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SELECTIVE OXIDATION OF PRIMARY HYDROXY GROUPS IN PRIMARY-SECONDARY DIOLS

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Abstract: The two-phase oxidation of primary-secondary diols with sodium hypochlorite, mediated by TEMPO, brings about selective oxidation at the primary position. Such 5 diols are oxidized to the corresponding hydroxyaldehydes.

Chemoselective oxidation of alcohols to carbonyl derivatives is an important synthetic transformation. There are many methods for the selective oxidation of secondary hydroxyls in the presence of primary ones[1], but relatively few reports describe procedures suitable for the oxidation of primary alcohols that leave secondary alcohols intact[2-4]. Semmelhack et al. reported briefly that electrooxidation as well as autoxidation of alcohols, mediated by 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO), demonstrated this rare kind of selectivity[3]. The two-phase oxidation of alcohols by aqueous sodium hypochlorite in the presence of 4-methoxy-2,2,6,6-tetramethylpiperidinyl-1-oxy (4-MeO-TEMPO), more convenient from practical point of view, also showed selectivity in the competitive reaction of a 1:1 mixture of 1- and 2-nonanol. However, experiments with substrates containing both primary and secondary hydroxyls failed[4a], and only recently, when our work was in progress, the same authors reported successful oxidation of 1,10-undecanediol to 10-hydroxyundecanal[4b].

Our interest in the two-phase catalyzed oxidations[5] led us to reinvestigate this interesting system[4], easily producing the bulky nitrosonium salts[6], in order to elaborate synthetically its remarkable selectivity. We found that use of commercially available TEMPO has advantage over 4-MeO-TEMPO since the former mediator strongly inhibited overoxidation of the aldehyde formed (Table 1), while still being an effective catalyst.

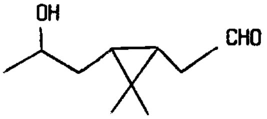
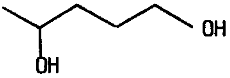
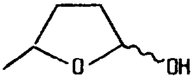
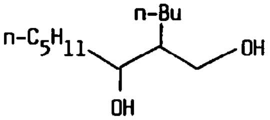
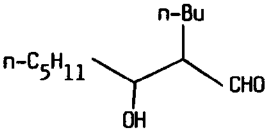
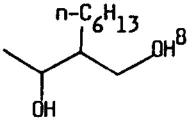
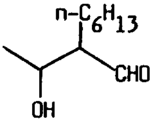
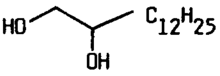
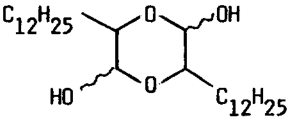
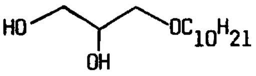
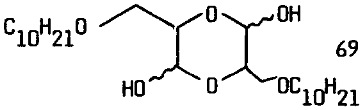
Table 1. Oxidation of undecanal with equimolar amounts of the mediator and sodium hypochlorite[a]

Mediator (equimolar amount)	Yield (%) Undecanal	Yield (%) Undecanoic acid
None	8	69
4-MeO-TEMPO	34	50
TEMPO	97	1

[a] For the reaction conditions, see Procedure.

The modified catalytic system was tested in oxidations of primary alcohols, 1:1 mixtures of primary and secondary ones, and diols possessing both these functions in one molecule.

Table 2. Oxidation of various alcohols with sodium hypochlorite in the presence of 1 mol % of TEMPO

Entry	Alcohol	Product	
		Yield[a]	(%)
1	1-Undecanol	Undecanal 100	
2	2-Phenylethanol	2-Phenylethanal 87, Phenylacetic acid 13	
3	$THPO(CH_2)_9CH_2OH$	$THPO(CH_2)_9CHO$ 79 (69)	
4	$n\text{-}C_6H_{13}SCH_2CH_2OH$	$n\text{-}C_6H_{13}S(O)CH_2CH_2OH$ (90)	
5	1-Decanol, 5-Decanol (1:1)	Decanal 99, 5-Decanol 99.8	
6	1-Phenylethanol, 2-Phenylethanol (1:1)	1-Phenylethanol 89, Acetophenone 9, 2-Phenylethanal 85, Phenylacetic acid 12	
7	1,10-Undecanediol	10-Hydroxyundecanal 58 (34), 10-Oxoundecanol 15	
8			65 (51)
9			43 (40)
10			76 (70)[7]
11			98 (82)[9]
12			(71)[10]
13			69 (63)[b]

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[a] Yields were calculated from GC. Yields of isolated products are listed in parentheses.

[b] From this mixture of diastereoisomers a single isomer[11] was isolated in 33% yield.

Procedure. A 50 ml flask was charged with a solution of the alcohol (3 mmol) in methylene dichloride (8 ml), TEMPO (4.5 mg, 1 mol %), and a saturated aqueous solution of sodium bicarbonate (5 ml) containing potassium bromide (30 mg, 10 mol %) and tetrabutylammonium chloride (40 mg, 5 mol %). To this cooled (0°C, a water-ice bath) and well stirred mixture, the solution made of 2 ml of 1.95 M sodium hypochlorite (3.9 mmol, 30% excess), 3 ml of saturated sodium bicarbonate solution and 6 ml of brine was added dropwise during 45 min. The mixture was stirred for 1 h at 0°, then for 20 min at 20°, and the phases were separated. The aqueous phase was extracted with methylene dichloride (3 x 10 ml) and the combined extracts were washed with saturated sodium bicarbonate solution (10 ml), brine (10 ml), and dried over anhydrous sodium sulfate. The evaporated crude product was analyzed (GC) and purified by distillation (entry 9), crystallization (entries 4, 12, 13), or chromatography on silica gel (entries 3, 7, 8, 10, 11). All the products gave IR and ^{1}H NMR spectra consistent with their structures. For the new compounds, satisfactory elemental analyses were obtained and their properties are reported in the Notes.

Selectivity of the system was confirmed by the results of oxidation of equimolar mixtures of primary and secondary alcohols and even the benzylic secondary alcohol was over ten times less reactive than the non-benzylic primary one. The reaction conditions used here were optimized for 1-undecanol and are not neccessarily optimum for other cases. We found that, contrary to the reported system[4], the presence of tetrabutylammonium chloride was beneficial for this oxidation (100% yield of undecanal with 5 mol % of Bu_4NCl vs. 85% of the aldehyde and 12% of 1-undecanol left in the absence of Bu_4NCl). Both the 1,3-diols as well as the resulting aldehydes were diastereoisomeric mixtures. Only for one diol, namely 1,10-undecanediol, could a product of oxidation of the secondary hydroxyl be observed, and in all other cases no compound containing a second carbonyl was detected. When the product was highly hydrophilic a decrease in yield was noted, probably due to the overoxidation taking place in an aqueous phase (entry 9). It is noteworthy that the crude aldehydes contained a very small amount of TEMPO, which apparently stabilized the aldehydes. After purification, the products were much less stable against autoxidation.

In conclusion, the developed procedure offers a convenient way for a practical preparation of hydroxyaldehydes by highly selective oxidation of primary hydroxy groups in the presence of secondary ones.

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7. IR (film) ν_{C-O} 1134, $\nu_{C=O}$ 1722, ν_{C-H}^{formyl} 2732, ν_{C-H} 2860, 2932, ν_{O-H} 3412; NMR ($CDCl_3$) 0.90 (t, 6H, J=6 Hz, CH_3-); 1.36 (m, 14H, -CH_2-); 2.35 (m, 1H, -C$\underline{H}$CHO); 3.92 (m, 1H, >C$\underline{H}$OH), 5.36 (br s, 1H, -OH); 9.73 (br s, 1H, -C$\underline{H}$O); GC (2% DEGS, 140°C) 8.6 min; R_f 0.70 (silica gel, i-Pr_2O).
8. IR (film) ν_{C-O} 1090, 1118, δ_{CH} 1432, ν_{C-H} 2860, 2932, ν_{O-H} 3348 br, 3634; NMR ($CDCl_3$) 0.98 (t, 6H, J=5 Hz, CH_3-); 1.40 (s, 13H, -CH<, -CH_2-); 3.25 (s, 2H, -OH); 3.7 - 4.1 (m, 3H, -C$\underline{H}_2$OH, >C$\underline{H}$OH); GC (2% DEGS, 140°C) 12.9 and 14.2 min, 1:2.5 mixture of diastereoisomers; R_f 0.20 (silica gel, i-Pr_2O and $CHCl_3$, 2:1).
9. IR (film) ν_{C-O} 1148, δ_{CH} 1466, $\nu_{C=O}$ 1724, ν_{C-H}^{formyl} 2732, ν_{C-H} 2860, 2940, ν_{O-H}3420; NMR ($CDCl_3$) 0.89 (t, 3H, J=6 Hz, CH_3-); 1.21 (t, 3H, J=6 Hz, CH_3-); 1.27 (s, 8H, -CH_2-); 2.35 (m, 1H, >C$\underline{H}$CHO); 4.20 (m, 1H, >C$\underline{H}$OH), 5.25 (br s, 1H, -OH); 9.76 (d, 1H, J=3 Hz, -CHO); GC (2% DEGS, 140°C) 5.7 min; R_f 0.42 (silica gel, i-Pr_2O and $CHCl_3$, 2:1).
10. M.p. 107-110°C, IR (KBr) ν_{C-O} 1088, 1142, 1172, δ_{CH} 1472, ν_{C-H} 2848, 2916, ν_{O-H} 3336; NMR ($CDCl_3$, 50°C) 0.88 (t, 6H, J=5 Hz, CH_3-); 1.24 (s, 44H, -CH_2-); 2.63 (br s, 2H,-OH); 3.67 (m, 2H, >CHO-); 5.10 (m, 2H, -OCHO-).
11. M.p. 101-103°C. IR (KBr) ν_{C-O} 1088, 1116, 1152, δ_{CH} 1468, ν_{C-H} 2856, 2932, ν_{O-H} 3372; NMR ($CDCl_3$) 0.90 (t, 6H, J=6 Hz, CH_3-); 1.27 (s, 32H, -CH_2-); 2.95 (br s, 2H, OH); 3.46 (m, 10H, -CH_2OCH_2CHO-); 5.33 (m, 2H, -OCHO-).

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