Tetrahedron Letters,Vol.25,No.22,pp 2295-2296,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

REACTIONS OF HYDROXYL GROUPS WITH TOSYLCHLORIDE-DIMETHYLAMINOPYRIDINE SYSTEM. DIRECT SYNTHESIS OF CHLORIDES FROM HYDROXYCOMPOUNDS

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Summary: The reactions of various hydroxyl groups with tosylchloride-dimethylaminopyridine system were investigated and direct syntheses of allyl, alkyl and glycosyl chlorides are described.

In the course of several programs directed towards the total synthesis of complex natural products we had the opportunity to observe a number of interesting and synthetically useful reactions of hydroxyl groups with tosylchloride-dimethylaminopyridine (TsCl-DMAP) system. Table 1 exhibits a series of results including examples from primary, secondary, 2,3-epoxy, allylic,[1] propargylic and glycosidic alcohols.[1] From these results the following general conclusions can be drawn: (a) Allylic, propargylic and glycosidic hydroxyls react rapidly with this system leading to chlorides; (b) 2,3-epoxy and some primary alcohols react to afford the chlorides but at a slower rate and (c) aliphatic secondary alcohols do not lead to chlorides but stop at the tosylate stage. Furthermore, TsBr-DMAP reacted with 1-tetradecanol to afford 1-bromodecane under the conditions of entry 8 suggesting a similar usage of this system.

The following experimental procedure for the preparation of 12a[2,3] from 12[3] is representative. To a magnetically stirred solution of 12[3] (150 mg, 0.58 mmole) in dry CH_2Cl_2 (1 ml) were added sequentially, under argon and at 25°C, DMAP (40 mg, 0.34 mmole, 0.6 eq.), TsCl (132 mg, 0.69 mmole, 1.2 eq.) and Et_3N (89 μl, 0.58 mmole, 1.0 eq.). The reaction mixture was stirred at ambient temperature for 1h (TLC check), diluted with ether, the precipitate removed by filtration, the solution washed sequentially with 10% aq. $CuSO_4$, 10% aq. $NaHCO_3$, sat. aq. NaCl solution and dried over anhydrous Na_2SO_4. Filtration, concentration and flash silica column chromatography (ether-pet. ether, 1:4 R_f= 0.39) afforded pure chloride 12a (140 mg, 87%). ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ : 6.08 (s, 1H, H-1), 4.98 (d, J = 7.3 Hz, 1H, H-2), 4.90 (dd, J = 7.3, 6.6 Hz, 1H, H-3), 4.44 (m, 1H, H-5), 4.22 (dd, J = 7.5, 6.6 Hz, 1H, H-4), 4.07 (m, 2H, H-6), 1.48 (s, 6H, acetonide), 1.41 and 1.34 (singlets, 3H each, acetonide).

References and Notes

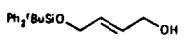
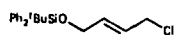
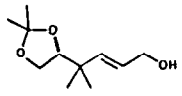
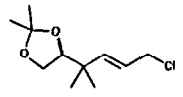
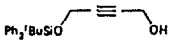
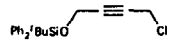
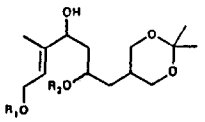
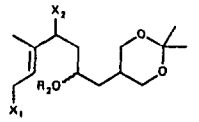
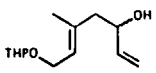
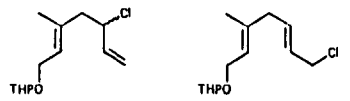
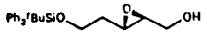
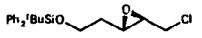
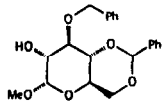
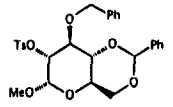
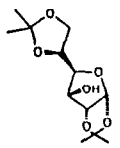
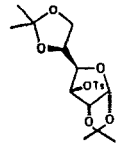
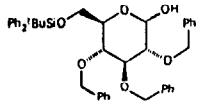
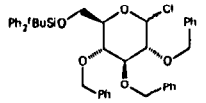
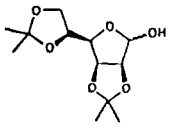
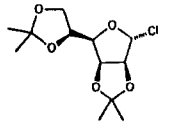
1. For some similar reactions see: (a) E. W. Collington, A. I. Myers, J. Org. Chem., 36, 3044 (1971); (b) Mukaiyama, T., S. Shoda, Y. Watanabe, Chem. Lett., 383 (1977); (c) H. Mrozik, J. C. Chabala, P. Eskola, A. Matzuk, F. Waksmunski, M. Woods and M. H. Fisher, Tet. Lett., 24, 5333 (1983).

2. All new compounds were characterized by spectroscopic means (^{1}H NMR, IR, MS) and exhibited satisfactory analytical and/or high resolution mass spectral data. Yields refer to chromatographically and spectroscopically homogeneous materials.

3. Prepared from D-mannose by (bis)acetonization (acetone, cat. H_2SO_4) see: J. B. Lee and T. J. Nolan, Tetrahedron, 23, 2789 (1967).

4. This work was financially supported by the National Institutes of Health and the Camille and Henry Dreyfus Foundation.

Table 1. Reactions of Hydroxycompounds with Tosylchloride Dimethylaminopyridine System

Entry	Substrate	Product	Method (time)	Yield (percent)
1			A (2 hr)	90
2			B (1 hr)	90
3			B (1 hr)	88
4	 R_1 = H, R_2 = Si^tBuMe_2	 X_1 = Cl, X_2 = OH	A (2 hr)	85
5	R_1 = THP, R_2 = Si^tBuMe_2	X_1 = OTHP, X_2 = Cl	A (48 hr)	80
6		 (ca 1 : 1)	A (48 hr)	80
7			B (24 hr)	80
8	$CH_3(CH_2)_{12}CH_2OH$	$CH_3(CH_2)_{12}CH_2Cl$	A (96 hr)	95
9			A (24 hr)	85
10			A (24 hr)	90
11			B (24 hr)	98
12			B (24 hr)	80
13	 12	 12a	B (3 hr)	86

Method A: TsCl (1 · 2 eq), DMAP (1 · 1 eq), CH_2Cl_2, 25° C

Method B: TsCl (1 · 2 eq), DMAP (0 · 8 eq), Et_3N (1 · 0 eq), CH_2Cl_2, 25° C

(Received in USA 30 January 1984)