

Received: June 23, 1987; accepted: November 5, 1987

REACTIONS OF NITRO ALCOHOLS WITH N,N-DIETHYL-1,1,2,3,3,3-HEXAFLUORO-
PROPYLAMINE

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SUMMARY

Fluorination of nitro alcohols with N,N-diethyl-1,1,2,3,3,3-hexafluoropropylamine (PPDA) was investigated. 3-Nitrobenzyl fluoride (II) was obtained from the reaction of PPDA and 3-nitrobenzyl alcohol (I) (yield 66%). The reaction of 2-methyl-2-nitro-1-propanol (IV) with PPDA gave 2-methyl-2-nitropropyl 2,3,3,3-tetrafluoropropionate (V). Reduction of 3-nitrobenzyl fluoride (II) with lithium aluminium hydride gave the corresponding amino compound, 3-aminobenzyl fluoride (VI) in poor yield.

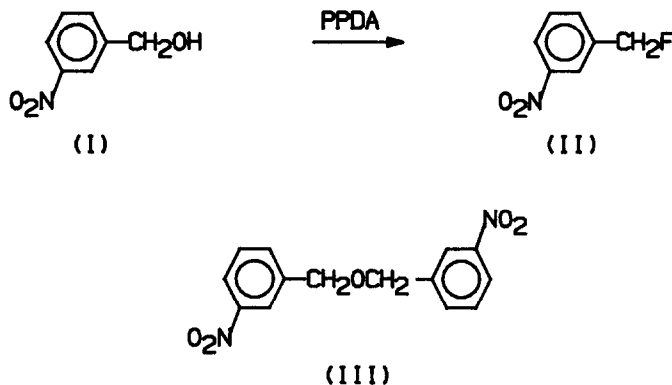
INTRODUCTION

Fluorinated compounds have been widely utilized in biochemical and other investigations. However, fluorinations of nitro alcohols by exchange of F for OH have not been described previously. Recently, it was reported that N,N-diethyl-1,1,2,3,3,3-hexafluoropropylamine (PPDA) is useful as a fluorinating agent for halogeno alcohols [1] and hydroxy

esters [2]. In this short paper, we describe the reaction of PPDA with a variety of nitro alcohols and the reduction of one of the products with lithium aluminium hydride.

RESULTS AND DISCUSSION

Convenient fluorinations of standard alcohols by the exchange of F for OH using PPDA have been reported [3]. We have now found that the corresponding fluorinated compounds are obtained from the reaction of excess PPDA with nitro benzyl alcohols. For example, 3-nitrobenzyl fluoride (II) was obtained by adding 3-nitrobenzyl alcohol (I) to excess PPDA. 4-nitrobenzyl fluoride was similarly obtained from 4-nitrobenzyl alcohol, but the reaction of PPDA with 2-nitrobenzyl alcohol gave its fluoride in low yields. When PPDA was added to the nitroalcohols, ethereal products were obtained as the main products interestingly. Di(3-nitrobenzyl) ether (III) was obtained from the reaction of (I) and PPDA. In contrast, 2,3,3,3-tetrafluoropropionate

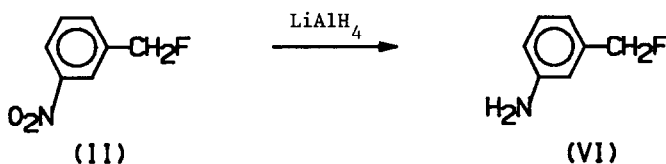


esters were obtained from the reaction of PPDA with aliphatic nitro alcohols. For example, 2-methyl-2-nitropropyl 2,3,3,3-tetrafluoropropionate (V) was produced by the reaction of PPDA with 2-methyl-2-nitro-1-propanol (IV).



This type of side reaction has been reported previously [1]. Details of the examples studied are given in Table 1.

Reduction of (II) with lithium aluminium hydride gave 3-aminobenzyl fluoride (VI) in low yield. In this case, the use of metallic iron or metallic tin gave many products.



EXPERIMENTAL

Reaction of 3-nitrobenzyl alcohol (I) with PPDA

To a solution of PPDA (3.0g, 13.5 mmol) in dry dichloromethane (30 ml), a solution of 3-nitrobenzyl alcohol (I) (1.5 g, 9.8 mmol) in dichloromethane (10 ml) was added dropwise at room temperature. After stirring for 6 hr, the reaction mixture was left overnight. It was then poured into water and the oily product was extracted with diisopropyl ether. The ether extract was washed with water, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was distilled to give the following fractions: (i) ~ 90°C/50 mmHg, 2.0 g; (ii) 90 ~ 140°C/50 mmHg, 0.5 g, and (iii) 140 ~ 142°C/50 mmHg, 1.0 g. Fraction (i) was N,N-diethyl 2,3,3,3-tetrafluoropropionamide. Fraction (ii) was a mixture of the amide and 3-nitrobenzyl fluoride (II). Fraction (iii) was the compound (II) (purity 95 % by gas chromatographic analysis using a column of silicone DC 200 on Celite 545 at 190 °C): ¹H NMR (δ, ppm): 5.42 (2H, d, J(HF)=47.0 Hz,

TABLE 1
Reactions of Nitroalcohols with PFDA

| Alcohol | Product ¹ | Boiling Point (°C/mmHg) (yield %) ² | ¹⁹ F NMR δ, ppm | | | Hz | | |
|-----------------------------|------------------------------------------------------|------------------------------------------------------|-------------------------------|------------------|--------------------|--------|--------|------|
| | | | -CHF | -CF ₃ | -CH ₂ F | J (HF) | J (FF) | |
| 4-Nitrobenzyl alcohol | 4-Nitrobenzyl fluoride | 110 ~ 115/18 mp 26°C (60 %) | | | +132.0(t) | | 46.0 | |
| 3-Nitrobenzyl alcohol | 3-Nitrobenzyl fluoride | 140 ~ 142/50 (66 %) | | | +130.7(t) | | 47.0 | |
| 2-Nitrobenzyl alcohol | 2-Nitrobenzyl fluoride | 80 ~ 90/20 (17 %) | | | +137.7(t) | | 47.6 | |
| 2-Methyl-2-nitro-1-propanol | 2-Methyl-2-nitropropyl 2,3,3,3-tetrafluoropropionate | 140 ~ 145/120 (45 %) | +125.0(dq) | | | | 44.4 | 11.5 |
| 2-Nitrobutanol | 2-Nitrobutyl 2,3,3,3-tetrafluoropropionate | 65 ~ 70/22 (51 %) | +124.0(dq) | | | | 45.0 | 11.3 |
| | | | | | | | 7.0 | 11.3 |
| 3-Nitro-2-butanol | 3-Nitro-butyl 2,3,3,3-tetrafluoropropionate | 77 ~ 79/17 (48 %) | +120.9(dq) | | | | 40.0 | 11.3 |
| | | | | | | | 5.6 | 11.3 |

1 These products are new compounds. The microanalyses were in satisfactory agreement with the calculated values: C ± 0.30 %, H ± 0.04 %.

2 The yield was calculated as isolated yield.

-CH₂F), 7.56 (2H, m, aromatic protons), 8.08 (2H, broad s, aromatic protons adjacent to NO₂).

A solution of PPDA (3.0 g, 13.5 mmol) in dry dichloromethane (30 ml) was added dropwise into a solution of *m*-nitrobenzylalcohol (I) (1.5 g, 9.8 mmol) in dichloromethane (10 ml) at room temperature. It was treated as mentioned above. The residue of the ether extracts was left overnight to give a crystalline product, which was recrystallized from a mixture of benzene and ethanol to give as white crystals, di-(3-nitrobenzyl) ether (III) (1.0g), mp 89 ~ 90 °C. IR (cm⁻¹): 1550 (NO₂), 1100 (-O-), 690 and 790 (*m*-substituted benzene). ¹H NMR (δ, ppm): 4.68 (4H, s, -CH₂-O-CH₂-), 7.60 (2H, m, aromatic protons), 8.19 (2H, m, aromatic protons adjacent to NO₂); MS (m/e): 289 [M + 1]⁺ (C₁₄H₁₂O₅N₂=288), 152 (C₇H₆NO₂=152), 137 (C₇H₆NO₂=136). From filtrated ether solution, 0.3 g of compound (II) was obtained by fractional distillation.

Reaction of 2-methyl-2-nitro-1-propanol (IV) with PPDA

A solution of PPDA (5.00 g, 22.4 mmol) in dry dichloromethane (15 ml) was added dropwise into a solution of 2-methyl-2-nitro-1-propanol (IV) (2.38 g, 20 mmol) in dichloromethane (20 ml) at room temperature. The reaction mixture was treated in the usual manner to give following fractions: (i) ~ 133°C/120 mmHg, 1.5 g; (ii) 133 ~ 140°C/120 mmHg, 1.5 g; and (iii) 140 ~ 145°C/120 mmHg, 2.2 g. Fraction (i) was *N,N*-diethyl 2,3,3,3-tetrafluoropropionamide. Fraction (ii) was a mixture of the amide and 2-methyl-2-nitropropyl 2,3,3,3-tetrafluoropropionate (V). Fraction (iii) was pure compound (V) (purity 98 % by gas chromatography using a column of Silicone DC 200 on Celite 545 at 180 °C). The isolated yield was 45 %. Compound (V) showed the following spectral data. IR (cm⁻¹): 1780 (-OCO-), 1550 (-NO₂). ¹H NMR (δ, ppm): 1.62 (6H, s, CH₃x2), 4.54 (2H, s, -C-CH₂-O-), 5.13 (1H, dq, J(HF)=44.4 Hz, J(HCF₃)=5.6 Hz, -CHF-). 3-Nitro-2-butanol was fluorinated in the same way, and the results are listed in Table 1.

Reduction of 3-nitrobenzyl fluoride (II) with lithium aluminium hydride

To a suspension of lithium aluminium hydride (0.379 g, 0.01 mol) in dry ether (20 cc), (II) (1.55 g, 0.01 mol) in dry ether (10 cc) was added drop by drop at 0 °C and stirred for 6 hr. It was poured onto excess ice water, and extracted with diethyl ether. The ether extract was washed with water, dried over anhydrous sodium sulphate, and distilled to give 0.2 g (yield 16.0 %) of 3-aminobenzyl fluoride (VI) boiling 65 ~ 70 °C at 20 mmHg. It showed the following spectral data. IR(cm^{-1}): 3350 (NH_2), 690 and 788 (meta-substitution); ^1H NMR (δ , ppm): 2.43 (2H, s, NH_2 -), 5.38 (2H, d, $J(\text{HF})=48.0$ Hz), 7.1 ~ 7.8 (4H, m, aromatic protons); ^{19}F NMR (δ , ppm): 128.7 upfield (triplet, $J(\text{HF}) = 48.0$ Hz) from an external standard CF_3COOH .

The reaction of (II) with sodium borohydride did not give its corresponding product. The reductive reaction of (II) with iron or tin using hydrochloric acid gave defluorinated products.

ACKNOWLEDGEMENTS

We thank Prof. Dr. N. Ishikawa of Tokyo Institute of Technology for cordial guidance throughout our research, and Miss A. Orihara for her technical assistance.

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