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# CROWN ETHER CATALYZED DEUTERIUM EXCHANGE IN THE SYNTHESIS OF BENZYL CYANIDES

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## SUMMARY

Nucleophilic substitution of benzyl-type chlorides with cyanide ion in deuterochloroform, deuteroacetonitrile or deuterobenzene catalyzed by 18-crown-6 results in the introduction of deuterium onto the benzyl carbon. Benzyl cyanides are labelled by refluxing with cyanide ion and crown ether in deutero solvent. Two such exchanges in deuterochloroform produced greater than 90% incorporation. Side-chain labelled phenylethylamine, tryptamine and m- and p-tyramine were synthesized in this way.

Key Words: Benzyl cyanides, deuterium exchange, crown ether

## INTRODUCTION

It has been reported that the nucleophilic substitution of alkyl halides by cyanide ion can be accomplished in aprotic organic solvents by the addition of catalytic amounts of a suitable crown ether (1,2). The advantages of the crown ether procedure are high yields, ease of isolation of the product and the absence of hydrolyzing conditions. In carrying out this reaction on some $\alpha,\alpha$-$^2H_2$ benzyl chlorides in acetonitrile, substantial loss of deuterium in the product was observed. This paper is a description of a short study of this phenomenon which has not been reported previously.

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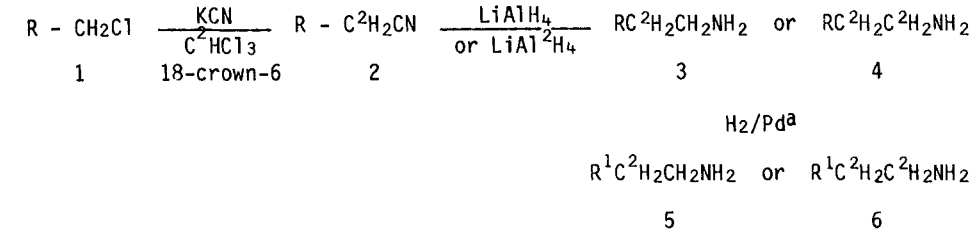
## RESULTS AND DISCUSSION

In the course of the synthesis of $\beta,\beta$-$^2H_2$ and $\alpha,\alpha,\beta,\beta$-$^2H_4$ phenylethylamine (3a, 4a), m- and p-tyramine (5ef, 6ef), and tryptamine (3d, 4d) (Figure 1) for use as tracers in




1 2 3 4 5 6

R = a) phenyl-, b) m- and, c) p-benzyloxyphenyl-, or d) 3-indolyl-

$R^1$ = e) m-, and f) p-hydroxyphenyl-

[a] This step required only in the synthesis of m- and p-tyramine.

Fig. 1. Structures of cyanide intermediates and final amine products.

metabolic studies and as internal standards in quantitative mass spectrometry, the $\alpha,\alpha$-$^2H_2$ benzyl cyanides (II, Figure 1) were synthesized from the corresponding chlorides (I) by the the 18-crown-6 catalyzed reaction with potassium cyanide in acetonitrile. The cyanide substitution was complete within 24 h as expected, but unexpectedly substantial loss of deuterium occurred (Table 1). When the reaction was carried out

Table 1. Deuterium on benzyl carbon after nucleophilic substitution of p-benzyloxybenzylchloride-$\alpha,\alpha$-$^2H_2$[a] by cyanide ion in proteo solvents catalyzed by 18-crown-6.

| Solvent | Reaction Time (h) | $d_0$(%) | $d_1$(%) | $d_2$(%) |
|---|---|---|---|---|
| $CH_3CN$ | 72 | 6.6 | 36.4 | 57.0 |
| $CH_2Cl_2$ | 72 | 3.9 | 29.7 | 66.4 |
| $CHCl_3$ | 72 | 57.8 | 34.7 | 7.5 |
| $CCl_4$ | 72 | no reaction (deutero chloride recovered) | | |
| Benzene | 72 | 1.5 | 23.5 | 75.0 |

[a] Initial deuterium incorporation = 98.3% $^2H_2$ in the $\alpha$-position.

in other solvents usually considered to be aprotic, such as benzene, chloroform or dichloromethane, loss of deuterium again occurred. In the absence of the crown ether no nucleophilic substitution occurred, but refluxing a benzyl cyanide in a deutero solvent without crown ether resulted in about 10% exchange.

The extent of the exchange does not appear to be related to the dielectric constant of the solvent, since chloroform, which has a relatively low constant, promotes the greatest exchange (Table 2). The addition of 1% methanol to the solvent increases not only the rate of cyanide substitution but also the rate of exchange, possibly because of improved solubility of the crown ether or crown-KCN complex (3). The solubility of the crown ether in the solvent may be a critical factor in determining the rate of exchange. Pederson (4) reports the solubility of dibenzo-18-crown-6 in several aprotic solvents, showing that chloroform is a better solvent than acetonitrile, benzene or carbon tetrachloride (Table 2); a similar trend probably applies to the solubility of 18-crown-6 in these solvents. The relative acidities of the hydrogen atoms in these solvents may also be an important factor in determining the rate of exchange. "Naked" cyanide ions are not only strong nucleophiles but should also be quite strong bases capable of abstracting a proton (or deuteron) from solvents such as chloroform, dichloromethane, acetonitrile and benzene. The strong electron-withdrawing character of the three chlorine atoms of chloroform should make the proton of chloroform more acidic than the protons of benzene or acetonitrile and, therefore, more readily abstracted and exchanged with the deuterons of benzyl cyanide-$d_2$.

Table 2. Dielectric constants of some solvents and the solubilities of dibenzo-18-crown-6.

| Solvent | Dielectric Constant | Solubility of Dibenzo-18-crown-6[a] |
|---|---|---|
| Acetonitrile | 38.8 | 0.079 |
| Dichloromethane | 9.1 | - |
| Chloroform | 5.05 | 0.210 |
| Carbon Tetrachloride | 2.24 | 0.005 |
| Benzene | 2.28 | 0.018 |

[a] moles/L

Having shown that deuterium is lost from the benzyl carbon under the conditions described above, the possibility of introducing deuterium by the reaction of benzyl chloride and m- and p-benzyloxybenzyl chloride with cyanide ion in deuterochloroform and deuteroacetonitrile ($^2H_3$) was investigated. After completion of the reaction, the product was analyzed for deuterium incorporation by mass spectrometry. Since the mass spectra of the benzyloxybenzyl cyanides exhibit no M-1 or M-2 ions, the calculations of deuterium incorporation required correction only for the natural isotopic contributions from the unexchanged proteo analogue. Indolylacetonitrile and benzyl cyanide, however, do show large M-1 ions so the calculation of deuterium incorporation was omitted, and instead, after two or three exchanges, the product was reduced and the isolated amines, phenylethylamine-β,β-$^2H_2$ and tryptamine-β,β-$^2H_2$ were analyzed as their dansyl derivatives by integrated ion current mass spectrometry (5). The deuterium incorporation on the benzyl carbon of the nitriles and amines after one, two or three exchanges is given in Table 3. Using 1% methanol-O$^2$H in deuterochloroform, two exchanges is sufficient to achieve greater than 90% deuterium incorporation.

Table 3. Deuterium on benzyl carbon after nucleophilic substitution of proteo benzyl chlorides by cyanide ion in deutero solvents catalyzed by 18-crown-6.

| Product | Solvent | After Exchanges | $^1H_2$ | $^2H_1$ | $^2H_2$ |
|---|---|---|---|---|---|
| m-Benzyloxybenzyl cyanide | $C^2H_3CN$ | 1 | 34.3 | 48.1 | 17.6 |
| | $C^2H_3CN$ | 2 | 1.0 | 15.5 | 83.5 |
| | $C^2HCl_3$ | 1 | 31.5 | 49.0 | 19.5 |
| | $C^2HCl_3$ | 2 | 5.0 | 33.4 | 61.6 |
| | $C^2HCl_3$ | 3 | n.d. | 5.6 | 94.4 |
| | $C^2HCl_3$-$CH_3O^2H$ | 1 | 4.9 | 29.1 | 66.0 |
| | $C^2HCl_3$-$CH_3O^2H$ | 2 | n.d. | 5.2 | 94.8 |
| p-Benzyloxybenzyl cyanide | $C^2HCl_3$ | 1 | 24.5 | 51.8 | 23.7 |
| | $C^2HCl_3$ | 2 | 5.1 | 37.6 | 57.3 |
| | $C^2HCl_3$ | 3 | 3.6 | 31.0 | 65.4 |
| | $C^2HCl_3$ | 4 | 1.7 | 21.7 | 76.6 |
| | $C^2HCl_3$-$CH_3O^2H$ | 1 | 7.1 | 40.7 | 52.2 |
| | $C^2HCl_3$-$CH_3O^2H$ | 2 | n.d. | 9.7 | 90.3 |
| Phenylethylethylamine-$^2H_2$ | $C^2HCl_3$-$CH_3O^2H$ | 2 | n.d. | <1.0 | >99.0 |
| Tryptamine-$^2H_2$ | $C^2HCl_3$-$CH_3O^2H$ | 2 | n.d. | 7.0 | 93.0 |

n.d. = not detected

## Experimental

### Materials and Instruments

18-Crown-6 (Aldrich) was purchased from Terochem (Edmonton, Alberta, Canada) and the deuterated solvents from Merck Sharp and Dohme (Montreal, Quebec, Canada). A Hewlett-Packard 5710A Gas Chromatograph equipped with a flame ionization detector and a 2 m x 2 mm i.d. 3% OV101 on Gas Chrom Q column was used for the determination of the purity of cyanide products and for the detection of the presence of crown ether. The mass spectra of the cyanides were obtained by direct probe injection into the ion source of an AEI MS902S mass spectrometer operated at 70 eV, ion source temperature of 200°C and resolution of 1000.

The proteo and deutero benzyl chlorides were synthesized from benzoic, m- or p-benzyloxybenzoic acid by esterification with ethanol-HCl, reduction of the ester in ether with either $LiAlH_4$ or $LiAl^2H_4$ to give the corresponding proteo or deutero benzyl alcohol, which was then converted to the respective benzyl chloride with thionyl chloride in chloroform-pyridine. The yields of all steps were greater than 90%.

### Crown ether catalyzed conversion of benzyl chloride to cyanides

The $\alpha,\alpha$-$^2H_2$ benzyl chloride (1 equiv.) and 18-crown-6 (0.05 equiv.) were dissolved in acetonitrile, benzene, chloroform, dichloromethane or carbon tetrachloride (50 ml for each 0.10 mole of chloride), in some experiments containing 1% methanol. Powdered potassium cyanide (2 equiv.) was added and the mixture was gently refluxed for 24 h to 72 h (Table 1). At the end of the refluxing period, the mixture was filtered with suction and the filtrate was rotary evaporated at 45°C. Removal of the crown ether, if desired, can be accomplished by passing a dichloromethane solution of the product through a column of silica gel (100-200 mesh) (3-4 g). For larger scale reactions, this step was repeated one or more times to ensure complete removal of the crown ether (2). The presence or absence of the crown ether was determined by gas chromatography. The same procedure was followed for the reaction of proteo benzyl chlorides in deutero solvents. A second or third exchange was carried out by dissolving the residue obtained after evaporation of the eluate from the silica column in fresh deutero solvent and refluxing with fresh crown ether (0.05 equiv.) and KCN (1 equiv.).

After the final exchange the nitriles were reduced with either $LiAlH_4$ to give the $\beta,\beta$-$^2H_2$ arylethylamine or with $LiAl^2H_4$ to give the $\alpha,\alpha,\beta,\beta$-$^2H_4$ amine. Subsequent hydrogenolysis of the benzyloxyphenylethylamines in ethanolic-HCl removed the protecting groups. Confirmation of the deuterium incorporation in the final products ($^2H_2$ or $^2H_4$ labelled phenylethylamine, tryptamine and m- and p-tyramine) was obtained by integrated ion current mass spectrometry of their dansyl derivatives by a procedure previously published (6).

## Conclusions

1) Crown ether catalyzed nucleophilic substitutions of $\alpha,\alpha$-$^2H_2$ benzyl chlorides by cyanide ion must be carried out in deutero solvents to avoid hydrogen-deuterium exchange with the solvent.

2) Proteo chlorides or cyanides can be converted to deutero benzyl cyanides by reaction with KCN in "aprotic" deutero solvents, two such exchanges usually providing greater than 90% deuterium incorporation.

3) Deuterochloroform would appear to be the solvent of choice because of the greater exchange which occurs in it and because it is the least expensive of the deutero solvents.

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