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CHIRAL SULFONYLMETHYL ISOCYANIDES. SYNTHESIS AND ASYMMETRIC INDUCTION[1]

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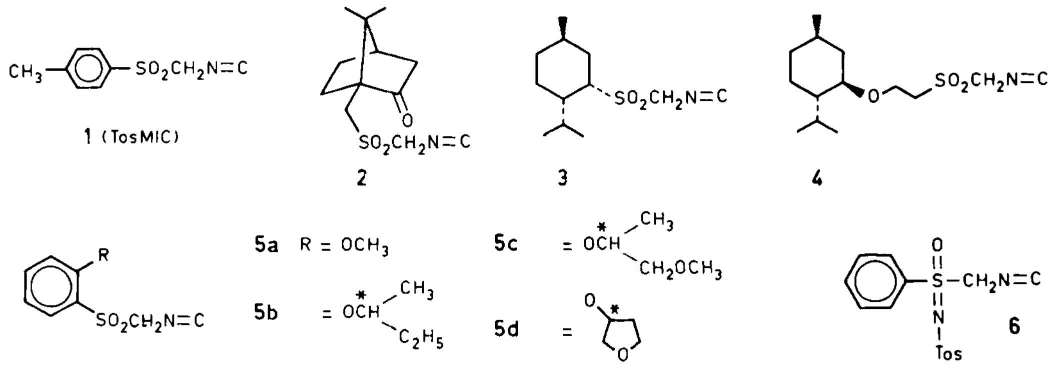
We are engaged in the synthesis and application of chiral derivatives of methyl isocyanides. Chart 1 depicts 7 chiral analogues (2 - 6) of tosylmethyl isocyanide (TosMIC, 1)[2] presently under investigation. This prelim gives a brief outline of the synthesis of 5d and 6 (vide infra), and a comparison of asymmetric inductions achieved with 3 - 6.

Asymmetric inductions were determined by reaction of 3 - 6 with trifluoroacetophenone (and with acetophenone) according to Eq. 1. Base-mediated cycloaddition of isocyanide 3[3] to trifluoroacetophenone gave in 96% yield a mixture of diastereomeric oxazolines 7 (R = neomenthyl, X = O, Table, entry 2). Asymmetric induction determines the configuration at C(5) in 7 and, after acid hydrolysis,[4] the configuration of hydroxy aldehyde 8. Thus, the e.e. (or o.p.)[5] of 8 is a measure of the asymmetric induction exerted by 3. The d.e. of 7, which is easily determined by ^{1}H NMR (using the C(4)H signal) and by ^{19}F NMR, also is a reflection of the asymmetric induction power of 3. Unlike the e.e. of 8, the value of the d.e. of 7 is independent of the e.e. of 3.[‡] For example, the asymmetric induction obtained with 3, 18% as determined from the d.e. of 7, is reduced to an e.e. of 16% for 8, due to the use of 3 of 90% e.e. (entry 2).[6] A somewhat higher asymmetric induction of 39% was obtained with isocyanide 5d, which carries potential chelating ether functions (entry 6). The best result, an asymmetric induction of 80% (80% d.e. of 7, entry 7), was obtained with sulfonimidoylmethyl isocyanide 6 which, unlike isocyanides 2 - 5, carries its chiral center next to the reactive methylene.

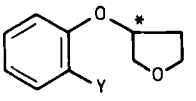
Absolute configuration and o.p. of 8 were determined by chemical correlation with Mosher's acid[7] 9 (Eq. 1).

(R)-(-)-[o-(3-Tetrahydrofuranyloxy)phenylsulfonyl]-methyl isocyanide (5d, a crystalline solid, stable at room temperature) was prepared in 6 steps and

Chart 1



[‡] Note added in proof: Changes in the e.e. of 3 only change the ratio of enantiomers of 7, which is not reflected in NMR.



11 Y = Br

12 = SH

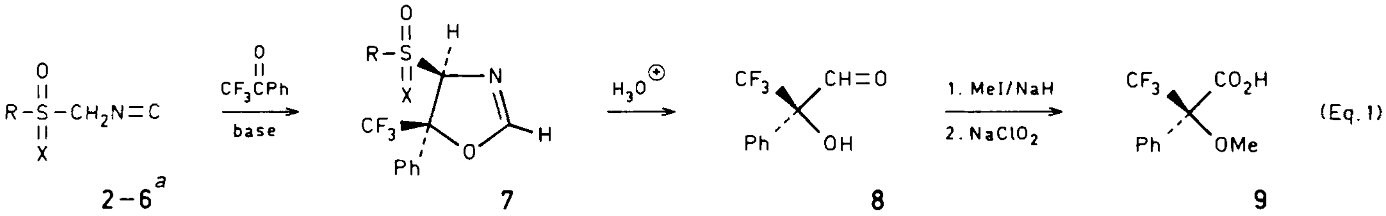
13 Y = SCH_2NHCHO

14 = SO_2CH_2NHCHO

5d = $SO_2CH_2N{=}C$

35% overall yield from optically pure (S)-(+)-3-hydroxytetrahydrofuran[8] (10) as follows: (1) o-bromophenol and 10-tosylate [mp 34.5-35.5°C, 80% from 10] heated at 100°C (0.5 h) with powdered KOH gave 11 [69%, bp 115-7°C (0.15 mmHg), $[\alpha]_D^{20}$ -35.8° ($CHCl_3$)] with inversion and 50% racemisation; (2) 11 with BuLi and freshly sublimed sulfur in Et_2O (-78 to 15°C, 3 h) gave 12 [73%, bp 105-108°C (0.2 mmHg), $[\alpha]_D^{22}$ -30.6° ($CHCl_3$)]; (3) 12 with N-(tosylmethyl)formamide[9] and t-BuOK analogously to a published procedure[3] gave 13 (80%) which was oxidized (mCPBA, 5 h, 20°C) to 14 (75%, mp 107.5-110°C, $[\alpha]_D^{22}$ -28.8° ($CHCl_3$)]; (4) 14 was dehydrated with $POCl_3$ and i-Pr_2NH according to the method of Ugi[10] to 5d [66%, mp 107.4-108.2°C, $[\alpha]_D^{20}$ -40.8° ($CHCl_3$), e.e. 47%]. (-)-S-Phenyl-N-tosylsulfonimidoylmethyl isocyanide (6) was prepared from partially resolved S-phenyl-N-tosylsulfonimidoyl fluoride,[11] methyl isocyanide and 2.1 equiv. of BuLi in THF (-70°C, 1.0 h) in 35% yield, $[\alpha]_D^{21}$ -2.2° ($CHCl_3$), e.e. 34%.

TABLE. Reactions of Isocyanides 3 - 6 with Acetophenones to Oxazolines 7 and Hydroxy Aldehydes 8



Entry		Isocyanides 2 - 6			Oxazolines 7[b]			(R)-(+)-8	
		mp(°C)[c]	c.y.(%)[d]	e.e.(%)	c.y.(%)[e]	d.e.[f]	cond.[g]	c.y.(%)[h]	e.e.(%)[i]
1	2	oil	28[j]	>98[k]	-				
2	3	67.7-68.4	39[l]	90[m]	96	18	A (B)	60	16
3	4	oil	12[n]	>98[k]	[74	33	C	47	31][o]
4	5b	oil	13[p]	50[q]	[76	40	D	50	15][o]
5	5c	oil	29[r]	rac.	[57	33	D][o]		
6	5d	107.4-108.2	35	47[s]	98	39	A (B)	43	18
7	6	93-96(d)	35	34[s]	91	83	B (A)	58	27

(a) For R and X, see Chart 1. (b) See footnote 6. (c) Oils are of limited stability at 20°C. (d) Overall chemical yields. (e) Chemical yields of crude 7, which were hydrolyzed as such to 8. (f) Determined by ^1H NMR [C(4)H doublets between δ 4.5-6.5] and by ^{19}F NMR. (g) Reaction conditions: A = $Ti(OEt)_4$, N-Etpiperidine, CH_2Cl_2, 0°C; B = Triton B, THF, 20°C; C = PTC (NaOH-benzene), TEBACl, 20°C; D = BuLi, THF, -78°C; conditions between brackets gave similar results. (h) Calculated on 7. (i) Determined through 9, ref. 5 and 7. (j) In 4 steps from (+)-10-camphorsulfonic acid. (k) According to ^{13}C NMR. (l) In 6 steps from (-)-menthol, ref. 3. (m) Determined via neomenthylthiol, ref. 3, and $MeP(O)Cl_2$, ref. 12. (n) In 5 steps from (-)-menthol. (o) The data between brackets refer to reactions with acetophenone, CH_3 instead of CF_3 in Eq.1; also footnote 6. (p) In 5 steps from (R)-(+)-2-butanol. (q) Determined with $Eu(dcm)_3$. (r) In 5 steps from rac-1-methoxy-2-propanol. (s) Calculated from d.e. of 7 and e.e. of 8.

References and Notes

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4. See ref. 2a.
5. Throughout this paper, e.e. and o.p. are assumed to be equal.
6. Further examples carried out with acetophenone, instead of trifluoroacetophenone, will be treated in a full paper.
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