A TWO-STEP SYNTHESIS OF BENZYLAMINE-^{15}N FROM AMMONIA-^{15}N

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SUMMARY

The reaction of ammonia-^{15}N with benzaldehyde in 50% aq. methanol followed by slow removal of solvent led to a high yield of a crystalline product (benzylimine-^{15}N). On reduction with sodium cyanoborohydride a good yield of benzylamine-^{15}N was obtained. The synthetic usefulness of this compound is discussed.

Key Words: Benzylamine-^{15}N, ^{15}N-Nuclear magnetic resonance

INTRODUCTION

The stable isotope ^{15}N is extremely useful for the study of biochemicals since nitrogen is one of the major components of biological systems. The interpretation of the mass spectra[1] and nuclear magnetic resonance spectra[2] of many nitrogen-containing compounds would be greatly simplified if ^{15}N could be incorporated at specific sites by simple, efficient methods. Benzylamine is exceptionally useful for introducing nitrogen atoms into synthetic schemes[3] because it is a good nucleophile, soluble in many solvents, and because the benzyl group can easily be removed from the product either by catalytic hydrogenation[4] or by use of sodium in liquid ammonia.[5] In our own laboratory benzylamine has been used in the synthesis of precursors of cyclic guanidines (iminoimidazolidines) some of which are substrates for creatine kinase.[6] Our interest in specifically enriching various parts of molecules with ^{15}N has been for purposes of structure elucidation via observations of ^{31}P-^{15}N coupling in the ^{31}P nuclear magnetic resonance spectrum.[7]

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Borch et al.[8] have extensively studied the use of sodium cyanoborohydride in the reductive amination of ketones and aldehydes. By forming the Schiff's base between an amino and a carbonyl group in the presence of reducing agent very respectable yields of amine product could be obtained. However, their results indicated that the synthesis of benzylamine from benzaldehyde and ammonia would be one of the unfavorable examples of these reactions. Ketones gave higher yields than aldehydes. Substituted amines were better than ammonia. An excess of amine was necessary in order to obtain good yields. In a synthesis of tryptophan-^{15}N (where conditions were comparable to those to be used for benzylamine synthesis) a yield of only 23% was obtained.

Our modifications of their method allow the use of equimolar amounts of ammonia-^{15}N and benzaldehyde and also allow the use of an inexpensive and conveniently obtained form of ^{15}N:ammonia gas. We have succeeded in obtaining reasonable yields of benzylamine by first forming and isolating the Schiff's base (benzylimine), and then reducing this with sodium cyanoborohydride under conditions where reversal of the Schiff's base formation is minimal; i.e.

$$\phi\text{-CH=O} + {}^{15}NH_3 \longrightarrow \phi\text{-CH=}{}^{15}NH + H_2O$$

$$\phi\text{-CH=}{}^{15}NH + CH_3COOH + BH_3CN^- \xrightarrow{CH_3OH} \phi\text{-}CH_2\text{-}NH_3^+ + CH_3CO_2^- + HCN + B(OCH_3)_3$$

METHODS AND RESULTS

Ammonia (99% ^{15}N enrichment) was obtained from KOR Isotopes (Cambridge, MA 02142, U.S.A.) and dissolved in distilled water in a sealed vessel to produce a concentrated solution ($\sim$ 10 M). Reagent grade benzaldehyde was redistilled. Sodium cyanoborohydride came from Aldrich Chemical Co. (Milwaukee, WI 43233, U.S.A.). Other reagents were analytical grade.

Benzylimine-^{15}N. Equal volumes of ammonia-^{15}N solution and benzaldehyde solution ($\sim$ 10 M in methanol) were mixed in a low, wide beaker. The beaker was set in a small desiccator well-packed with KOH pellets. Since ammonia in solution is in equilibrium with ammonia in the air space of the desiccator, high yields of product could only be obtained if this air space was kept small. Within hours well-formed white crystals appeared, and, when all the solvent had been absorbed

by the KOH, the dry crystals were collected and stored under cool, dry conditions. These crystals were relatively unstable and decomposed at 93-96°. When converted to the hydrochloride by addition of HCl in ether, benzyliminium-^{15}N chloride was obtained: m.p. 179-181° (lit.[9] 181°). The best yield of benzylimine-^{15}N obtained was 97% of the theoretical amount.

Benzylammonium-^{15}N chloride. To 0.01 mol of benzylimine-^{15}N crystals was added 10 ml of dry methanol containing 0.01 mol acetic acid and 0.014 mol $NaCNBH_3$. After 1 hr the solvent was removed and 5 N NaOH added. This solution was repeatedly extracted with ether which was in turn extracted with 1 N HCl. The HCl solution was filtered and the solvent removed. The product was recrystallized from methanol-hexane and from hot methanol and a final yield of 69% from ammonia-^{15}N was obtained: m.p. 254-256° (lit.[10] 255-256°); proton n.m.r. δ 4.20 and 7.42 ppm from tetramethylsilane; percent ^{15}N enrichment > 98%.

DISCUSSION

This facile synthesis of benzylamine-^{15}N in reasonable yield allows the introduction of ^{15}N into many compounds of chemical and biological interest at high levels of enrichment and at reasonable cost. The ease with which the benzyl group may be removed is one of the major attractions of this method. The usefulness of ^{15}N enrichment at specific sites in enzymes or small biologically active molecules has not yet been thoroughly exploited but the technique promises to be one of major importance since nitrogen is so abundant in living systems.

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