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[A004]

Direct synthesis of a-hydroxy acids through selective oxidation of diols mediated by homogeneous and heterogeneous TEMPO

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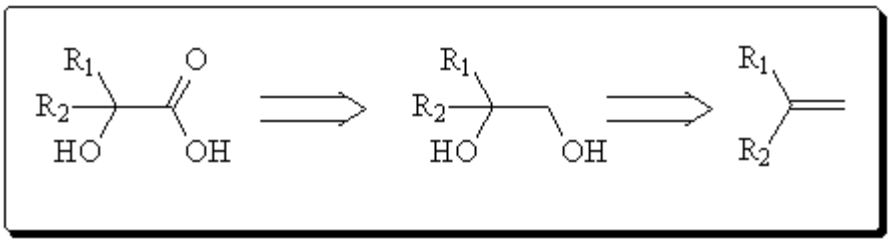
INTRODUCTION

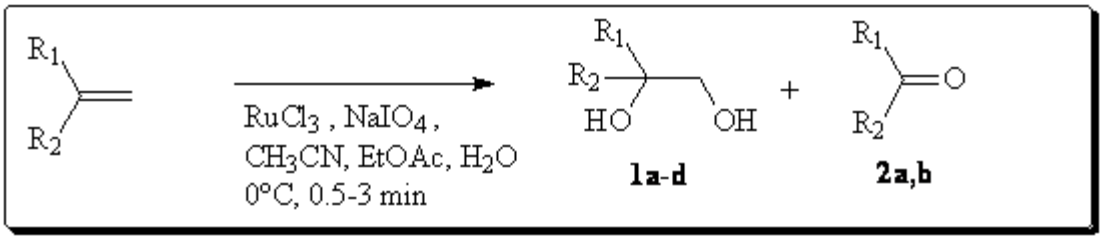
a-Hydroxy acids are pivotal components in a variety of compounds with important biological activity.[1] Here we report an easy strategy which allows to synthesise a-hydroxy acids in a two-step oxidation process, involving first the *cis*-dihydroxylation of a terminal alkenes (catalyzed by ruthenium) followed by subsequent oxidation with TEMPO either dissolved in the homogeneous phase or entrapped in a sol-gel matrix. This work extends what we recently found concerning the synthesis of amino hydroxy acids by oxidation of the primary hydroxyls in aminodiols.[2]



Scheme 1

RESULTS AND DISCUSSION

The diols **1a-d** were obtained starting from terminal alkenes by using the oxidative ruthenium catalysis protocol.[3] Hence, using a biphasic solvent system of ethyl acetate, acetonitrile and water (3:3:1 volumes ratio) in the presence of 0.07 mol equiv. of $RuCl_3$•$(H_2O)_3$ and 1.5 mol equiv of $NaIO_4$ at 0-5 •C, very rapid dihydroxylation (within minutes) of olefins occurs giving *syn*-diols (**1**) in good yields. When aromatic alkenes are used, the corresponding ketones (**2**) are isolated in very low yield due to concurrent oxidation of the benzylic alcohol moiety.



Scheme 2

Table 1. Dihydroxylation of alkenes with the Shing$\diamond$s protocol

Diols	R_1	R_2	Time (min)	diol / ketone*
1a	Ph	CH_3	0.5	97 : 3
1b	4-ClPh	CH_3	0.5	94 : 6
1c	C_4H_9	H	3	100 : 0
1d	$C_3H_7CH(OH)$-	H	3	100 : 0

*calculated by GC-MS. All the diols were identified by usual spectroscopic methods including NMR and data correspond to those of the literature

The reactions are very rapid. Hence, when diol **1a** was synthesised, only 0.04 mol equiv of $RuCl_3\diamond(H_2O)_3$ and 0.5 min were necessary to obtain the diol, with longer reaction times or the classical 0.07 mol equiv of $RuCl_3\diamond(H_2O)_3$ leading to ketone as the only product, as a result of the competitive glycol cleavage. When aliphatic alkenes (1-hexene and 1-hexen-3-ol) were used only the desired diols **1c,d** were isolated and no traces of cleavage products were found.

Identification of diols

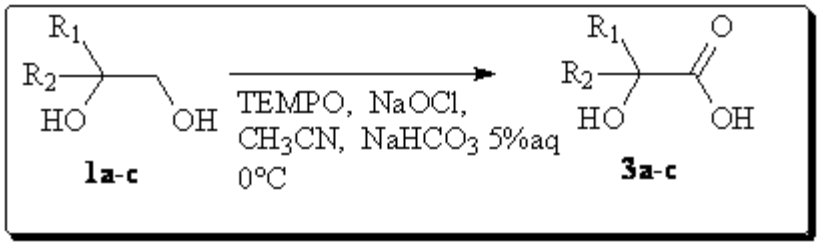
1a FTIR spectra [v cm^{-1} 3404 (OH); 3088-2876 (ArH, CH)]
mass spectrum [m/z (%) 152 (1); 121 (100); 43(85)]
m.p. 43-44 $\diamond$C

1b FTIR spectra [v cm^{-1} 3418 (OH); 2978-2932 (ArH, CH); 829 (C-Cl)]
mass spectrum [m/z (%) 186 (1); 155 (88); 43(100)]
^{1}H-NMR [δ : 1.40 (s, 3H); 5.02 (s, 2H); 7.34 (d, *J* = 7.9 Hz, 2H); 7.49 (d, *J* = 7.9 Hz, 2H)]
^{13}C-NMR [δ : 26.05 (q); 70.34 (t); 73.47 (s); 127.44 (d); 127.56 (d); 130.80 (s); 146.50 (s)]
m.p. 69-70 $\diamond$C

1c FTIR spectra [v cm^{-1} 3383 (OH); 2932-2862 (CH)]
mass spectrum [m/z (%) 87 (36); 69 (100); 57 (12); 43 (22); 41(44)]
oil

1d FTIR spectra [v cm^{-1} 3381 (OH); 2961-2874 (CH)]
mass spectrum [m/z (%) 103 (8); 91 (4); 73 (61); 61 (17); 55 (100); 44 (66); 43 (54)]
m.p. 65-67 $\diamond$C

Diols thereby obtained were further oxidised with TEMPO/NaOCl at 0 $\diamond$C to afford the corresponding a-hydroxyacids exploiting the TEMPO selectivity for primary alcohols at alkaline pH.[4]



Scheme 3

Table 2. TEMPO-mediated oxidation of diols in homogeneous phase

Acids	R_1	R_2	% yield acid*	% yield ketone*
3a	Ph	CH_3	24	55
3b	4-ClPh	CH_3	65	20
3c	C_4H_9	H	79	0

Calculated after purification by chromatographic column

Identification of acids

3a FTIR spectra [v cm^{-1} 3427 (OH); 1728 (CO)]
mass spectrum [m/z (%) 132(1); 122(8); 121(86); 105(11); 91(2); 77(16); 63(2); 51(13); 43(100)]
m.p. 86-88 °C

3b FTIR spectra [v cm^{-1} 3410 (OH); 1732 (CO); 655 (CCl)]
mass spectrum [m/z (%) 156 (9); 154 (26); 141 (33); 139 (100); 113 (16); 111(48); 75 (17)]
^{1}H-NMR [δ : 1.64 (s, 3H); 7.39 (d, *J* = 7.9 Hz, 2H); 7.57 (d, *J* = 7.9 Hz, 2H)]
^{13}C-NMR [δ : 27.34 (q); 74.62 (s); 127.58 (d); 127.87 (d); 131.85 (s); 143.42 (s); 176.58 (s)]
m.p. 127-128 °C

3c FTIR spectra [v cm^{-1} 3412 (OH); 2959-2858 (CH); 1722 (CO)]
mass spectrum [m/z (%) 87 (47); 69 (100); 57 (14); 43 (26); 41 (50)]
m.p. 60-61 °C

Under said homogeneous conditions, the oxidation of diol **1a** led to (±)atrolactic acid **3a** in 24% yield and 55% of ketone due to the cleavage of benzylic moiety; while when the p-Cl derivative was used as substrate the acid/ketone ratio changed in favour of the acid compound (65:20 in percent terms). In case of aliphatic 1,2-hexanediol only the corresponding acid was found in good yield of 79%.
Since the homogeneous TEMPO/bleach reaction protocol applied to the conversion of diols **1a,b** yields the moderate selectivity reported above, we used our heterogeneous sol-gel entrapped TEMPO catalyst [5] to improve the selectivity. Again, the heterogenous reaction of diol **1a** gave an inversion of the selectivity and now an acid/ketone of 60:40 was observed. We ascribed this change in selectivity to the separation of the catalyst from the reactants.

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