet at 115.1 ppm with the coupling constant $J_{24} = J_{46} = 3$ Hz and the relative intensity 1 for the 2,6-carbon atoms; 2. a doublet at 129.3 ppm with the coupling constant $J_{34} = J_{45} = 56.1$ Hz and the relative intensity 1 for the 3,5-carbon atoms, with a weak singlet at the center of the doublet arising from aniline with ^{13}C in natural abundance; 3. a singlet at 118.6 ppm with the relative intensity 40 for the ^{13}C enriched carbon atom in the 4-position. The ^{13}C signal of the carbon atom in position 1 was not observed because of the long relaxation times of quarternary carbon atoms. The chemical shifts and the coupling constants are in agreement with the literature values.[12] The intensities of the three signals and the splitting patterns prove the successful incorporation of ^{13}C into the 4-position of IVa. Within the margin of error of our intensity measurements the isotopic enrichment of IV corresponded to the isotopic enrichment of the precursor acetone (i.e. 90%).

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