Optically Active Trifluoromethylcarbinols as Chiral Solvating Agents for Asymmetric Transformations at a Ring-nitrogen Atom

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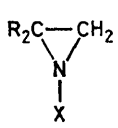
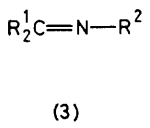
Summary Asymmetric chlorination of the nitrogen atom of aziridines can be carried out using achiral t-butyl hypochlorite in the presence of optically active trifluoromethylcarbinols; the absolute stereochemistry of the reaction may be correlated with the chirality of the alcohol used.

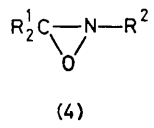
ALTHOUGH several studies have been devoted, during the last few decades, to stereochemical problems linked to the inversional process at trivalent nitrogen,[1] and many nitrogen invertomers stable at room temperature have been identified and isolated,[2] asymmetric syntheses of optically active compounds whose asymmetry is due solely to a trivalent non-bridgehead nitrogen atom, have been reported only in the case of chlorination of 2,2-diphenylaziridine by optically active chlorinating reagents,[3] and of oxidation of prochiral ketimines by optically active peracids.[4,5]



(1) X = H
(2) X = Cl
a; R = CO_2Et
b; R = Ph

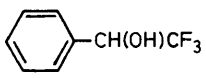


(3)

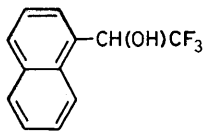


(4)

R^1 = Me, Ph
R^2 = Me, Bu^t, CH(Me)Ph



(S)—(+)—(5)



(R)—(−)—(6)

Recently we observed that optically active trifluoromethylcarbinols are powerful chiral media for asymmetric inductions involving basic prochiral substrates and achiral reagents.[6] More particularly, it was shown that results obtained from the asymmetric synthesis of oxaziridines of type (**4**), by oxidation with *m*-chloroperoxybenzoic acid of ketimines (**3**) carrying two Ph substituents at the carbon site of the C=N bond (R^1 = Ph), and in the presence of chiral trifluoromethylcarbinols, can be compared with the best results reported in the asymmetric oxidation of the same substrates with chiral peracids.[6] We now report the results of chlorination of aziridines (**1a**)‡ and (**1b**)[3] with t-butyl hypochlorite (Bu^tOCl), in the presence of (*S*)-(+)-2,2,2-trifluoro-1-phenylethanol (**5**)[6] and (*R*)-(−)-2,2,2-trifluoro-1-(1-naphthyl)ethanol (**6**).[6]

In a typical experiment, a mixture of the aziridine (**1**) (1 mmol) and the chiral alcohol (2 mmol) was diluted with CH_2Cl_2 (2·5 ml) and treated at −60 °C with a solution of freshly prepared Bu^tOCl (1 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was kept for 3 h at this temperature, and the CH_2Cl_2 solvent was then evaporated *in vacuo*. Optically active *N*-chloroaziridines (**2**) were easily recovered (80—90% yield) free from traces of the optically active solvent (n.m.r. spectroscopy, t.l.c., and g.l.c. analysis) by column chromatography on silica gel using n-hexane–ether (9 : 1) as eluant for (**2b**), or on alumina [n-hexane/CH_2Cl_2 (4 : 6)] for (**2a**).

The results reported in the Table show that the absolute stereochemistry of the reaction depends on the chirality of alcohol used: *i.e.*, positive (**2a**) or negative (**2b**) *N*-chloroaziridines are obtained when (*S*)-(**5**) is used as chiral solvating agent, and opposite results are observed when the reaction is carried out in the presence of (*R*)-(**6**) carbinol.

Chlorination of aziridine (**1a**), which contains two $-CO_2Et$ substituents at the same carbon of the ring, gives an *N*-chloroaziridine (**2a**) of very low optical activity. In contrast, chlorination of (**1b**), whose structure is characterized by having two phenyl substituents at the same carbon of the aziridine ring, gives the *N*-chloro-derivative (**2b**) with quite high optical activity. The racemization of (**2b**) is easily followed in CCl_4 solution and in the 30—60 °C temperature range, by polarimetric determination of the optical decay of a sample having $[\alpha]_D^{20}$ +20·2°. N.m.r. spectra and t.l.c. showed that no decomposition of the product occurs during the thermal racemization. Therefore, the observed loss of optical activity of (**2b**) may be reasonably attributed to the pyramidal inversion at the ring-nitrogen. The inversion barrier observed agrees well with the experimental[7] and calculated (MNDO)[1] barriers reported for *cis*-*N*-chloro-2-methylaziridine.

TABLE. Asymmetric chlorination of aziridines (**1a**) and (**1b**) with t-butyl hypochlorite in the presence of optically active trifluoromethylcarbinols at −60 °C.[a] First order rate constant and activation parameters for pyramidal inversion at nitrogen from racemization of (**2b**) in CCl_4.[b]

	(**2a**)[c]	(**2b**)[d]				
Alcohol	$[\alpha]_D^{20}$	$[\alpha]_D^{20}$	$k \times 10^5$ (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e.u.)
(*S*)-(+)-(**5**)	+0·7[e]	−4·5[e]				
(*R*)-(−)-(**6**)	−0·5[e]	+20·2[e,f]	65·5[g]	24·4	24·7	+0·9

[a] Reaction mixture composed of aziridine-alcohol (1 : 2 mmol) in CH_2Cl_2 (2·5 ml) + t-butyl hypochlorite (1 mmol) in CH_2Cl_2 (2 ml). [b] Racemization carried out in the temperature range 30—60 °C. [c] *N*-chloroaziridine (**2a**) has b.p. 67 °C at 0·02 mmHg (with racemization); δ (CCl_4) 1·31 (3H,t), 1·38 (3H,t), 2·84 (1H,d), 3·00 (1H,d), 4·26 (2H,q), and 4·39 (2H,q). [d] The physical and n.m.r. properties of (**2b**) are consistent with the properties reported in ref. 3. [e] Data for chloroform solution; values corrected for optically pure carbinols. [f] $[\alpha]_D^{20}$ + 19·4° (acetone). [g] Rate constant at 60 °C.

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‡ Aziridine (**1a**) can be obtained from 1,2-dibromo-1,1-diethoxycarbonylethane, by reaction with ammonia (A. V. Prosyanik, personal communication). It shows b.p. 55—56 °C at 0·02 mmHg; δ (CCl_4): 1·35 (6H,t), 1·70 (1H,t), 2·15 (2H,m), and 4·25 (4H,q).

These results, coupled with the very simple reaction process and with the easy separation of the optically active solvent from the reaction products, suggest that chiral trifluoromethylcarbinol–aziridine (**1**) solvate can be used as a model in the study of several types of asymmetric syntheses at nitrogen, by reaction with achiral reagents.

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