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Facile Hydrolysis of Esters with KOH-Methanol at Ambient Temperature

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Summary. A simple, rapid, and efficient method is reported for the hydrolysis of a variety of mono- and diesters of aromatic, aliphatic, fatty, and heterocyclic acids with potassium hydroxide in methanol at ambient temperature (~35°C).

Keywords. Esters; Hydrolysis; Potassium hydroxide; Methanol.

Introduction

Ester hydrolysis has been known for long and is usually catalyzed by acids and bases. Both acidic and alkaline hydrolysis are equilibrium reactions [1]. However for preparative purposes, ester hydrolysis is invariably performed in basic solution in order to shift the equilibrium unless the compound is base sensitive. The basic hydrolysis is carried out with aqueous hydroxides in presence of co-solvents at high temperatures and generally requires long durations for complete ester hydrolysis. Micellar catalysis [2], phase transfer catalysis [3], ultrasonic irradiation [4], and microwaves [5] have been employed to overcome the problem of heterogeneous systems. In view of the importance of ester hydrolysis in organic synthesis, there is scope for facile ester hydrolysis at ambient temperature. To the best of our knowledge, we did not find any alkaline hydrolysis method wherein water had not been used as a co-solvent. While working on reactions of different functionalities with Al-KOH in methanol at ambient temperature [6], we realized that esters could be hydrolyzed rapidly at ambient temperature with potassium hydroxide and methanol without any co-solvent. Therefore, a detailed investigation on optimizing the reaction conditions was taken up.

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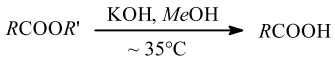
Results and Discussion

This paper reports a simple, rapid, and efficient procedure for the hydrolysis of a large variety of esters at ambient temperature (~35°C) using potassium hydroxide in methanol unlike most other methods which require aqueous hydroxides with co-solvents and refluxing of the reaction mixtures for long durations. The hydrolysis has been carried out on different mono- and diesters of aromatic, aliphatic, fatty, and heterocyclic acids which gave the corresponding carboxylic acids in high yields by a simple quenching procedure (Scheme 1). All the esters underwent complete hydrolysis in 2 to 60 min. Our results are listed in Table 1.



R = XC_6H_4: *X* = H, 4-Cl, 3-Cl, 2-Cl, 4-NO_2, 3-Br, 4-Br, 4-O*Me*, 2-O*Me*, 4-*Me*; $X_2C_6H_3$: X_2 = 3,5-$(NO_2)_2$, 3,4-(O-CH_2-O), 3,4-$(OMe)_2$; $XC_6H_5OCH_2$: *X* = H, 4-Br, 4-*Me*, 4-Cl; *Ph*CH=CH; 1-$C_{10}H_7$; 2-furyl; phthalyl; CH_3; $ClCH_2$; -$(CH_2)_4$-; $CH_3(CH_2)_{10}$; $HO(CH_2)_6CH(OH)CH(OH)(CH_2)_7$

R' = *Me*, *Et*, *i-Pr*, *n*-butyl, benzyl, *ph*, 4-cresyl, 2-cresyl, n-octyl, cholesteryl

Scheme 1

Table 1. Hydrolysis of esters with KOH-methanol[a] at ~35°C

Run no.	Ester *R*COO*R'*	Molar ratio (Ester:KOH)	Time/min	Method	Yield/%	mp (Ref. [7])/°C
1	Methyl benzoate	1:2	10	A	94	122–123 (121)
2	Ethyl benzoate	1:2	20	A	96	123 (121)
3	*i*-Propyl benzoate	1:2	60	A	95	122–123 (121)
4	*n*-Butyl benzoate	1:2	60	A	92	123 (121)
5	Benzyl benzoate	1:2	60	C	86	121 (121)
6	Phenyl benzoate	1:3	60	C	87	122–123 (121)
7	*p*-Cresyl benzoate	1:3	60	C	92	123 (121)
8	*o*-Cresyl benzoate	1:3	60	C	95	122 (121)
9	Methyl *p*-chlorobenzoate	1:2	5	B	92	242 (243)
10	Ethyl *p*-chlorobenzoate	1:2	20	B	89	245 (243)
11	Methyl *m*-chlorobenzoate	1:2	5	B	86	157–160 (158)
12	Methyl *o*-chlorobenzoate	1:2	5	A	84	139 (141)
13	Methyl *p*-nitrobenzoate	1:2	2	B	90	238 (239)
14	Ethyl *p*-nitrobenzoate	1:2	10	A	83	243 (239)
15	Methyl 3,5-dinitrobenzoate	1:2	2	A	86	212 (207)
16	Methyl *m*-bromobenzoate	1:2	5	B	80	153 (155)
17	Methyl *p*-bromobenzoate	1:2	20	B	86	250–257 (252)
18	Methyl cinnamate	1:2	25	A	96	131 (133)
19	Methyl *p*-anisate	1:3	60	B	87	183 (184)
20	Methyl *o*-anisate	1:2	60	A	93	97 (101)
21	Methyl *p*-toluate	1:3	30	B	90	182 (178)
22	Methyl phenylacetate	1:2	20	A	87	76–78 (76)
23	Methyl diphenylacetate	1:2	30	A	83	148–150 (148)
24	Amyl phenylacetate	1:3	60	A[b]	70	76 (76)
25	Methyl phenoxyacetate	1:2	60	A	96	101 (99)

(*continued*)

Table 1 (*continued*)

Run no.	Ester *RCOOR′*	Molar ratio (Ester:KOH)	Time/min	Method	Yield/%	mp (Ref. [7])/°C
26	Methyl *p*-bromophenoxyacetate	1:2	60	B	87	160–161 (160-1)
27	Methyl *p*-methylphenoxyacetate	1:2	60	B	87	153 (152)
28	Methyl *p*-chlorophenoxyacetate	1:2	60	B	82	158 (157)
29	Methyl α-naphthoate	1:2	60	B	87	162–163 (162)
30	Methyl 2-furoate	1:2	60	A	79	132–134 (132)
31	Methyl piperonoate	1:2	60	B	81	228–230 (229)
32	Methyl veratrate	1:3	60	A	94	181 (179–182)
33	Diethyl phthalate	1:4	5	B[c]	90	208–209 (210)
34	Di *n*-butyl phthalate	1:4	30	B[c]	84	208 (210)
35	Di *n*-octyl phthalate	1:4	60	B[c]	88	208 (210)
36	Diethyl oxalate	1:4	5	D	96	197 (198)[d]
37	Ethyl acetate	1:2	60[e]	D	87	136 (136)[d]
38	Methyl chloroacetate	1:2	60[e]	D	62	156 (160)[d]
39	Dimethyl adipate	1:4	60	D	67	160 (163)[d]
40	Cholesteryl acetate	1:2	60	A[f]	97	148–149 (148.5)
41	Methyl stearate	1:4	60	B	73	65 (67-8)
42	Methyl aleuritate	1:4	60	B	90	97 (100)

[a] Methanol used was 3 cm^3/g of ester; [b] acid obtained after washing with water; [c] a part of the acid was obtained as its S-benzylisothiouronium salt because of its partial solubility in water; [d] mp of the corresponding S-benzyl isothiouronium salt; [e] TLC could not be monitored and so it was worked up after 60 min; [f] isolated yield of cholesterol

Methanol is the solvent of choice for rapid hydrolysis of esters at ambient temperature. Methyl benzoate was also observed to undergo hydrolysis with KOH-ethanol and KOH-*n*-propanol, albeit in poorer yields. This could be due to the higher solubility of KOH in methanol compared to other protic solvents. The reactions were carried out using 3 cm^3 of methanol/g of ester. Higher dilution or temperatures below 35°C slowed the hydrolysis significantly. Hydrolysis attempted in polar aprotic solvents like acetonitrile, dioxane, *DMF*, *etc*. under identical conditions was very sluggish. Addition of water as co-solvent also affected the hydrolysis drastically and reactions were not complete even after 6 h at ~35°C.

Most esters of aromatic acids formed a solid lump within a few minutes of the reaction suggesting the formation of insoluble sodium salt of carboxylic acid unlike esters of aliphatic acids. The alcoholic portion of the ester was also varied in order to study the generality of the reaction. It was observed that methyl esters are most readily hydrolyzed and increasing bulk of the alkyl group requires longer reaction times. Esters of aromatic acids gave clean hydrolysis products unlike esters of aliphatic acids having α-hydrogens probably due to competing aldol type condensations. It was also observed that aromatic esters with electron withdrawing groups underwent hydrolysis faster than those containing electron releasing groups in accordance with *Hammett* equation. Hydrolysis was very sluggish in case of esters containing acidic protons (*e.g*., methyl salicylate, methyl *p*-hydroxybenzoate, diethyl malonate, and ethyl acetoacetate) and a large amount of starting material was recovered unchanged obviously due to the formation of stabilized anions. This method helps to save time and energy to achieve the desired goals.

Experimental

Potassium hydroxide (Qualigens) and methanol (SD Fine) were used. The esters obtained from commercial sources were distilled/recrystallized before use and others were prepared by known procedures. The IR spectra were recorded on a Perkin Elmer FT-IR and NMR spectra were recorded on a FT-NMR model R-600 (60 MHz) with TMS as internal standard.

General Procedure

In a typical experiment, 1 g of ester and 3 cm^3 of methanol were placed in a 25 cm^3 round-bottomed flask mounted over a magnetic stirrer and maintained at ~35°C. KOH (see Table 1) was added and the contents were stirred. The reactions were quenched invariably after 60 min by addition of 10 cm^3 of water. Unreacted ester, if any, was removed by ether extraction (2×5 cm^3) and the carboxylic acid was recovered by one of the methods given below. The carboxylic acids were characterized by their mp, mixed mp, and NMR spectra.

Method A: The aqueous portion was acidified to $pH = 2$ with 6 *N* hydrochloric acid and extracted with ether (3×5 cm^3). The combined ether extracts were dried with Na_2SO_4 and concentrated on a *Buechi* rotavapor. The carboxylic acid was obtained after drying under vacuum.

Method B: The aqueous portion was acidified to $pH = 2$ with 6 *N* hydrochloric acid. The carboxylic acid precipitated on standing, was filtered off, and dried under vacuum.

Method C: The aqueous portion was acidified to $pH = 2$ with 6 *N* hydrochloric acid and treated with aq. sodium bicarbonate solution (~5%) with stirring till basic to litmus. The phenol was removed by extraction with ether (2×5 cm^3). The aqueous layer was acidified with 6 *N* hydrochloric acid and the acid was extracted with ether (3×5 cm^3). The combined ether extracts were dried with Na_2SO_4 and concentrated on a *Buechi* rotavapor. The carboxylic acid was obtained after drying under vacuum.

Method D: The aqueous portion was acidified to $pH = 2$ with 6 *N* hydrochloric acid and treated with aq. sodium bicarbonate solution (~5%) with stirring till basic to litmus. A saturated solution of S-benzyl isothiouronium chloride was added and the carboxylic acid was recovered as S-benzyl isothiouronium salt from the solution.

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