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LETTERS

Esterification of carboxylic acids catalyzed by in situ generated tetraalkylammonium fluorides

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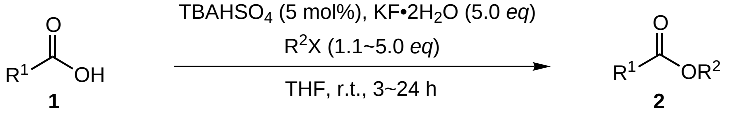
Abstract—Esterification of carboxylic acids with alkyl halides can be efficiently catalyzed by tetrabutylammonium fluoride (TBAF) generated in situ from tetrabutylammonium hydrogensulfate ($TBAHSO_4$) and $KF·2H_2O$ in THF. The general applicability and the characteristic feature of this approach has been amply demonstrated. © 2001 Elsevier Science Ltd. All rights reserved.

Undoubtedly, esterification of carboxylic acids by reaction with alkyl halides represents a fundamental and often encountered transformation in organic synthesis,[1] and a number of useful procedures using metal halides[2] and carbonates[3] have been introduced. Our recent contribution to this subject is the facile conversion of trialkylsilyl esters to the corresponding alkyl esters with commercially available tetrabutylammonium fluoride trihydrate ($TBAF·3H_2O$) by taking advantage of the high affinity of the fluoride ion toward the silicon atom.[4] However, preparation of silyl esters and the use of a stoichiometric amount of highly hygroscopic $TBAF·3H_2O$ with careful handling turned out to be an inevitable drawback. Quite recently, we disclosed that desired quaternary ammonium fluoride can be efficiently generated in situ from the corresponding hydrogensulfate and potassium fluoride dihydrate ($KF·2H_2O$) in THF,[5] which led us to investigate the possibility of direct esterification of carboxylic acids with catalytic, in situ prepared TBAF, taking the basic character of the fluoride ion into account.[6] Herein we wish to report an efficient esterification of carboxylic acids with alkyl halides catalyzed by TBAF generated under solid–liquid phase-transfer conditions (Scheme 1).

Initial treatment of tetrabutylammonium hydrogensulfate ($TBAHSO_4$) (10 mol%) with $KF·2H_2O$ (5 equiv.) in THF at room temperature for 1 h and subsequent addition of 3-phenylpropionic acid [**1a**, $R^1=Ph(CH_2)_2$] and benzyl bromide ($R^2=PhCH_2$) with continuous stirring for 3 h gave rise to the corresponding benzyl ester **2a** [$R^1=Ph(CH_2)_2$, $R^2=PhCH_2$] quantitatively.[7] Further, we found that the premixing of $TBAHSO_4$ and $KF·2H_2O$ was not necessarily required in this reaction, and that a catalytic amount of $TBAHSO_4$ could be reduced to 5 mol% with no sign of the reactivity decrease (entry 1 in Table 1), which simplifies the operation of the present direct esterification procedure without TBAF itself.[8,9] It should be added that the esterification did not proceed at all in the absence of either $TBAHSO_4$ or $KF·2H_2O$ under otherwise identical conditions, as included in Table 1 (entries 2 and 3).

Table 1, which summarizes the results with a wide variety of carboxylic acids and alkyl halides, shows that the desired esters were generally obtained in excellent isolated yields. Not only reactive alkyl halides such as allyl and propargyl bromides but simple aliphatic halides can be employed as an electrophile as also demonstrated in the reaction of **1a** (entries 4–9). The catalytic esterification of *sec*- and *tert*-alkylcarboxylic acids proceeded smoothly (entries 12–14). Notably, even triphenylacetic acid and 1-adamantanecarboxylic



Scheme 1.

Keywords: esterification; phase transfer; potassium fluoride dihydrate; tetraalkylammonium hydrogensulfate.

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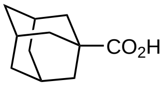
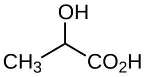
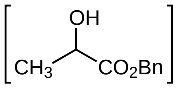
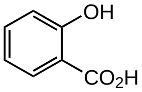
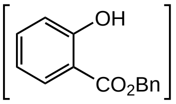
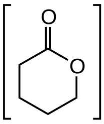
Table 1. In situ generated TBAF-catalyzed esterification of carboxylic acids[a]

Entry	R^1CO_2H, **1**	R^2X	React. time (h)	Yield of **2**[b] (%)
1	$Ph(CH_2)_2CO_2H$ (**1a**)	$PhCH_2Br$	3	99
2			12	N.r.[c,d]
3			12	N.r.[c,e]
4		$CH_2{=}CHCH_2Br$	3	88
5		*trans*-$PhCH{=}CHCH_2Br$	3	99
6		$CH\equiv CCH_2Br$	3	99
7		EtBr	3	97[f]
8		BuBr	6	99[f]
9		*i*-PrBr	6	77[f,g] (99)[f,g,h]
10	$CH_3(CH_2)_7CO_2H$	$PhCH_2Br$	3	99
11		BuBr	6	99[f]
12	*c*-$C_6H_{11}CO_2H$	$PhCH_2Br$	3	99
13		EtBr	3	93[f]
14	*t*-$BuCO_2H$	$PhCH_2Br$	3	98
15	Ph_3CCO_2H	$PhCH_2Br$	3	99
16		EtBr	3	99[f]
17		$PhCH_2Br$	3	99
18		$CH_2{=}CHCH_2Br$	3	99
19		BuBr	3	99[f]
20		*i*-PrBr	24	71[f] (99)[f,g]
21	$PhCO_2H$	$PhCH_2Br$	3	99
22		$CH_2{=}CHCH_2Br$	3	99
23		BuBr	3	88[f]
24	*trans*-$EtCH{=}CHCO_2H$	$PhCH_2Br$	3	96
25		BuBr	6	86[f]
26	*trans*-$PhCH{=}CHCO_2H$	$PhCH_2Br$	6	85
27	$PhC\equiv CCO_2H$	$PhCH_2Br$	3	99
28		EtBr	3	91[f]
29	$CH_3O_2C(CH_2)_5CO_2H$	$PhCH_2Br$	3	96
30		BuBr	6	97[f]
31		$PhCH_2Br$	24	51 
32		$PhCH_2Br$	24	80 
33	$Br(CH_2)_4CO_2H$		5	96 

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[a] Unless otherwise specified, the reaction was carried out in dry THF (0.5 M) with $TBAHSO_4$ (5 mol%), $KF{\cdot}2H_2O$ (5 equiv.) and 1.1 equiv. of alkyl halides at room temperature.

[b] Isolated yield.

[c] N.r. = no reaction.

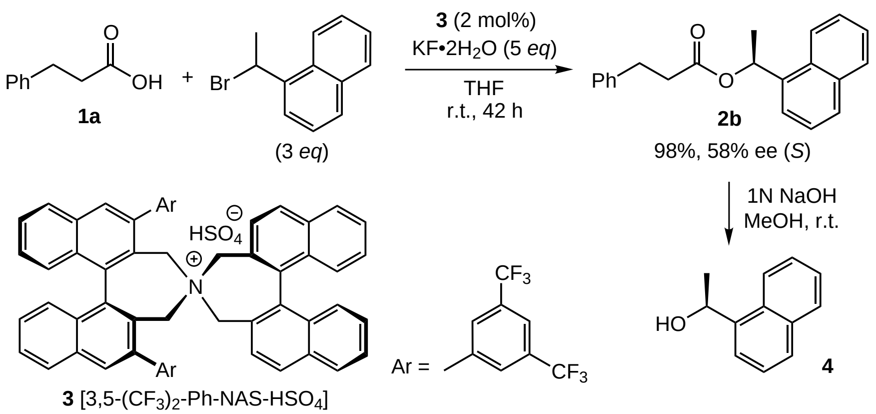
[d] In the absence of $TBAHSO_4$.

[e] Without $KF{\cdot}2H_2O$.

[f] Use of 5 equiv. of alkyl halide.

[g] At 55°C.

[h] Stirring for 12 h.



Scheme 2.

acid can be efficiently transformed into the corresponding primary esters, despite their steric bulkiness (entries 15–20). Aromatic as well as α,β-unsaturated carboxylic acids including phenylpropiolic acid were found to be good candidates for the present method, giving the desired product in high yields (entries 21–28). The synthetic utility of this procedure was further exemplified by the facile conversion of adipic acid monomethyl ester to the corresponding unsymmetrical ester (entries 29 and 30). Moreover, selective transformation of carboxylic acids possessing hydroxy functionality appeared feasible to produce the corresponding hydroxy esters, though a certain decrease of the chemical yield was observed (entries 31 and 32). As expected from our previous study, 5-bromovaleric acid, upon exposure to the standard reaction conditions, afforded δ-valerolactone in 96% yield (entry 33).

The distinct advantage of our approach over the ordinary metal fluoride-mediated esterification is highlighted by the facile preparation of optically active esters via alkylative kinetic resolution of *sec*-alkyl halides using in situ generated chiral ammonium fluorides as catalyst. For instance, simple stirring of the mixture of **1a**, 1-(1-bromoethyl)naphthalene [$R^2 = 1\text{-Np}(CH_3)CH$], C_2-symmetric chiral quaternary ammonium hydrogensulfate **3** (2 mol%)[5] and $KF{\cdot}2H_2O$ (5 equiv.) in THF at room temperature for 42 h afforded the desired ester **2b** [$R^1 = Ph(CH_2)_2$, $R^2 = 1\text{-Np}(CH_3)CH$] in 98% yield with 58% ee,[10] from which enantioenriched *sec*-alcohol **4** was readily obtained by basic hydrolysis as shown in Scheme 2.

Acknowledgements

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7. After the reaction of the in situ formed ammonium carboxylates with alkyl bromides, the resulting tetrabutylammonium bromide (TBAB) would be converted into TBAF by the anion exchange with the excess potassium fluoride, establishing the catalytic cycle.
8. Use of catalytic $TBAF{\cdot}3H_2O$ (5 mol%) and $KF{\cdot}2H_2O$ (5 equiv.) in the reaction of **1a** with benzyl bromide brought a slight decrease of the chemical yield of **2a** (94%). The carboxylic ester **2a** was obtained in only 2% yield, when the reaction was simply performed with 5 mol% of $TBAF{\cdot}3H_2O$ as a catalyst.
9. A typical experimental procedure is as follows. Tetrabutylammonium hydrogensulfate (8.7 mg, 0.025 mmol) and potassium fluoride dihydrate (purchased from Kanto Chemical Co., Ltd., 240 mg, 2.5 mmol) were placed in a two-neck flask with a stirring bar under argon and dried in vacuo (0.6 mmHg) for 10 min.[11] After being flushed back with argon, freshly distilled THF (1 mL) was introduced. Then, 3-phenylpropionic acid (**1a**, 76.6 mg, 0.5 mmol) and benzyl bromide (66.8 μL, 0.55 mmol) were added sequentially at room temperature. After being stirred for 3 h at room temperature, the resulting reaction mixture was poured into water (5 mL) and extracted with ether (10 mL×2). The combined organic extracts were

washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (hexane/ether = 10:1 as eluant) gave pure benzyl ester **2a** (120 mg, 99% yield) as a colorless oil (entry 1 in Table 1).

10. Absolute configuration was determined by comparison of the optical rotation of **4** with the value of commercially available (*R*)-(+)-α-methyl-1-naphthalenemethanol.
11. Attempted esterification of **1a** with benzyl bromide using anhydrous KF gave **2a** in only 9% yield, suggesting the importance of *omega phase* [KF(nH_2O)] for facile anion exchange. See: Ref. 5.