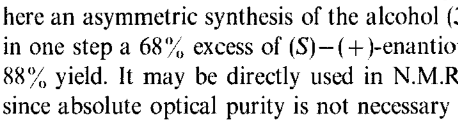
COMMUNICATIONS

Asymmetric Synthesis of 2,2,2-Trifluorophenylethanol of High Optical Purity

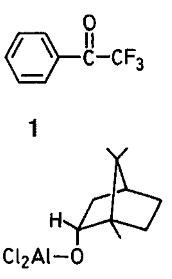
D. Nasipuri, Pranab K. Bhattacharya

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

Nuclear magnetic resonance spectroscopy in appropriate optically active solvents provides a valuable tool for determining the absolute configuration and optical purity of a large number of chiral molecules. The method which is based on the diastereotopical behaviour[1] of the enantiotopic nuclei in chiral solvents is simple, convenient, and absolute for determining the optical purity. 2,2,2-Trifluorophenylethanol (**3**) is a common chiral solvent which induces enantiomeric nonequivalence in a variety of compounds, e.g. alcohols, amines, sulfoxides and related compounds, phosphine and amine oxides[2], and epoxides[3,4] (see ref.'s 5 and 6 for similar uses). This alcohol is obtained by reduction of trifluoroacetophenone (**1**) with metal hydrides, but the resolution is either tedious[7] or involves too many steps[8]. We report here an asymmetric synthesis of the alcohol (**3**) which gives in one step a 68% excess of (*S*)-(+)-enantiomer in nearly 88% yield. It may be directly used in N.M.R. experiments since absolute optical purity is not necessary for the above purpose.



1 **3**



2

(−)-Borneol, obtained by hydrolysis of (−)-bornyl acetate[9] was converted into its dichloroalumino-derivative (**2**)[10] and the latter used for asymmetric reduction of trifluoroacetophenone (**1**)[11]. 2,2,2-Trifluorophenylethanol (**3**) was isolated from the reaction mixture by first converting the total alcohols into hydrogen phthalates, dissolving the latter in aqueous sodium hydrogen carbonate, and warming the solution at 70–80°. Under this condition, only the fluoro-alcohol (**3**) was liberated and was obtained in pure state and in almost quantitative yield. The optical rotation corresponded to a mixture of 84% of (*S*)- and 16% of (*R*)-form. Other related reactions and the nature of the transition state will be published elsewhere, (cf. ref. 12).

(*R*)-Bornyloxyaluminium Dichloride (2):

To an ice-cold solution of anhydrous aluminium chloride (9.1 g, 0.068 mol) in ether (60 ml), was added 1 *M* ethereal solution of lithium aluminium hydride (17 ml, 0.017 mol). After a few min, (−)-borneol (10.8 g, 0.069 mol) in ether (70 ml) was dropped in with stirring. A slight excess of the alcohol was used to avoid any excess of hydride. The reaction vessel was taken out of the ice-bath and stirring was continued till the temperature rose to 10°.

2,2,2-Trifluorophenylethanol (3):

To the above solution of bornyloxyaluminium dichloride was now added trifluoroacetophenone (**1**; 5.6 g, 0.032 mol) in ether (10 ml) with efficient stirring while the temperature was kept at 5–10°. After 1 h, the temperature was allowed to rise to 25° and the stirring continued for 1 h more. The solution was cooled and carefully decomposed with 2*N* sulphuric acid. The ethereal layer was separated and the aqueous solution extracted once with ether (50 ml). The combined ethereal solution was washed with cold water, dried (potassium carbonate), and solvent removed using a fractionating column. The residual semisolid mass was heated with a mixture of phthalic anhydride (15 g, 0.1 mol) and pyridine (5 ml) on the steam-bath for 6 h. The cooled product was treated with crushed ice and hydrochloric acid and the organic matter was taken in ether (150 ml). The ethereal solution was extracted several times with an excess of aqueous sodium hydrogen carbonate. The hydrogen carbonate extract was washed with ether (2 × 50 ml) to remove any neutral matter. The entire operation was done as quickly as possible keeping the temperature of the solution below 15°. The solution was now warmed at 70–80° in a water-bath for 1 h with constant shaking. Turbidity appeared and the fluoro-alcohol formed a separate layer. It was cooled and thoroughly extracted with ether. The ethereal extract was dried (Na_2SO_4), solvent removed through a fractionating column, and the residue distilled to give 2,2,2-trifluorophenylethanol (**3**) as a colourless oil; yield: 4.9 g (88%); b.p. 80°/10 torr; $n_D^{25} = 1.4600$; $\alpha_D^{25} = +28.0°$ (neat, $l = 1$) (lit.[7] $= \alpha_D^{25}$ 41.18°). G.L.C. analysis (conditions: a column, 6 ft × 0.25 in, of 10% polyester of diethylene glycol adipate (DEGA), alternatively succinate (DEGS), supported on Gas-chrom-Z, 60–80 mesh, at temperatures of 90 to 120° under nitrogen pressure of 1.36–2.04 atm.) showed only one peak due to 2,2,2-trifluorophenylethanol. The identity was further confirmed by I.R. and N.M.R. spectra. Duplicate experiment gave similar result.

Received: July 18, 1975

---

[1] M. Raban, K. Mislow, *Topics Stereochem.* **2**, 199 (1967).

[2] W. H. Pirkle, S. D. Beare, *J. Amer. Chem. Soc.* **91**, 5150 (1969) and the references cited therein.
W. H. Pirkle, S. D. Beare, R. L. Muntz, *J. Amer. Chem. Soc.* **91**, 4575 (1969).
W. H. Pirkle, R. L. Muntz, I. C. Paul, *J. Amer. Chem. Soc.* **93**, 2817 (1971).

[3] I. Moretti, F. Taddei, G. Torre, *J. Chem. Soc. Chem. Commun.* **1973**, 25.

[4] Review: A. Ejchart, J. Jurczak, *Wiad. Chem.* **24**, 857 (1970).

[5] A. Mannschreck, V. Jonas, B. Kolb, *Angew. Chem.* **85**, 994 (1973); *Angew. Chem. Internat. Edit.* **12**, 909 (1973).

[6] M. D. Joesten, H. E. Smith, V. A. Vix, *J. Chem. Soc. Chem. Commun.* **1973**, 18.

[7] D. M. Feigl, H. S. Mosher, *J. Org. Chem.* **33**, 4242 (1968).

[8] W. H. Pirkle, S. D. Beare, T. G. Burlingams, *J. Org. Chem.* **34**, 470 (1969).

[9] (−)-Bornyl acetate was supplied by Aldrich Chemical Co., U.S.A.

[10] D. Nasipuri, C. K. Ghosh, R. J. L. Martin, *J. Org. Chem.* **35**, 657 (1970).

[11] Trifluoroacetophenone was kindly donated by Professor J. D. Morrison, Department of Chemistry, University of New Hampshire, Durham, New Hampshire, U.S.A.

[12] D. Nasipuri, P. R. Mukherjee, *J. Indian Chem. Soc.* **51**, 171 (1974).