

Mild and Versatile Potassium Fluoride/Tetrabutylammonium Fluoride Protocol for Ester Hydrolysis

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A mild and versatile protocol of potassium fluoride/tetrabutylammonium fluoride (KF/TBAF) in aqueous tetrahydrofuran for ester hydrolysis has been developed. The method is applied on variety of aliphatic and aromatic ester moieties bearing acid or base sensitive functional groups. The conditions have been also applied on acetates to yield alcohols. The chirality of optically pure esters remained intact with the conditions of the reaction.

Keywords: Carboxylic acids, Esters, Hydrolysis, Potassium fluoride, Tetrabutylammonium bromide.

INTRODUCTION

The functional group transformations play an important role to change the properties of the organic compounds and to utilize them for various applications from medical to material world. In the way, the success of the transformation is achieved when the other sensitive functional groups present in the substrates are unaffected. The hydrolysis of ester is an important conversion, which leads to variety of carboxylic acid derivatives. The carboxylic acid functional groups are found in many bioactive natural and synthetic organic compounds. Generally this conversion is being accomplished either by acidic [1] or alkaline [2] reagents and the reaction mechanism is well studied theoretically [3,4]. The drawback of these reaction conditions are seen when the substrates are holding other sensitive functional groups. In this view, various methods were developed for the ester hydrolysis viz., solid acids (e.g. zirconium phosphate), acidic ion-exchange resins (e.g. amberlite and zeolite) and even lipid-coated lipases [5]. Ishihara *et al.* [6] reported micelle-type *N,N*-diarylammonium pyrosulfate catalyst for the hydrolysis of various esters. But the reagents used by them are not easily available and expensive chemicals are needed for the preparation of the same.

The hydrolysis conditions reported in this communication are mild, high yielding and performed under neutral conditions with commercially available reagents. Further, the chiral centres of the optically pure esters are unaffected under the reaction conditions.

EXPERIMENTAL

Benzothiazolinone was purchased from Sigma-Aldrich. The solvents used in the synthesis were distilled before use. All other chemicals were of AR grade and were used without further purification. All melting points were obtained on Elico instrument, India (model MP96) and are uncorrected. NMR spectra were recorded on Bruker Top Spin Instrument. IR spectra were recorded using Bruker Alpha T OPUS instrument

Synthetic procedure for compound 4: To a solution of compound **3** (227 mg, 1 mmol) in DMF (5 mL) was added K_2CO_3 (276 mg, 2.0 mmol) followed by ethyl bromo acetate (167 mg, 1.1 mmol) and the resultant suspension was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with water (3×30 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude product which was triturated with hexane to give a off white coloured solid (300 mg, 0.96 mmol); m.p. 49-53 °C; 1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.29 (s, 1H), 7.14 (d, $J = 8.1$ Hz, 1H), 6.83 (d, $J = 8.1$ Hz, 1H), 4.66 (s, 2H), 4.24 (q, $J = 7.2$, 2H), 3.52 (t, $J = 6.3$, 1H), 3.39 (t, $J = 6.3$, 1H), 2.81 (t, $J = 7.2$ Hz, 2H), 2.22-2.01 (m, 2H), 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm): 167.1, 162.9, 136.5, 135.1, 126.9, 122.8, 122.6, 110.3, 62.2, 44.0, 43.6, 34.2, 32.3, 14.2; ESI-MS ($M+1$) = 314.

General procedure for ester and acetate hydrolysis: To a solution of ester or acetate (1 mmol) in THF (5 mL) was added alkali metal fluoride (2 mmol) followed by quaternary

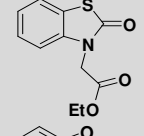
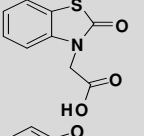
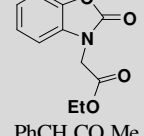
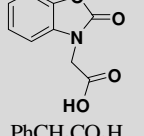
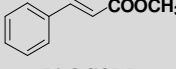
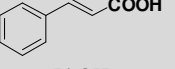
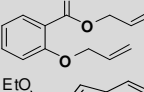
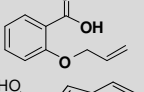
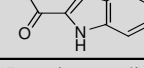
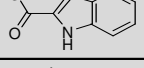
ammonium salt (1 M in THF, 2 mL) and the resultant solution was stirred for 7 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (2 × 20 mL) followed by brine solution (20 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure to get a crude compound, which was triturated with hexane to get the corresponding product in 60-95 % yield.

Compound 6: Off white solid, m.p. 166-169 °C; ¹H NMR (CD₃OD, 300 MHz): δ (ppm) 7.42 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.69 (s, 2H), 3.54 (t, *J* = 6.3, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.12-2.02 (m, 2H); ¹³C NMR (CD₃OD, 75 MHz): δ (ppm): 172.2, 162.7, 136.6, 135.3, 126.5, 122.8, 122.3, 110.2, 45.9, 43.6, 32.1, 31.7; ESI-*m/z* (M+1) = 286.

RESULTS AND DISCUSSION

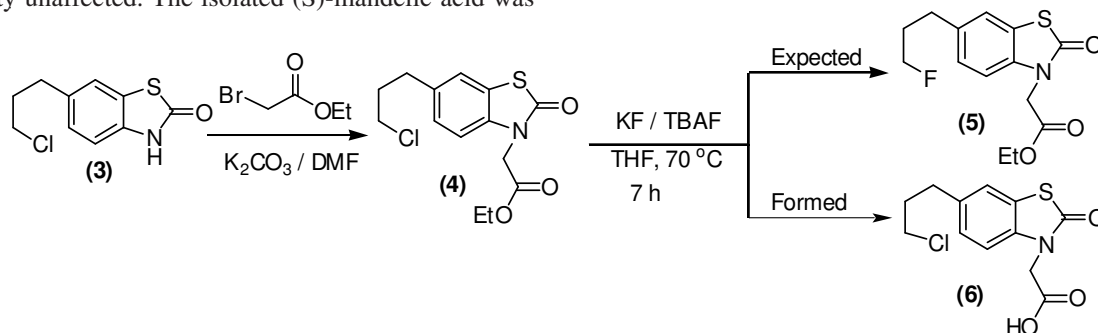
The initial aim was to synthesize the fluoro compound **5** (**Scheme-I**) and to utilize the further modified derivatives for PET studies [6]. The chloro compound **3** was synthesized using a known procedure [7]. The same compound **3** was N-alkylated with ethyl bromo acetate to form compound **4** which was confirmed by its ¹H NMR spectrum which showed the corresponding N-CH₂ peak at δ 4.6 ppm as a singlet for two protons and the corresponding ester peaks at δ 4.25 as a quartet for -CH₂ and at δ 1.27 as a triplet for -CH₃ protons. When the fluorination reaction was performed on **4** using KF/TBAF in THF under refluxing conditions a more polar spot was observed on TLC. After completion of the reaction the compound was isolated and ¹H NMR spectrum of the same showed the absence of ethyl signals for the ester group. The CH₂Cl peaks of **3** at 3.5 ppm were not disappeared in the spectrum, which indicated the presence of CH₂Cl functionality as such under the reaction conditions. When the same reaction was performed for 15 h, a mixture of chloro and fluoro acid compounds with 3 to 2 of respective ratio was observed.

The same conditions including 2 eq. of water were applied on various aliphatic and aromatic ester moieties (Table-1) and to the surprise the hydrolysis was observed in all the reactions and the carboxylic acids were formed about 70-95 % yield. Then the conditions were applied to de protect acetate group of phenol and 2-naphthol. The reaction was yielded free phenol and 2-naphthol in 62 and 64 % yield, respectively. Further the conditions were applied on optically pure methyl-(S)-mandelate of optical rotation [α]_D+144°, (*c* = 1 in methanol) and on *N*-(*tert*-butoxycarbonyl)-L-phenylalanine methyl ester of optical rotation [α]_D-4°, (*c* = 2 in methanol). The two optically active esters afforded the corresponding carboxylic acids with the chirality unaffected. The isolated (S)-mandelic acid was

$R_1-C(=O)OR_2 \xrightarrow[7h]{THF, 70^\circ C} R_1-C(=O)OH + R_2OH$			
Entry	Ester	Carboxylic acid	Yield (%)
a	<i>p</i> -NO ₂ -PhCO ₂ Me	<i>p</i> -NO ₂ -PhCO ₂ H	93
b	<i>p</i> -OMe-PhCO ₂ Me	<i>p</i> -OMe-PhCO ₂ H	95
c			81
d			84
e	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ H	90
f			81
g	PhOCOMe	PhOH	71
h	2-Naphthyl-OCOMe	2-Naphthyl-OH	73
i	(S)-PhCH(OH)COOMe	(S)-PhCH(OH)COOH	72
j	L-PhCH(NHBOC)COOMe	L-PhCH(NHBOC)COOH	70
k	<i>trans</i> -2-Octenoic methylester	<i>trans</i> -2-Octenoic acid	90
l	<i>p</i> -NO ₂ -PhCO ₂ Bn	<i>p</i> -NO ₂ -PhCO ₂ H	86
m			88
14			76

Ph = Phenyl, Reaction conditions: All the reactions were performed on 0.5 mmol scale with 2 eq. potassium fluoride, 2 eq. of tetrabutylammonium fluoride, 2 eq. of H₂O in 0.2 M THF

shown optical rotation of [α]_D+140°, (*c* = 2.0 in water) and that of *N*-(*tert*-butoxycarbonyl)-L-phenylalanine was shown [α]_D+25°, (*c* = 2.0 in methanol). The esters (**7a**, **7b**, **7e**, **7f**, **7g**, **7h**, **7i**, **7j**, **7k** and **7l**) and the carboxylic acids (**8a**, **8b**, **8e**, **8f**, **8g**, **8h**, **8i**, **8j**, **8k** and **8l**) mentioned in the Table-1 are commercially known compounds and are confirmed by matching with the authentic compounds. The esters **7c**, **7d**, **7m**, **7n**, **7o** and the carboxylic acids **8c**, **8d**, **8m**, **8n**, **8o** are reported in the literature [8-16] and are confirmed by matching the analytical data with the authentic compounds.



Scheme-I: Unexpected hydrolysis of ester derivative

Further the reaction was tried on *p*-nitromethyl benzoate (**7a**) in different solvents (Table-2) and the solvent THF was found the best in terms of time and yield of the reaction. The hydrolysis reaction was performed on *p*-nitromethyl benzoate (**7a**) using other potassium halides under standardized conditions (Table-3). After 7 h the reaction with KCl/TBAF and KBr/TBAF was shown only 15-20 % conversion. The prolonged reaction times upto 24 h did not increase more than a 5 % further conversion. The reaction with KI/TBAF was still slow and showed only 8-10 % conversion after 7 h. The reaction was performed with TBAB, TBAI quaternary ammonium salts using potassium fluoride as alkali metal salt in aq. THF. But the reactions showed no formation of trace of corresponding carboxylic acids.

TABLE-2
HYDROLYSIS REACTION IN DIFFERENT SOLVENTS

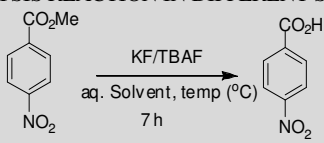
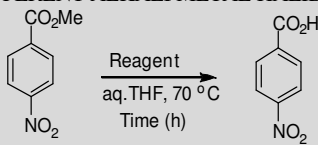
		
Solvent	Temperature (°C)	Yield (%)
Benzene	Reflux	10
MeCN	80	25
DCM	40	20
DMF	100	Trace
DMSO	100	Trace
EtOH	70	No reaction
THF	70	93

TABLE-3
HYDROLYSIS REACTION UNDER
DIFFERENT ALKALI METAL HALIDES

			
Entry	Reagent	Time (h)	Yield (%)
1	KCl/TBAF	7	17
2	KBr/TBAF	7	15
3	KCl/TBAF	24	23
4	KBr/TBAF	24	21
5	KI/TBAF	7	9
6	KI/TBAF	24	10
7	KF/TBAB	24	0
8	KF/TBAI	24	0
9	KI/TBAI	24	0
10	KBr/TBAI	24	0
11	CsF/TBAF	30	68
12	LiF/TBAF	2	40
13	NaF/TBAF	4	48

The combination of KI/TBAI, KBr/TBAB in THF was also tried but the reaction did not show any hydrolysis reaction. Further the hydrolysis reactions were tried with other alkali metal fluorides. The reaction with CsF was very slow and took 30 h to complete. The reaction with LiF was very fast and the ester was consumed on TLC within 2 h of time but the isolated yield was only 40 % of acid along with 50 % of the regenerated ester. The same reaction with NaF was comparatively slower than LiF which took almost 4 h to consume the ester and the isolated yield was around 48 % along with 50 % of the regenerated ester. Therefore,

the reactivity and yields are found to be in the order of LiF > NaF > KF > CsF and KF > CsF > NaF > LiF, respectively. The mechanistic studies and the ester hydrolysis reactions with alkaline earth metal halides and transition metal salts are in progress.

Conclusion

A mild and versatile method for ester hydrolysis is disclosed. Under the optimized conditions, diverse esters have undergone the hydrolysis reactions to yield the corresponding carboxylic acids. The KF/TBAF combination is found as a best combination for ester hydrolysis reaction in terms of time, mildness and yield of the reaction. LiF and NaF were comparatively more reactive but the yield of the product was less compared to potassium fluoride. CsF needed prolonged times for ester hydrolysis. The acetate functionalities have also been undergone hydrolysis reaction to yield corresponding phenols. Under the reaction conditions, the chirality of the optically pure esters remain intact. The trial reactions with alkaline earth metal fluorides and transition metal fluorides are ongoing.

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