An Effective Hydrolysis of Crowded Chiral Esters

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Abstract: Trifluoromethanesulfonic acid-coated silica in the absence of solvents is an effective reagent for hydrolysis of sterically crowded chiral esters giving chiral acids in good chemical and optical yield. On the other hand, the method was unsuitable for the separation of optically pure alcohols from chiral esters because dehydration usually takes place during the reaction course.

Key words: silica, hydrolysis, chiral, catalysis, trifluoromethanesulfonic acid

We had occasion to prepare pure (*R*)- and (*S*)-(1-naphthyl)phenylacetic acids (**1**). The most convenient way to obtain **1** (Figure 1) seemed to be hydrolysis of ester **1a** after separation of the diastereomers by crystallization. However, all attempts to hydrolyze **1a** or to use the other currently used methods of C-O bond fission failed due to the steric problems since the reaction was slow and, consequently, it was accompanied by racemization or acid/ester decomposition. For instance, **1a** resisted alkaline hydrolysis[1] for three days giving racemic **1** in a negligible yield, while in acidic media[2] no hydrolysis took place at all. Similarly, reaction with trimethylsilyl iodide[3] or *t*-BuOK[4] did not afford any product. Alkaline hydrolysis with phase-transfer catalysis[5] or in a water-tetrahydrofuran-lithium hydroxide system,[6] both reported as giving acids without racemization, also failed. A synthetic route to the desired product, reduction of **1a** with lithiumaluminium hydride and subsequent oxidation led to the racemic acid **1** in low yield. However, we noted that **1a** did not change its optical rotation when refluxed in diluted sulfuric acid for several days, indicating high optical stability in acidic medium. Since base could not be used, acid hydrolysis appeared to be the only simple way to obtain the desired product.

Methanesulfonic acid in methylene chloride has already been proposed as a possible medium for ester hydrolysis because its pK_a is about equivalent to that of mineral acids.[7] On the other hand, its trifluoromethyl analog has a higher pK_a and its efficiency might be increased even by further activation, e.g., on a silica surface. Similar techniques are widely used and a variety of reagents nonbonded chemically to the silica surface have been published as potent catalysts. For instance, fission of the C–O–C bond, dehydration of alcohols as well as acetalization of aldehydes and ketones is well documented.[8] Reduction,[9] oxidation[10] and many other methods also demonstrate the versatility of this technique.

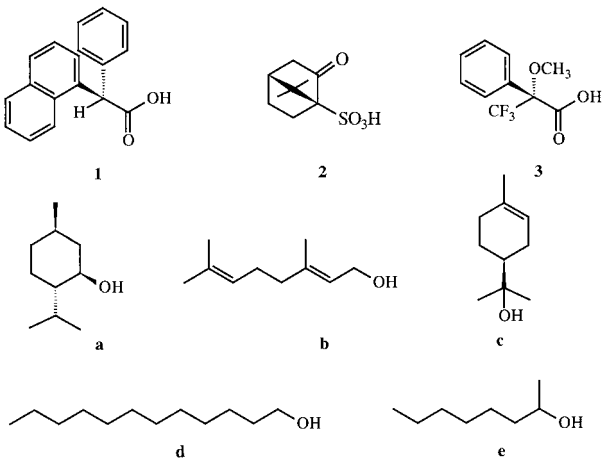

Figure 1

Here we report successful hydrolysis of crowded chiral esters using trifluoromethanesulfonic acid-modified silica as a hydrolysis-mediating reagent. Model studies for this novel reagent were carried out with several compounds derived from optically pure acids.

Table 1 Composition of the Prepared Esters, Reaction Time and the Yield of their Hydrolysis

Ester	Composition		Reaction Time[a]	Yield[b]
	Acid	Alcohol	[min]	[%]
1a	**1**	**a**	12	76
2a	**2**	**a**	3	86
3a	**3**	**a**	30	48
1b	**1**	**b**	5	61
1c	**1**	**c**	3	53
1d	**1**	**d**	270	0[c]
1e	**1**	**e**	30	56

[a] Reaction time was estimated from at least three repeated experiments at 125 °C when the ester disappeared from the reaction mixture (TLC).
[b] Overall yield including the hydrolysis with subsequent re-esterification with (–)-menthol.
[c] No acid detected, dodecan-1-ol obtained instead (86%).

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In addition to acid **1**, two additional of crowded chiral acids were chosen for the experiment. They were combined with five structurally different alcohols (**a**–**e**) so that two different groups of esters are listed in the Table 1. All compounds were prepared using either the DCC method[11] (**1**) or the acylchloride/ pyridine esterification [**2**, **3**; optically pure 2-(1-naphthyl)-2-phenylacetic acid (**1**) spontaneously racemized during the DCC-mediated reaction].

All esters were subjected to the trifluoromethanesulfonic acid-modified silica treatment under different temperatures and 125 °C was finally found to be optimal. In addition to trifluoromethanesulfonic acid, $FeCl_3$- and H_2SO_4-coated silica as well as neat silica have also been tried. Trifluoromethanesulfonic acid-modified silica showed the best results. Depending on the ester composition, the whole process took minutes or several hours (see Table 1): while the esters of tertiary or allylic alcohols (**1c** or **1b**) or ester **2a** gave the free acid within minutes, esters of secondary alcohols (**1a**, **1e**, **3a**) liberated the acid within 30 minutes. Surprisingly, the only product of **1d** decomposition was dodecan-1-ol, probably from decarboxylation of free acid during the long reaction time. On the other hand, relatively unstable ester (**3a**)[12] derived from Mosher's acid (**3**) showed surprising high stability giving acid **3** in a relatively good yield. A salient feature of the procedure is the absence of acid racemization during the hydrolysis even in the case of very optically labile molecule (**1**). This result was confirmed by evaluating the NMR spectra of esters prepared from liberated acids by re-esterification with (–)-menthol.

Apart from the expected product, an alcohol is a logical counterpart of every hydrolytic process. The results indicate that either, i) the preferential fission of the oxygen-alkyl group bond takes place during the reaction (see Table 1, compare the reaction time vs. structure) or, ii) the subsequent dehydration occurs thus affording hydrocarbons as side-products. Therefore, the method cannot be used for separation of optically pure alcohols.

In conclusion, we demonstrated that trifluoromethanesulfonic acid-modified silica can be used to efficiently mediate hydrolysis of sterically hindered esters under solvent-free conditions. The acids are produced in medium to high yield, with retention of configuration of the optically labile model compound. This method can be added to existing methodologies for hydrolysis of hindered esters frequently synthesized to allow separation of diastereomeric pairs.

General procedure for hydrolysis of esters:
To 400 mg of trifluoromethanesulfonic acid-coated silica (10%), ester (**1**–**3, a**–**e**, 100 mg) was added at room temperature in CH_2Cl_2 (500 μL). The solvent was evaporated under reduced pressure and the reaction mixture was placed in an oil bath preheated to 125 °C. The conversion was checked every 5 min (TLC) and as soon as the reaction was finished (as indicated by the disappearance of starting ester), the solid was transferred to the top of a silica column (10 g) and eluted with 15 mL of light petroleum (non-polar compounds) and then with 15 mL of diethyl ether (product). Evaporation of the solvent afforded the acid pure enough for further processing.
Representative analyses of starting esters:
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl (2R)-2-(1-naphthyl)-2-phenylethanoate (**1a**)
Anal. Cald for $C_{28}H_{32}O_2$: C 83.96% C, H 8.05%; Found: C 83.68%, H 7.76%; ^{1}H NMR (200 MHz, $CDCl_3$/TMS): 0.64 [d, 3 H, *J*(8,7) = 7.0 Hz, C(8)H_3]; 0.74 [d, 3 H, *J*(9,7) = 7.0 Hz, C(9)H_3]; 0.89 [d, 3 H, *J*(10,5) = 6.6 Hz, C(10)H_3]; 0.83 and 1.67 [2 × m, 2 × 1 H, C(4)H_2]; 0.95 and 2.05 (2 × m, 2 × 1 H, C(6)H_2]; 1.00 and 1.62 [2 × m, 2 × 1 H, C(3)H_2]; 1.33 [m, 1 H, C(2)H]; 1.48 [m, 1 H, C(5)H]; 1.65 [m, 1 H, C(7)H]; 4.74 [dt, 1 H, *J*(1,2) = *J*(1,6a) = 10.6 Hz, *J*(1,6b) = 4.4 Hz, C(1)H]; 5.75 (s, 1 H, Ar_2-CH-CO); 7.25–7.37 (m, 6 H, Ar-H); 7.41–7.48 (m, 3 H, Ar-H); 7.79 (m, 1 H, Ar-H); 7.86 (m, 1 H, Ar-H); 7.98 (m, 1 H, Ar-H). MS (EI, *m/z*, %): 400 [M^+] (17), 262 (4), 217 (100), 139 (16), 97 (18), 83 (96); IR (CCl_4, cm^{-1}): 1725, 1625, 1599, 1585, 1590, 1511, 1496, 1455, 1307, 1080, 1038, 955, 699; $[\alpha]_D$ –64,7 (c 2.56, $CHCl_3$) {lit.[11] $[\alpha]_D$ –68.7 ($CHCl_3$)}.
(2E)-3,7-Dimethyl-2,6-octadienyl 2-(1-naphthyl)-2-phenylethanoate (**1b**)
Anal. Cald for $C_{28}H_{30}O_2$: C 84.38%, H 7.59%; Found: C 84.52%, H 7.46%; ^{1}H NMR (200 MHz, $CDCl_3$/TMS): 1.58, 1.64 and 1.66 (3 × s, 3 × 3 H, 3 × CH_3); 2.01 [m, 2 H, C(4)H_2]; 2.06 [m, 2 H, C(5)H_2]; 4.67 and 4.71 [2 × m, 2 × 1 H, C(1)H_2]; 5.06 [m, 1 H, C(6)H_2]; 5.33 [m, 1 H, C(2)H]; 5.78 (s, 1 H, Ar_2-CH-CO); 7.26–7.36 (m, 6 H, Ar-H); 7.40–7.49 (m, 3 H, Ar-H); 7.79 (m, 1 H, Ar-H); 7.86 (m, 1 H, Ar-H); 8.00 (m, 1 H, Ar-H). MS (EI, *m/z*, %): 398 [M^+](14), 290(17), 262(11), 217(100), 202(16), 136(19), 69(68); IR (CCl_4, cm^{-1}): 3091, 3064, 1739, 1627, 1512, 1496, 1304, 1080, 1033, 697.
1-Methylheptyl 2-(1-naphthyl)-2-phenylacetate(**1e**)
Anal. Cald for $C_{26}H_{30}O_2$: C 83.38%, H 8.07%; Found: C 83.31%, H 8.37; ^{1}H NMR (200 MHz, $CDCl_3$/TMS, two diastereomers in the ratio 3: 2 – some signals are doubled): 0.85 (t, 3 H, ^3J = 7.2 Hz, CH_3); 1.19 and 1.21 (2 × d, 3 H, ^3J = 6.2 Hz, CH_3); 5.00 (m, 1 H, >CH-O); 5.75 and 5.74 (2 × s, 1 H, Ar_2-CH-CO); 7.25–7.36 (m, 6 H, Ar-H); 7.40–7.50 (m, 3 H, Ar-H); 7.78 (m, 1 H, Ar-H); 7.86 (m, 1 H, Ar-H); 8.02 (m, 1 H, Ar-H). MS (EI, *m/z*, %): 374 [M^+] (17), 217 (100), 202 (11), 149 (8), 71 (15), 57 (23); IR (CCl_4, cm^{-1}): 3089, 3065, 3032, 1735, 1627, 1512, 1496, 1427, 1379, 1306, 1033, 698.

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