Highly stereoselective chlorination of β-substituted cyclic alcohols using PPh_3–NCS: factors that control the stereoselectivity†

E. A. Jaseer, Ajay B. Naidu, Sreehari S. Kumar, R. Koteshwar Rao, Krishna G. Thakur and G. Sekar*

Received (in Cambridge, UK) 5th October 2006, Accepted 30th October 2006
First published as an Advance Article on the web 28th November 2006
DOI: 10.1039/b614512d

A variety of *trans*-β-substituted cyclic alcohols were stereoselectively chlorinated to either the corresponding *cis*-chloride or *trans*-chloride (inversion or retention of configuration) with good to excellent yields; the stereochemical outcome is determined by the size of the ring and the nature of the β-substituents, especially the electronegativity of the substituted atom.

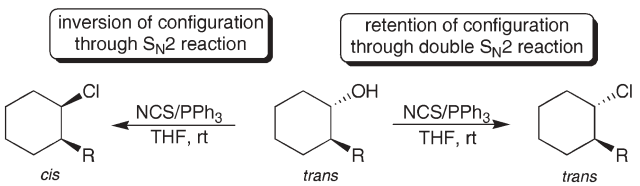
The halogenation of alcohols into alkyl halides is a ubiquitous transformation in organic chemistry and numerous halogenating agents are available to affect this key step. The conventional method for the preparation of alkyl halides is by reacting readily available alcohols with halogenating agents such as hydrohalic acid,[1] $SOCl_2$,[2] PX_3,[3] PX_5[4] and POX_3.[5] However, these reagents are corrosive, highly toxic, often result in very poor yields and usually are intolerable for several acid-sensitive functional groups due to the very strong acidic conditions. *N*-Halosuccinimide–PPh_3 being a mild halogenating agent can be used as an alternative (modified Mitsunobu reaction), which provides inversion of configuration through a S_N2 reaction.[6]

In recent years, chlorination through modified Mitsunobu conditions has become very attractive as we discovered the chiral version of this reaction by using chiral phosphine (BINAP) and *N*-chlorosuccinimide (NCS) to produce highly enantiomerically enriched alkyl chlorides and alcohols through non-enzymatic kinetic resolution.[7] Our continuous interest in this field has led us to the finding that the stereochemical outcome of this reaction can be stereoselectively controlled (retention or inversion of configuration) by having an appropriate substituent at the β-position of the alcohol.

In general, chlorination of alcohol is a S_N1 reaction (mixture of inversion and retention of configurations) or S_N2 reaction (inversion of configuration) depending on the halogenating agent. Although neighbouring group participation (NGP) has been extensively studied in the literature,[8] the effect of NGP on stereoselective halogenation of cyclic alcohols is not well established.[9] For the first time, we report that the stereochemical outcome of halogenation using PPh_3–NCS can be stereoselectively controlled to give either inversion of configuration (through S_N2 reaction) or retention of configuration (through double S_N2 reaction) by having an appropriate substituent (heteroatom with lone pair of electrons) at the β-position of the alcohol (Scheme 1). We also report that the neighbouring group participation ability of the β-substituted heteroatom can be controlled using appropriate electron withdrawing groups or electron releasing groups.

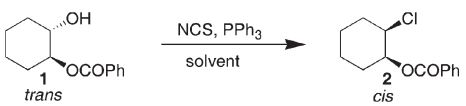
First, we have chosen racemic-*trans*-2-hydroxycyclohexyl benzoate **1**, as a model substrate, which was subjected to chlorination with NCS (1 equiv.) and PPh_3 (1 equiv.) in THF at room temperature. Surprisingly, *trans*-2-hydroxycyclohexyl benzoate **1** gave *cis*-2-chlorocyclohexyl benzoate **2** with 23% yield (Table 1; entry 1). The *cis* stereochemistry of the chloride was deduced from the coupling constant of the methine proton (dt, J = 8.8, 2.8, and 2.8 Hz) at 5.16 ppm (–C*H*–OCO–Ph) in the ^{1}H NMR spectrum.

We optimized the reaction conditions using a variety of solvents, varying the ratio of NCS/PPh_3 and the temperature to improve the yield and the results are summarized in Table 1. Use of 1.5 equivalents of PPh_3 with 2 equivalents of NCS in dry THF at room temperature turned out to be the best conditions that



Scheme 1 Chlorination of β-substituted cyclohexanol.

Table 1 Optimizing the halogenation of (±)-*trans*-2-hydroxycyclohexyl benzoate **1**



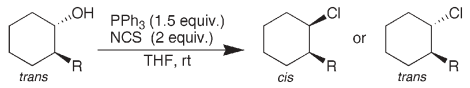
Entry	PPh_3	NCS	Solvent	Temp.	Time	Yield[a] (%)
1	1 equiv.	1 equiv.	THF	rt	1 h	23
2	1 equiv.	1.5 equiv.	THF	rt	10 min	39
3	1 equiv.	2 equiv.	THF	rt	10 min	47
4	1.5 equiv.	2 equiv.	THF	rt	2 h	86
5	1.5 equiv.	2 equiv.	Diethyl ether	rt	1 h	30
6	1.5 equiv.	2 equiv.	Hexane	rt	24 h	00
7	1.5 equiv.	2 equiv.	Benzene	rt	7 h	82
8	1.5 equiv.	2 equiv.	Toluene	rt	7 h	76
9	1.5 equiv.	2 equiv.	CH_2Cl_2	rt	10 min	68
10	1.5 equiv.	2 equiv.	$CHCl_3$	rt	1 h	59
11	1.5 equiv.	2 equiv.	CH_3CN	rt	10 min	55
12	1.5 equiv.	2 equiv.	EtOAc	rt	1 h	15
13	1.5 equiv.	2 equiv.	Acetone	rt	10 min	51

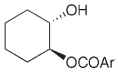
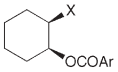
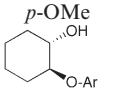
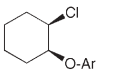
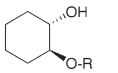
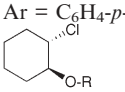
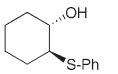
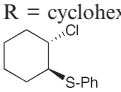
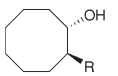
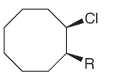
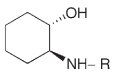
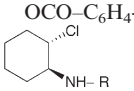
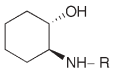
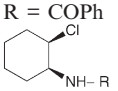
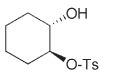
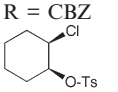
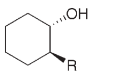
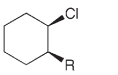
[a] Isolated yield

Department of Chemistry, Indian Institute of Technology Madras, Chennai, Tamil Nadu, 600 036, India. E-mail: gsekar@iitm.ac.in; Fax: +91 44 2257 4202; Tel: +91 44 2257 4229

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra for *cis*- and *trans*-chlorides; X-ray crystal structures and data. See DOI: 10.1039/b614512d

Table 2 Stereoselective halogenation of β-substituted cyclohexanols



Entry	Alcohol	Halide	Time	Yield[a] (%)
				
1	Ar = Ph	X = Cl	2 h	86
2	Ar = Ph	X = Br	2 h	60[b]
3	Ar = Ph	X = I	20 h	08[c]
4	Ar = $-C_6H_4$-*p*-Cl	X = Cl	10 min	51
5	Ar = $-C_6H_4$-*p*-OMe	X = Cl	1 h	75
6	Ar = $-C_6H_4$-*o*-Br	X = Cl	10 min	62
7	Ar = $-C_6H_3$-*m*,*p*-$(OMe)_2$	X = Cl	10 min	52
8	Ar = $-C_6H_3$-*o*-OH, *p*-OMe	X = Cl	30 min	65
				
9		Ar = Ph	10 min	61
10		Ar = C_6H_4-*p*-OMe	1 h	55
11		Ar = C_6H_4-*p*-Ph	10 min	50
				
12		R = H	10 min	40[d]
13		R = cyclohexyloxy	10 min	55
				
14			10 min	55[e]
				
15		R = OH	10 min	53
16		R = $OCO-C_6H_4$-*p*-NO_2	10 min	85
				
17		R = Ph	10 min	30[f]
18		R = C_6H_4-*p*-NO_2	10 min	40[g]
19		R = COPh	10 min	35[h]
				
20		R = Ts	10 min	65
21		R = CBZ	10 min	79
				
22			10 min	35[i]
				
23		R = Ph	10 min	75
24		R = C_6H_4–OMe	10 min	60
25		R = *n*-hexyl	10 min	37[j]

[a] Isolated yields, reasonable quantities of unreacted starting material was recovered wherever the reaction provided low yield for the chloride.[13] [b] NBS–PPh_3 as halogenating reagent. [c] NIS–PPh_3 as halogenating reagent and 70% unreacted alcohol was recovered. [d] 35% unreacted alcohol and 15% cyclohexene oxide were recovered. [e] Around 50% of the chloride (β-sulfide) was oxidized to the corresponding β-sulfoxide while doing column chromatography purification. [f] 32% unreacted alcohol was recovered. [g] An equivalent amount of unknown compound was also isolated along with the product. [h] 55% unreacted alcohol was recovered. [i] 25% unreacted alcohol was recovered. [j] 50% unreacted alcohol was recovered.

provided the highest yield (86%) of the product *cis*-chloride **2** (Table 1; entry 4).‡

Under the optimized reaction conditions, we performed halogenations of several β-substituted cyclohexanols and the results are summarized in Table 2. The reaction is highly stereoselective as the reaction provides exclusively either the *cis*-chloride or the *trans*-chloride.[10] The inversion of stereochemistry took place when the β-substituent is aryloxy (–OAr), ester (–OCOAr), tosyloxy (–OTs), alkyl, aryl, NH–CBZ, and toluenesulfonamido (–NH-Ts) groups, whereas retention of configuration was observed when the β-substituent is hydroxy (–OH), alkyloxy (–OR), amino (–NH–Ar), amido (–NHCOPh), and phenylthio groups (–SPh). The ring size of the cyclic alcohols also have a significant effect in determining the stereochemical outcome of the product (six-membered *vs*. eight-membered ring).

2-Aryloxy cyclohexanols provided *cis*-chloride through inversion of configuration (entries 9–11), whereas 2-(phenylthio)cyclohexanol (entry 14) provided *trans*-chloride through a three membered thiiranium ion intermediate (double S_N2 reaction: retention of configuration). We inferred that this might be because of the higher electronegativity of oxygen atom which prevents its lone pair of electrons from neighbouring group participation.[11] An attempt to increase the electron density on the oxygen atom of the phenoxy group by having electron releasing methoxy groups on the phenyl ring did not provide retention of configuration for product chloride (entry 10). Surprisingly, when the aryl group of the aryloxy was replaced by hydrogen (*trans*-dihydroxy cyclohexane) or alkyl groups (entries 12 and 13), the β-substituted oxygen atom participates in NGP and provides the *trans*-chloride through a double S_N2 reaction.

As expected, *trans*-2-phenylaminocyclohexanol produced *trans*-2-phenylaminocyclohexyl chloride. This is due to the formation of the three-membered aziridinium ion intermediate by the lone pair of electrons on the low electronegative nitrogen atom. We could not stop the NGP by substituting the highly electron withdrawing nitro group at the *para* position of the phenyl group or by

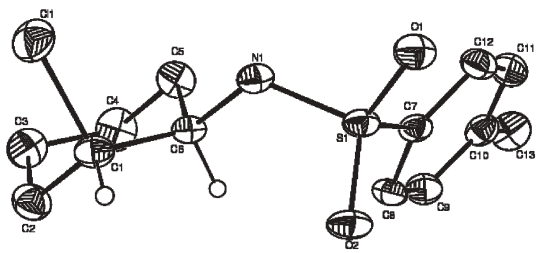


Fig. 1 X-Ray crystal structure of *cis*-*N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (CCDC 621755). 30% Probability.

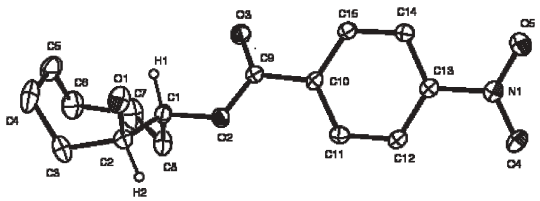
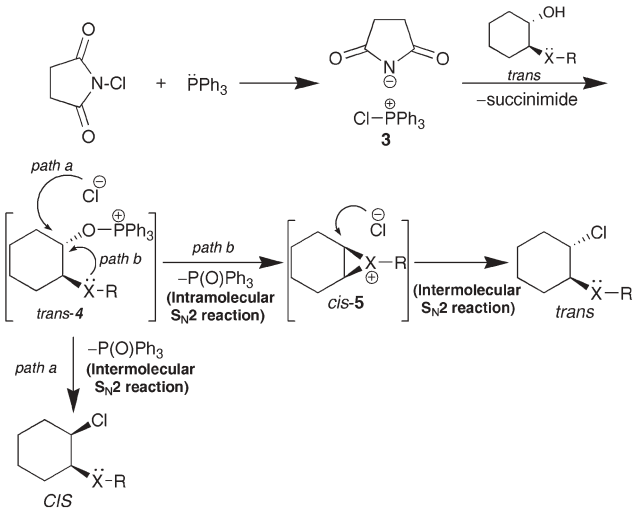


Fig. 2 X-Ray crystal structure of *trans*-2-hydroxycyclooctyl-4-nitrobenzoate (CCDC 621756). 30% Probability.

This journal is © The Royal Society of Chemistry 2007



Scheme 2 Possible mechanism for the formation of *cis*- and *trans*-chloride.

replacing the arylamino group by an electron withdrawing amide group (entries 17–19). Interestingly, we were able to prevent the NGP ability of the nitrogen atom by replacing the aryl moiety of the arylamino group by electron withdrawing groups such as CBZ and tosyl groups (entries 20 and 21). The *cis* stereochemistry of the product was confirmed by X-ray crystal structure analysis (Fig. 1).§

When the β-substituent is a phenyl group, it produced *cis*-chloride through a S_N2 reaction. In this case, the π-electrons of the phenyl ring did not take part in NGP. Increasing the π-electron density of the phenyl ring by keeping an electron releasing methoxy group at the *para* position did not make the π-electrons participate in NGP to provide *trans*-chloride (entries 23 and 24).

The *trans*-dihydroxycyclohexane yielded *trans*-chlorohydrine whereas *trans*-dihydroxycyclooctane produced *cis*-chloride (entries 12 *vs*. 15). This may be because the *trans* disubstituted cyclohexane exists in a chair conformation and the dihedral angle between the two diaxial substituents is nearly 180°.[12] *trans* Disubstituted cyclooctane, exists in a boat–chair conformation and the dihedral angle between the two diaxial substituents is not close to 180°. This phenomena was confirmed from the XRD analysis of *trans*-1,2-disubstituted cyclooctane (*trans*-2-hydroxycyclooctyl-4-nitrobenzoate). The disubstituted cyclooctane has a boat–chair conformation and the dihedral angle between the two vicinal hydrogens (diaxial) is 167° (Fig. 2).§ These data clearly show that the β-substituent should be exactly or nearly 180° (*anti*) to the hydroxy group (*trans*; in the di-axial conformer) to have effective NGP.

We assumed that the stereoselective chlorination takes place as shown in Scheme 2. However, very detailed mechanistic studies, complete analysis of the factors that control the stereoselectivity, kinetic study and the chiral version of this chlorination using chiral phosphines or chiral halogenating agents are in progress.

In conclusion, the stereochemical outcome of the product chloride is completely determined by the nature of the β-substituents and the ring size of the cyclic alcohols. All the β-substituents with lone pairs of electrons or π-electrons do not provide retention of configuration. Importantly, the NGP ability of the β-substituted heteroatom can be controlled using appropriate electron withdrawing groups or electron releasing groups.

We thank DST, CSIR, New Delhi for financial support. We also thank Dr Babu Varghese and Mr V. Ramkumar for solving the crystal structures.

Notes and references

‡ Typical experimental procedure: To a stirred mixture of *trans*-2-hydroxycyclohexyl benzoate **1** (220 mg, 1 mmol), NCS (267 mg, 2 mmol) and triphenylphosphine (394 mg, 1.5 mmol) was added dry THF (3 mL) at room temperature. A change from white turbidity to a colorless homogenous solution showed the completion of the reaction (2 h). The THF was removed by rotary evaporation and the resulting residue was purified by silica gel column chromatography (hexane–ethyl acetate) to provide pure *cis*-2-chlorocyclohexyl benzoate **2** as a colorless liquid (205 mg, 86% yield). *Rf* = 0.67 (15% ethyl acetate in hexane); IR (neat) 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34–1.49 (m, 2H), 1.60–1.81 (m, 3H), 1.85–1.94 (m, 1H), 1.95–2.12 (m, 2H), 4.35 (m, 1H, >C*H*–Cl), 5.16 (dt, J = 8.8, 2.8, 2.8 Hz, 1H, >C*H*–OCO–Ph), 7.39 (t, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 8.02 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.0, 26.4, 31.2, 59.5, 67.4, 127.2, 128.5, 131.9, 164.6; MS (*m*/*z*): 239.1 (M^+); HRMS for calcd mass: 239.0839 (M^+); Found: 239.0884.

§ Crystallographic data: for $C_{13}H_{18}ClNO_2S$, M = 287.79, triclinic, a = 6.7769(4), b = 9.7641(8), c = 11.4462(8) Å, α = 76.916(5), β = 80.416(4), γ = 74.897(4)°, V = 707.58(9) $Å^3$, T = 273(2) K, space group $P\bar{1}$, Z = 2, μ = 0.411 mm^{-1}, R_{int} = 0.0280 (for 4438 measured reflections), $R1$ = 0.0626 [for 1996 unique reflections with $I > 2\sigma(I)$], $wR2$ = 0.1733 (for all 2382 unique reflections). For $C_{15}H_{19}N_1O_5$, M = 293.31, triclinic, a = 7.2564(6), b = 7.4017(5), c = 15.5988(13) Å, α = 88.923(5), β = 85.403(5), γ = 62.334(4)°, V = 739.47(10) $Å^3$, T = 293(2) K, space group $P\bar{1}$, Z = 2, μ = 0.099 mm^{-1}, R_{int} = 0.0237 (for 9003 measured reflections), $R1$ = 0.0826 [for 2033 unique reflections with $I > 2\sigma(I)$], $wR2$ = 0.2637 (for all 2530 unique reflections), CCDC 621755 and 621756. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614512d

1 (*a*) J. B. Conant and O. R. Quayle, *Org. Synth.*, 1932, **Coll. Vol. 1**, 292; (*b*) J. F. Norris and A. W. Olmsted, *Org. Synth.*, 1941, **Coll. Vol. 1**, 144.
2 F. F. Caserio, G. E. Dennis, R. H. Dewolfe and W. G. Young, *J. Am. Chem. Soc.*, 1955, **77**, 4182.
3 A. G. Anderson, Jr., N. E. T. Owen, F. J. Freenor and D. Erickson, *Synthesis*, 1976, 398.
4 C. W. Shoppee, *J. Chem. Soc.*, 1946, 1138.
5 R. S. Tipson, *J. Org. Chem.*, 1962, **27**, 1449.
6 (*a*) S. Hanessian, M. M. Ponpipom and P. Lavallee, *Carbohydr. Res.*, 1972, **24**, 45; (*b*) A. K. Bose and B. La1, *Tetrahedron Lett.*, 1973, 3937; (*c*) A. K. Bose, B. Lal, W. A. Hoffman, III and M. S. Manhas, *Tetrahedron Lett.*, 1973, 1619.
7 (*a*) G. Sekar and H. Nishiyama, *J. Am. Chem. Soc.*, 2001, **123**, 3603; (*b*) G. Sekar and H. Nishiyama, *Chem. Commun.*, 2001, 1314.
8 J. March, *Advanced Organic Chemistry; Reaction, Mechanisms and Structure*, John Wiley & Sons, New York, 4th edn., 1992.
9 For a similar type of selective chlorination of alcohols, see: (*a*) R. Boschan and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 4921; (*b*) C. N. Barry and S. A. Evans, Jr., *J. Org. Chem.*, 1983, **48**, 2825.
10 The stereochemistry of the product chlorides was determined by the coupling pattern of the methine protons in the ^1H NMR spectra. All the *cis*-chlorides have a doublet of triplets (dt) pattern due to one *trans* coupling and two *cis* couplings. Whereas the *trans*-chlorides gave a triplet of doublets (td) coupling pattern due to two *trans* couplings and one *cis* coupling (see ESI† for ^1H NMR spectra of selected compounds).
11 Pauling scale for the electronegativity of O, N, and S: O (3.5) > N (3.0) > S (2.58). In other words, we can explain this NGP ability by the nucleophilicity of the β-substituted atoms. The nucleophilicity of O, N, and S: S > N > O.
12 The XRD analysis of *trans*-2-(4-nitrophenylamino)cyclohexanol shows that the compound exits in a chair conformation and the dihedral angle between the diaxial hydrogens is 177°. See ESI† for X-ray structure and crystal data.
13 Allowing these reactions to continue for longer times or using excess halogenating agents did not help to improve the yield.