Tetrahedron: Asymmetry Vol. 3, No. 6, pp. 749-752, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

A Useful Synthesis of Chiral Sulfonyl Cyanides: *(1S,2S,5R)*-2-Isopropyl-5-methylcyclohexanesulfonyl Cyanide

José M. Blanco, Olga Caamaño, Franco Fernández*, Generosa Gómez and Carmen López

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago, 15706-Santiago de Compostela, Spain.

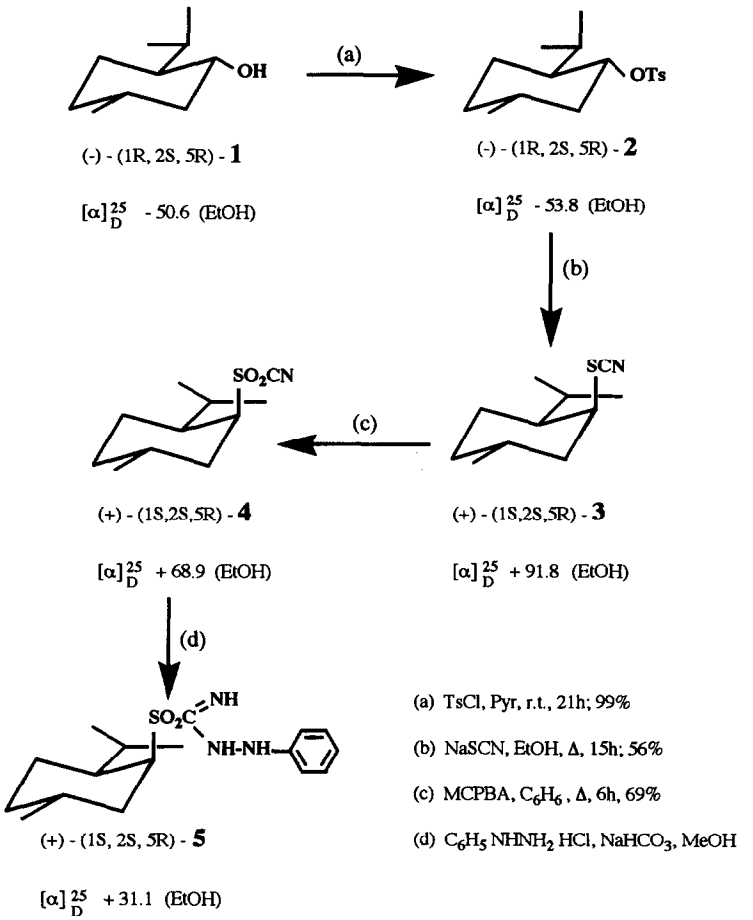
(*Received* 29 *April* 1992)

Abstract: A convenient method for the preparation of chiral alkanesulfonyl cyanides, by oxidation of readily available alkyl thiocyanates with *m*-$ClC_6H_4CO_3H$, has been developed.

Sulfonyl cyanides are highly reactive nitriles used for the preparation of a variety of aromatic[1] and aliphatic[2] heterocycles, for stereospecific synthesis of 2-alkenenitriles[3] and for α-cyanation of ketone enolates.[4] Except in the case of the aromatic target molecules, enantioselectivity can be pursued by the use of chiral sulfonyl cyanides; for example, reaction of (*1S*)-10-camphorsulfonyl cyanide with cyclopentadiene leads to the preferential obtention of one of the enantiomers of 2-azabicyclo[2.2.1]hept-5-en-3-one.[5] Our desire to use chiral sulfonyl cyanides has led to our developing a very general method for the preparation of chiral sulfinic acids from alcohols,[6] the commonest route to sulfonyl cyanides being reaction of cyanogen chloride with the appropiate sodium sulfinate.[7] However, our approach failed to afford *(1S,2S,5R)*-2-isopropyl-5-methylcyclohexanesulfinic acid from (-)-menthol. We describe here an alternative route from alcohols to chiral sulfonyl cyanides that is satisfactorily simple and efficient and is applicable to substrates prone to structural and/or stereochemical alteration; its key step is the oxidation of readily available alkyl thiocyanates. As a typical example we describe the synthesis of *(1S,2S,5R)*-2-isopropyl-5-methylcyclohexanesulfonyl cyanide (see Scheme).

Neomenthyl thiocyanate (**3**) was prepared from (-)-menthol (**1**) *via* (-)-menthyl tosylate (**2**), which was obtained from **1** in virtually quantitative yield and subjected to nuceophilic atack by sodium thiocyanate in ethanol; column chromatography of the crude product gave a yield of 56% that compares favourably with those afforded by reaction of the same substrate with other sulfur nucleophiles.[8] ^1H n.m.r. spectroscopy confirmed that an S_N2 reaction had stereospecifically led to the configuration shown for **3**, as well as the high diastereomeric purity of the product: the *axial* 1-H of **2** appears as a triplet of doublets at δ 4.40 ppm with coupling constants of 10.3 Hz ($J_{ax,ax}$) and 4.4 Hz ($J_{ax,eq}$) respectively, whereas the *equatorial* 1-H of **3** appears at δ 4.02 ppm as an unresolved multiplet with $w_{1/2}$ *ca.* 8.1 Hz.

H_2O_2, $NaIO_4$, $KMnO_4$ and fuming HNO_3 , wich usually oxidize sulfides to sulfones, failed to convert **3** to **4**, most of the starting material being recovered unaltered. However, *m*-chloroperoxybenzoic acid



SCHEME

(MCPBA), which has been reported to oxidize *p*-tolyl thiocyanate to tosyl cyanide (79% yield) but ethyl thiocyanate to ethanesulfonyl cyanide with a yield of only 6%,[9] oxidized **3** and other secondary cycloalkyl thiocyanates in satisfactory yields when the reaction was carried out in boiling anhydrous benzene (80°C) using an MCPBA/thiocyanate mole ratio of 6-7. In the case of **3**, the reaction was best monitored by g.l.c. and halted when the ratio **4**:**3** reached *ca.* 19 (typically 5-6 h). Crude yields similar to those generally accomplished by the standard method[7] were achieved when excess MCPBA and the co-product *m*-chlorobenzoic acid were *rapidly removed in the cold* to prevent the decomposition of the desired product (sulfonyl cyanides are readily decomposed even by nucleophiles as weak as water).[10]

The crude product included 4-6 % of **3** (g.l.c., ^{1}H n.m.r.). Attempts of purifying **4** by flash column chromatography failed, even when anhydrous toluene was used as eluent, extensive decomposition of **4** leading to useless mixtures. Though **4** can be vacuum distilled, since **3** is considerably less reactive than **4**, for most purposes it may be more convenient to use the crude product and purify at a later stage.

The configuration and diastereomeric purity of **4** were confirmed by its ^{1}H n.m.r. spectrum: 1-H appeared at δ 3.85 ppm as an unresolved multiplet ($w_{1/2}$ *ca.* 9.8 Hz), and there was no other signal in the region δ 3.00-4.50 ppm (except for the multiplet at δ 4.02 ppm for crude samples containing **3**). We further confirmed the structure of **4** by treating it with phenylhydrazine[1b] to obtain crystalline *C*-neomenthanesulfonyl-*N*^{1}-phenylformamidrazone (**5**), which was duly characterized.

Experimental part

Silica gel (230 mesh) was purchased from Merck. Other reagents and solvents were of commercial quality, purchased from Aldrich Chemical Co. Melting points were determined on a Kofler Thermopan Reichert apparatus and are uncorrected. Observed rotations at the Na-D line were obtained at 25°C using a Zeiss Winkel polarimeter. Microanalyses were performed with a Perkin-Elmer 240B element analyser by the Microanalysis Service, University of Santiago, for analytical samples and were all within $\pm$0.3 % of the calculated values. I.r. spectra were recorded on a Perkin-Elmer 681 spectrometer and ^{1}H n.m.r. spectra on a Bruker WN 250 (250 MHz) spectrometer. G.l.c. was carried out on a Hewlett Packard 5710A instrument equipped with an FID and an HP-3380S integrator: column, 10 % OV-210 on Chromosorb W-HP (2 m x 1/8 ") at 170°C; carrier gas, N_2 , 20 mL/min; ratio of retention times, **4/3** = 1.16.

(*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl *p*-toluenesulfonate (2). *p*-Toluenesulfonyl chloride (62.34 g, 327 mmol) was added to a precooled (0°C) solution of **1** (30.0 g, 192 mmol) in dry pyridine (140 mL). The mixture was stirred for 21 h at r.t. and then poured into 3N HCl (300 mL). The white crystalline product was isolated by suction, washed with 3N HCl (50 mL) and H_2O (300 mL), and air dried. Yield: 58.9 g (99%). An analytical sample was readily obtained by recrystallization from 2-propanol; m.p. 96-97°C; $[\alpha]_D^{25}$ -53.8 (*c* = 1.1, EtOH). (Lit.[1] m.p. 92.5-93.5°C; $[\alpha]_D^{25}$ -69.5 (*c* = 2.99, $CHCl_3$)). IR (KBr): ν = 1598 (*arom* C=C), 1356 and 1177 (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$)/TMS): δ = 0.53 and 0.83 (two d, 6H, J = 6.9 Hz, -CH(C*H*$_3$)$_2$), 0.88 (d, 3H, J = 6.4 Hz, 5-CH_3), 0.90-1.24 (m, 3H), 1.32-1.41 (m, 2H), 1.62-1.68 (m, 2H), 1.89 (sept x d, 1H, J_{sept}= 6.9 Hz, J_d= 1.9 Hz,-C*H*(CH$_3$)$_2$), 2.10-2.18 (m, 1H), 2.44 (s, 3H, Ar-CH_3), 4.40 (t x d, 1H, J_t = 10.3 Hz, J_d = 4.4 Hz, 1-H), 7.32 (d, 2H, J = 8.1 Hz, *arom*-3,5-H), 7.80 (d, 2H, J = 8.1 Hz, *arom*-2,6-H).

(*1S,2S,5R*)-2-Isopropyl-5-methylcyclohexyl thiocyanate (3). A solution of **2** (24.83 g, 80 mmol) in dry EtOH (100 mL) was added to one of sodium thiocyanate (7.78 g, 96 mmol) in the same solvent (75 mL), and the stirred mixture was refluxed for 15 h under argon. The precipitated sodium tosylate was filtered out and thoroughly washed with CH_2Cl_2 (2 x 60 mL), the washings being added to the filtrate. The pooled liquids were washed with H_2O (2 x 100 mL) and dried (Na_2SO_4), and the solvents were removed at reduced pressure to leave a liquid residue (13.75 g), that was purified by column chromatography on silica gel (330 g; elution by 8:1 hexane-ethyl acetate, 18 x 300 mL; t.l.c. monitoring). Fractions 9-16 left pure **3** (99+ %, by g.l.c.). Yield: 8.84 g (56 %). $[\alpha]_D^{25}$ +91.8 (*c* = 1.08, EtOH). IR (film): ν = 2151 (C$\equiv$N) cm^{-1}. ^{1}H NMR ($CDCl_3$)/TMS): δ = 0.73-1.29 (m, 3H), 0.91 (d, 6H, J = 6.3 Hz, -CH(C*H*$_3$)$_2$), 0.98 (d, 3H, J = 6.4 Hz, 5-CH_3), 1.35-1.47 (m, 2H), 1.74-1.84 (m, 3H), 2.21 (d x q, 1H, J_d = 14.3 Hz (gem), J_q = 2.5 Hz, *eq*-H), 4.02 (m, 1H, $w_{1/2}$ = 8.1 Hz, 1*eq*-H).

(*1S,2S,5R*)-2-Isopropyl-5-methylcyclohexanesulfonyl cyanide (4). A solution of *m*-chloroperoxybenzoic acid (51.77 g, 300 mmol) in benzene (550 mL) was added to one of **3** (8.49 g, 43 mmol) in benzene (50 mL), the mixture was refluxed for 6 h under argon and then cooled to r. t., and the resulting precipitate was filtered off. The filtrate was quickly washed with *cold* 2M aq. $NaHSO_3$ (2 x 200 mL), *cold* 1M aq. $NaHCO_3$ (2 x 100 mL) and *cold* H_2O (3 x 100 mL) and dried (Na_2SO_4), and the solvent was removed at reduced pressure to leave the crude sulfonyl cyanide. Yield: 6.81 g (69 %). $[\alpha]_D^{25}$ +68.9 (*c* = 1.7, EtOH). IR (film): ν = 2184 (C≡N), 1365 and 1163 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$)/TMS): δ = 0.77-1.28 (m, 2H), 0.96 and 0.99 (two d, 6H, J = 6.5 Hz, -CH(CH_3)$_2$), 1.12 (d, 3H, J = 6.4 Hz, 5-CH_3), 1.41-2.14 (m, 6H), 2.58 (d x q, 1H, J_d = 14.4 Hz (gem), J_q = 2.6 Hz, *eq*-H), 3.85 (m, 1H, $w_{1/2}$ = 9.8 Hz, 1*eq*-H).

(*1S,2S,5R*)-*C*-(2-Isopropyl-5-methylcyclohexanesulfonyl)-*N*^{1}-phenylformamidrazone (5). $NaHCO_3$ (1.64 g, 19.5 mmol) was added over 1 h to a stirred solution of crude **4** (3.60 g, 15.7 mmol) and phenylhydrazine hydrochloride (2.52 g, 17.4 mmol) in MeOH (46 mL) at 0°C. After stirring for 1 h at 0-5°C, the reaction mixture was diluted with H_2O (150 mL) and stored overnight in the refrigerator. The precipitate was filtered off, washed with H_2O and dried, yielding a solid of m.p. 159-162°C. Yield: 1.20 g (23 %). An analytical sample of **5** was obtained by recrystallization from EtOH; m.p. 168-169°C, $[\alpha]_D^{25}$ +31.1 (*c* = 0.32, EtOH). IR (KBr): ν = 3433 (NH), 3346 (NH), 1654 (C=N), 1290 (SO_2), 1232, 1120 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6)/TMS): δ = 0.79 and 0.96 (two d, 6H, J = 6.4 Hz, -CH(CH_3)$_2$), 0.85-0.98 (m, 1H), 0.87 (d, 3H, J = 6.6 Hz, 5-CH_3), 1.25 (t x d, 1H, J_t = 13.4 Hz, J_d = 4.3 Hz), 1.35-1.45 (m, 1H), 1.66-1.85 (m, 3H), 1.99-2.14 (m, 3H), 3.94 (m, 1H, $w_{1/2}$ = 9.2 Hz, 1*eq*-H), 6.39 (broad s, 2H, -NH-NH-), 6.71 (virtual t, 1H, J_t = 7.4 Hz, *arom*-4-H), 6.93 (virtual d, 2H, J_d = 8.4 Hz, *arom*-2,6-H), 7.18 (virtual d x d, 2H, J_d = 8.4 Hz, J_d = 7.4 Hz, *arom*-3,5-H), 8.64 (virtual s, 1H, C=NH).

References

1. *a*) U. Treuner, *Synthesis*, **1972**, 559; *b*) J. C. Jagt and A. M. van Leusen, *Recl. Trav. Chim. Pays-Bas*, **1975**, *94*, 12; *c*) A. M. van Leusen and J. C. Jagt, *Tetrahedron Lett.*, **1970**, 971.
2. *a*) Dihydropyridines: J. C. Jagt and A. M. van Leusen, *Recl. Trav. Chim. Pays-Bas*, **1973**, *92*, 1343; *b*) 2-Azabicyclo[2.2.n]alkenes: J. C. Jagt and A. M. van Leusen, *J. Org. Chem.*, **1974**, *39*, 564.
3. H. Westmijze and P. Vermeer, *Synthesis*, **1977**, 784.
4. D. Kahne and D. B. Collum, *Tetrahedron Lett.*, **1981**, *22*, 5011.
5. O. Caamaño, A. Eirín, F. Fernández, G. Gómez and E. Uriarte, *Heterocycles*, **1988**, *27*, 2839.
6. J. M. Blanco, O. Caamaño, A. Eirín, F. Fernández, and L. Medina, *Synthesis*, **1990**, 584.
7. S. Daluge and R. Vince, *J. Org. Chem.*, **1978**, *43*, 2311.
8. M. Mikolajczyk, W. Perlikowska and J. Omelanczuk, *Synthesis*, **1987**, 1009.
9. R. G. Pews and F. P. Corson, *J. C. S. Chem. Commun.*, **1969**, 1187. Oxidation of thiocyanates to sulfinyl cyanides by MCPBA is reported in: A. Boerma-Markerink, J. C. Jagt, H. Meyer, J. Wildeman and A. M. van Leusen, *Synth. Commun.*, **1975**, *5*, 147.
10. A. M. van Leusen and J. C. Jagt, *Tetrahedron Lett.*, **1970**, 967.