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A SIMPLE METHOD FOR TOSYLATION WITH INVERSION.

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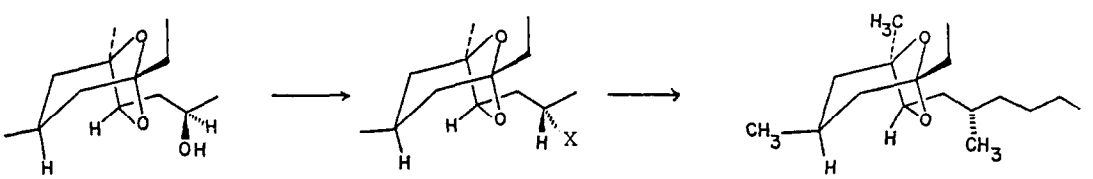
SUMMARY. In this paper we describe a simple one-step procedure for tosylation with inversion, using zinc tosylate, diethylazodicarboxylate and triphenylphosphine.

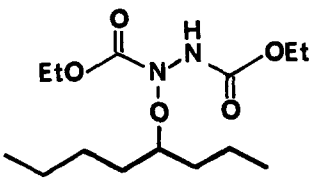
In a previous paper (1) we reported a stereospecific conversion of 1 to 3. In our hands all attempts to accomplish this transformation via corresponding halides (2a X = Br; 2b X = I) failed (2), leading to elimination products and very low yields of 3 as a mixture of stereoisomers (3). On the other hand the tosylate 2c (X = OTs) upon treatment with Bu_2CuLi produced 3 stereospecifically and in acceptable yield (47%). The desired tosylation with inversion of configuration can be achieved in three steps using Mitsunobu inversion (4) with diethylazodicarboxylate - triphenylphosphine (DEAD-Ph_3P) and benzoic acid, subsequent hydrolysis of the benzoate and conventional tosylation with p-toluenesulfonylchloride in pyridine. However, since this procedure is somewhat lengthy and requires base treatment, we thought of applying Mitsunobu methodology directly to the tosylation reaction.



1 2 3

When dihydrocholesterol was treated with DEAD-Ph_3P in THF in the presence of p-toluenesulfonic acid, no reaction occurred. However, when the same reaction was repeated with lithium tosylate (5) as a nucleophile, a

single tosylate was produced in 75% yield. Under the same conditions 1 produced 2c in 52% yield, which was still higher than in the case of conventional three-step synthesis. Further investigation revealed that the reaction outcome is particularly sensitive to reaction conditions and tosylate counterion. For example 4-octanol, when treated with DEAD-Ph_3P and lithium tosylate in benzene, produced the tosylate in 78% yield. When potassium, tetraethylammonium and barium tosylates were used, compound 4 [^{1}H NMR: δ 0.871(6H, broad t); 1.237(3H, t); 1.255(3H, t); 1.33(10H, m); 4.18(4H, q); 6.07(1H, broad s)] was produced as a major product, while magnesium tosylate gave a 1 : 1 mixture of 3 and 4. When other substrates were treated with lithium tosylate under Mitsunobu conditions, it was found that formation of products of type 4 was a general problem and in many cases reduced yields drastically (see Table 1). It was also found that when lithium tosylate was dried rigorously over phosphorus pentoxide at 65° overnight and reacted with 4-octanol under usual conditions, 4 was produced as the sole product. This result is in accord with the proposed reaction mechanism (6) requiring protonation of a quaternary phosphonium salt 5.



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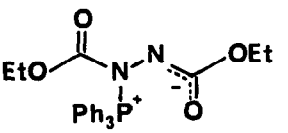


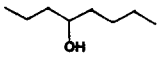
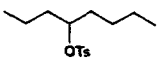
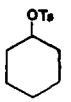
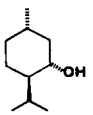
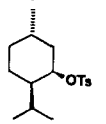
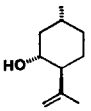
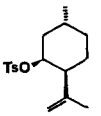
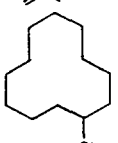
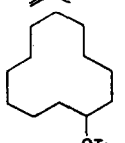
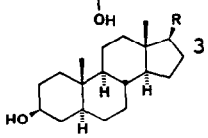
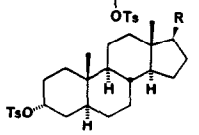
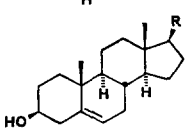
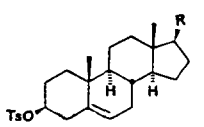
5

Since it seemed clear that a more covalent character of the metal-oxygen bond led to higher yields, zinc tosylate was prepared and investigated next. Indeed, it was found that a variety of secondary alcohols produced the desired tosylates with clean inversion (as judged by NMR) and in good yields (see Table 1).

The reaction seems to be general and is slower and milder than conventional Mitsunobu inversion with benzoic acid. It is noteworthy that although attempted inversion of 3β-hydroxyl of cholesterol produced four possible products of homoallylic rearrangement, in our case a single tosylate was formed in 85% yield. However, NMR data showed that the reaction proceeded with complete retention. This result can be rationalized by cyclopropane intermediate formation and its subsequent opening with the tosylate ion, both reactions proceeding with clean inversion.

The only limitation of this reaction seems to be its sensitivity to steric crowding at the reacting sp^3 center: each isomer of 2-t-butylcyclohexanol produced no detectable tosylate. Moderately hindered alcohols like menthol require prolonged reaction times, and sometimes one or

TABLE 1

Substrate	Reaction time(hrs)	Product	Isolated yield (%) TsOLi	Isolated yield (%) $(TsO)_2Zn$	^1H NMR(δ, $CDCl_3$)
	24		78* 10	84	2.45(3H,s);4.57(1H,m); 7.33(2H,d);7.80(2H,d);
	2		-	82	0.87(3H,t);1.25(3H,d); 1.60(1H,m);2.47(3H,s); 4.61(1H,m);7,30(2H,d); 7.78(2H,d);
	2		48	86	2.45(3H,s);4.90(1H,m); 7.32(2H,d);7.78(2H,d);
	2		15	80	2.44(3H,s);4.50(1H,m); 7.31(2H,d);7.78(2H,d);
	48		67	94#	2.45(3H,s);5.02(1H, broad s);7.31(2H,d); 7.78(2H,d);
	48		68	90##	0.84(3H,d);1.50(3H,s); 2.47(3H,s);4.69(2H,dd) 4.89(1H, broad s); 7.29(2H,d);7.75(2H,d);
	48		-	62##	2.43(3H,s);4.67(1H,m); 7.32(2H,d);7.80(2H,d);
	3		75	88	0.65(3H,s);0.73(3H,s); 0.88(6H,dd);0.91(3H,d) 2.45(3H,s);4.78(1H, broad s);7.32(2H,d); 7.81(2H,d)
	1		-	85	0.67(3H,s);0.88(6H,dd) 0.91(3H,d);0.98(3H,s); 2.46(3H,s);4.39(1H,m); 5.31(2H,m);7.34(2H,d); 7.82(2H,d)

* Dry LiOTs was used(see text).
\# Based on 72% conversion.
\## 1 extra equivalent of DEAD and Ph_3P was added after 36 hrs.

two extra equivalents of DEAD and Ph_3P must be added to drive the reaction to completion.

Typical experimental procedure.

Zinc tosylate. To a solution of 11.2 g (59 mmol) of p-toluenesulfonic acid monohydrate in 5 ml of water was added a solution of 4.0 g of zinc chloride (purchased from J.T. Baker) in 2 ml of water. The white precipitate (8.4 g) was filtered off, was dried in vacuo at room temperature for one hour and was stored in a stoppered flask.

3-α-tosyloxycholestane. To a solution of 39 mg (0.1 mmol) of dihydrocholesterol in 2 ml of benzene at room temperature were added 132 mg (0.5 mmol) of Ph_3P and 24 mg (0.06 mmol) of zinc tosylate. To the resulting suspension was added dropwise 80 μl (0.5 mmol) of DEAD. The resulting clear light-yellow solution was stirred at room temperature for 2 hours (8), loaded in benzene onto a chromatographic column and purified by flash chromatography on silica gel with 5% ethyl acetate in petroleum ether to afford 47 mg (86%) of 3-α-tosyloxycholestane as a single isomer (determined by 250 mhz NMR, see Table 1)(9).

REFERENCES AND NOTES.

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2. G.M. Whitesisdes, W.F. Fisher, J.S. Filippo, R.W. Badie and H.O. House, J. Am. Chem. Soc., 91, 4871(1969).
3. After the completion of the synthesis a new procedure for coupling of organic cuprates with alkyl halides was published [B.H. Lipshutz, R.S. Wilhelm and D.M. Floyd, J. Am. Chem. Soc., 103, 7672(1981)]. However, its application to our substrate gave only 20-40% yields of 3 as a mixture of stereoisomers.
4. O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, 44, 3427(1971).
5. Lithium tosylate was prepared as follows: An excess of saturated solution of p-toluenesulfonic acid in methanol was added to a saturated solution of lithium hydroxide in methanol. The salt was precipitated by the addition of ether, filtered and dried overnight at room temperature in vacuo. If an excess of LiOH was used, the reaction was accompanied with rearrangements and elimination.
6. O. Mitsunobu, Synthesis, 1(1981).
7. R. Aneja, A.P. Davies and J.A. Knaggs, Tetrahedron lett., 1033(1975).
8. If an excess of Ph_3P is used, it must be destroyed before chromatography with DEAD.
9. This work was supported in part by NIH grant CA23094.
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