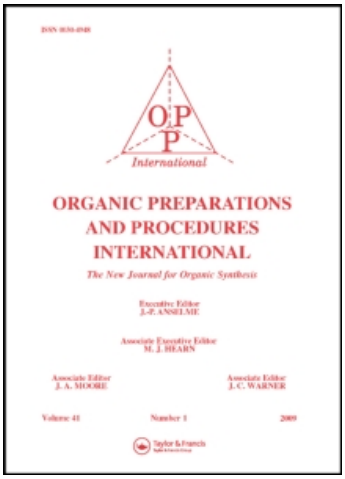

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A STRAIGHTFORWARD SYNTHESIS OF *O*-PROTECTED 3-HYDROXYPROPANAL DERIVATIVES

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A STRAIGHTFORWARD SYNTHESIS OF *O*-PROTECTED 3-HYDROXYPROPANAL DERIVATIVES

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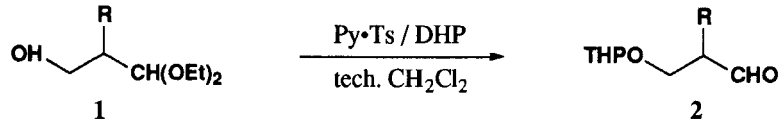
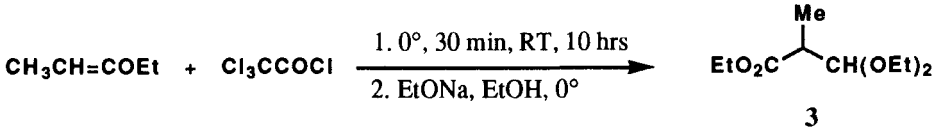
Bifunctional compounds like 3-tetrahydropyranyloxypropanal derivatives are very useful intermediates for the synthesis of various products.[1-3] As part of our research program, we sought a method for the synthesis of compound **2b** from ethyl 3,3-diethoxy-2-methyl propanoate **3**.[4] Herein, we report a convenient method for the one-pot preparation of aldehydes **2** from alcohols **1**.



1 **2**

a) R = H b) R = CH_3 DHP = dihydropyran; THP = tetrahydropyran

Pyridinium tosylate (Py•Ts) is a widely used catalyst for the tetrahydropyranylation of alcohols.[5] Miyashita *et al.*[6] reported that Py•Ts led to tetrahydropyranyl (THP) ether formation in the presence of acid-sensitive groups such as ketals. Sterzycki[7] found that Py•Ts also catalyzes the formation and the cleavage of dioxolane-type acetals. The present work describes a one-step preparation of aldehydes **2** (*e. g.* **2a**[1] and **2b**[2]) from alcohols **1** by simultaneous tetrahydropyranylation of the hydroxyl group and cleavage of the diethyl acetal. Compound **1a** is commercially available and **1b** was obtained by reduction of the ester **3** with lithium aluminium hydride. Ester **3** was prepared in one step from ethyl propenyl ether and trichloroacetyl chloride, according to the literature procedure (60% yield).[4]



3

Simultaneous tetrahydropyranylation and diethyl acetal cleavage occurred when a solution of one equivalent of alcohols **1** was stirring in technical quality dichloromethane with 0.1 equivalent of Py•Ts and 2 equivalents of dihydropyran (DHP). All attempts to improve yields (30% for **2a**, 45% for **2b** from **1**) were unsuccessful, *e. g.* these values could not be increased by using 4 equivalents of DHP or high quality dichloromethane.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded in $CDCl_3$, on a Bruker BZH 200/52 spectrometer at 200 MHz and are reported in ppm downfield from TMS. Refractive indices were obtained on an Abbe refractometer.

Typical Procedure. Synthesis of 2-Methyl-3-tetrahydropyranyloxypropanal (2b).- To a stirred mixture of $LiAlH_4$ (1 g, 26 mmol) and Et_2O (20 mL) was added dropwise a solution of ester **3** (8 g, 39 mmol)[4] in Et_2O (10 mL). After stirring for 5 min, excess hydride was hydrolyzed by dropwise addition of H_2O (15 mL), followed by 5N H_2SO_4 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were dried (Na_2SO_4) and evaporated to afford 4.49 (71%) of pure alcohol **1b** as a colorless liquid. $n_D^{22°}$ = 1.4280; ^{1}H NMR: δ 0.91 (d, 3H, C$\underline{H}_3$CH-, J = 6.8 Hz), 1.22 (t, 3H, -OCH$_2$C$\underline{H}_3$, J = 7.1 Hz), 1.24 (t, 3H, OCH$_2$C$\underline{H}_3$, J = 6.9 Hz), 2.02-2.08 (m, 1H, C$\underline{H}$CH$_2$OH), 2.64 (s, 1H, OH), 3.57 (d, 2H, -C$\underline{H}_2$OH, J = 5.7 Hz), 3.68 (q, 2H, -OC$\underline{H}_2$CH$_3$, J = 7 Hz), 3.78 (q, 2H, -OC$\underline{H}_2$CH$_3$, J = 7.2 Hz), 4.37 (d, 1H, OCHO, J = 6.3 Hz), lit.[8] ^{1}H NMR (60 MHz): δ 0.9 (d, 3H), 1.25 (t, 6H), 1.7-2.3 (m, 1H), 3.15 (s, 1H), 3.55 (d, 2H), 3.35-3.9 (m, 4H), 4.35 (d, 1H).

A mixture of alcohol **1b** (0.6 g, 3.7 mmol), dihydropyran (0.62 g, 7.4 mmol) and Py•Ts (0.1 g, 0.37 mmol) in technical quality CH_2Cl_2 (30 mL) was stirred for 24 hrs at room temperature, then washed with half-saturated brine. After evaporation of the solvent, chromatography on silica gel using 80/20 petroleum ether/ethyl acetate as eluent, provided 0.29 g (45%) of aldehyde **2b** as a colorless liquid. $n_D^{21°}$ = 1.4512; ^{1}H NMR: δ 1.15 (d, 3H, C$\underline{H}_3$CH, J = 7.1 Hz), 1.38-1.8 (m, 6H, CH(C$\underline{H}_2$)$_3$CH$_2$), 2.62-2.71 (m, 1H, C$\underline{H}$CHO), 3.44-3.64 (m, 2H, CH$_2$O), 3.77-3.89 (m, 2H, CH$_2$O), 4.62-4.65 (m, 1H, OCHO), 9.75 (s, 1H, CHO), lit.[2] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 and 1.16 (2d, 3H, J = 7 Hz), 1.45-1.85 (m, 6H), 2.63 (m, 1H), 3.48-3.62 (m, 2H), 3.78-4.00 (m, 2H), 4.58 (m, 1H), 9.83 (m, 1H).
3-Tetrahydropyranyloxypropanal (2a): 30% yield; $n_D^{21°}$ = 1.4520; ^{1}H NMR: δ 2.62 (dt, 2H, C$\underline{H}_2$CHO, J = 6.0 Hz and 1.8 Hz), 4.48-4.64 (m, 1H, OCHO), 9.75 (t, 1H, CH$_2$C$\underline{H}$O, J = 1.8 Hz), lit.[1] ^{1}H NMR (CCl_4): δ 2.6 (dt, 2H, J = 5.2 Hz and 1.0 Hz), 4.55 (m, 1H), 9.84 (t, 1H, J = 1.0 Hz).

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SIMPLE AND FACILE OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS

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We needed an efficient and practical method for the large scale oxidation of unsaturated aldehydes, phenolic aldehydes, aminobenzaldehyde and pyrrole-2-carboxaldehyde to the corresponding acids. Though numerous reagents and methods are described in literature,[1-5] none of these was suitable for the oxidation of 4-(dimethylamino)benzaldehyde, 4-hydroxybenzaldehyde, and pyrrole-2-carboxaldehyde, which are very sensitive to the oxidative conditions. In most of the known methods the major disadvantages are complex operating conditions, low-conversions, and expensive reagents. The method of Dalcanale and Montanari[6] for the oxidation of aldehydes to carboxylic acids based on sodium chlorite-H_2O_2 was found to be excellent for the oxidation of simple aromatic aldehydes. However, this procedure was quite unsatisfactory and afforded tarry products and chlorinated compounds in the case of crotonaldehyde, 4-hydroxybenzaldehyde, and 4-(dimethylamino)benzaldehyde. We herein describe a simple and practical method for the oxidation of aldehydes to carboxylic acids using sodium chlorite-aqueous acetonitrile.

This procedure proved satisfactory even in the sensitive cases of unsaturated aldehydes (entries 2 and 3), phenolic aldehydes (entries 4 and 5), aminobenzaldehyde (entry 9) and heterocyclic aldehydes (entries 10 and 11). Esteban[7] reported the oxidation of an aliphatic aldehyde (entry 1) with sodium chlorite in the presence of aqueous H_2NSO_3H to give the corresponding carboxylic acid in 77% yield. However, the generality of this method and particularly its utility for the oxidation of sensitive aldehydes were not discussed. The present $NaClO_2$-aqueous acetonitrile combination is superior to existing methods in terms of operation, yield and adaptability to large scale.

The reactions were carried out by the slow addition of 1.0-1.4 equiv. of $NaClO_2$ to a solution of 1.0 equiv. of aldehyde in aqueous acetronitrile at 5-10°. In most cases, the yields were high and the products were acceptably pure.