RAPID PAPER

Simple and Convenient Synthesis of Esters from Carboxylic Acids and Alkyl Halides Using Tetrabutylammonium Fluoride

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Abstract: A simple and convenient method has been developed for the synthesis of esters from the corresponding carboxylic acids and alkyl halides by using a stoichiometric amount of tetrabutylammonium fluoride (Bu_4NF) as the base. The reaction of carboxylic acids and a Bu_4NF /THF solution in DMF or THF as the solvent generates carboxylate ions in situ. The carboxylate ions thus generated and accumulated are highly reactive. They are then allowed to react with alkyl halides as the electrophiles, and afford the corresponding esters in moderate to good yields. The reaction without Bu_4NF does not afford any product; therefore, Bu_4NF seems to play an important role as the base in these reactions. A bulky counteranion such as the tetrabutylammonium cation seems to increase the reactivity of the carboxylate ions in the solution phase.

Key words: tetrabutylammonium fluoride, base, deprotonation, carboxylate ion, esterification

1 INTRODUCTION

Esters are one of the most important functional groups in organic chemistry, and are present in several organic compounds such as biologically active molecules and compounds relevant to materials chemistry. For ester synthesis, condensation reactions have mainly been employed, in which carboxylic acids and alcohols are combined in the presence of acid catalysts such as Brønsted acids. In addition, efficient esterification methods have been developed using orthoesters, condensation reagents such as N,N' -dicyclohexylcarbodiimide, N,N' -diisopropylcarbodiimide, and diazomethane¹⁻⁴⁾.

A more straightforward method involving the reaction of carboxylate ions and alkyl halides via an $\text{S}_{\text{N}}2$ mechanism seems to be an attractive procedure for constructing ester groups⁵⁻²⁰⁾. Maruoka and co-workers reported that the reaction of trialkylsilyl esters and alkyl halides in the presence of $\text{Bu}_4\text{NF} \cdot \text{H}_2\text{O}$ affords the corresponding esters, owing to the affinity of the fluoride ion (derived from

Bu_4NF) for the silicon atom^{21, 22)}. Although the resulting ammonium carboxylates²³⁻³⁰⁾ seem to be attractive from the viewpoint of reactivity, this protocol involves an additional step of preparing the trialkylsilyl esters from the carboxylic acids. These authors also demonstrated the esterification of carboxylic acids and alkyl halides using Bu_4NF generated in situ from $\text{KF} \cdot 2\text{H}_2\text{O}$ and a catalytic amount of Bu_4NHSO_4 under solid-liquid phase-transfer conditions³¹⁾. The reaction yields are high and the procedure is simple, but a long reaction time (3-24 h) and an excess amount of $\text{KF} \cdot 2\text{H}_2\text{O}$ are required.

To the best of our knowledge, the esterification of carboxylic acids and alkyl halides using a stoichiometric amount of Bu_4NF as a base has not been reported. Herein, we demonstrate that a stoichiometric amount of Bu_4NF serves as a useful base in the deprotonation of the carboxylic acids, and the ammonium carboxylates thus generated can react with alkyl halides to afford the corresponding esters in good yields (Scheme 1). This procedure shortens

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Scheme 1 Esterification of carboxylic acids and alkyl halides using a stoichiometric amount of Bu_4NF .

the reaction time required, and simplifies and facilitates the synthesis of various esters.

2 EXPERIMENTAL PROCEDURES

2.1 General Remarks

^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Varian MERCURY 300 (^1H , 300 MHz; ^{13}C , 75 MHz) or JEOL-AL 400 (^1H , 400 MHz; ^{13}C , 100 MHz) spectrometer with Me_4Si as an internal standard unless otherwise noted. Mass spectra were obtained on JEOL JMS SX-102A (EI) and Thermo Fisher Scientific EXACTIVE (APCI and ESI) mass spectrometers. Thin-layer chromatography (TLC) was performed by using Merck precoated silica gel F254 plates (thickness 0.25 mm). Flash chromatography was carried out on a column of silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). Preparative gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-9201 instrument equipped with JAIGEL-1H and JAIGEL-2H, using CHCl_3 as an eluent. All reactions were carried out under a nitrogen atmosphere unless otherwise noted.

2.2 Materials

Unless otherwise noted, all materials, including dry THF, dry DMF, carboxylic acids, alkyl halides, and Bu_4NF (1.0 M in THF), were obtained from commercial suppliers and used without further purification.

2.3 Reaction of carboxylic acid and alkyl halide

Typical procedure for the reaction of benzoic acid (**1**) and *n*-butyl iodide (*n*-BuI) using Bu_4NF (1.0 M in THF) solution. *n*-Butyl benzoate (**2**) (condition A): Bu_4NF (1.0 M in THF, 1.2 mL, 1.2 mmol) was added at room temperature to a solution of benzoic acid (**1**, 121.9 mg, 1.0 mmol) in DMF (1.0 mL), and the mixture was stirred for 20 min. Then, the solution was allowed to react with *n*-butyl iodide (*n*-BuI) (281.6 mg, 1.5 mmol) for 60 min at the same temperature. Subsequently, water (5.0 mL) was added to the resulting solution, and the aqueous phase was extracted with Et_2O (15 mL $\times$ 3). The combined organic extracts were washed with saturated aqueous NaCl solution (20 mL) and dried over Na_2SO_4 . After removal of the solvent, the resulting crude product was purified by flash chromatography (hexane/ EtOAc 20:1) to obtain *n*-butyl benzoate (**2**) (99.7

mg, 0.56 mmol, 56%). The product was identified through the comparison of its spectral data with that of reported literature³².

2.4 Spectroscopic data

Isopropyl nonanoate (**10**)

^1H NMR (300 MHz, CDCl_3) δ 0.88 (t, J = 6.6 Hz, 3H), 1.23 (d, J = 6.3 Hz, 6H), 1.24–1.36 (m, 9H), 1.54–1.66 (m, 2H), 2.26 (t, J = 7.5 Hz, 2H), 5.00 (septet, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.1, 21.8, 22.6, 25.0, 29.1, 29.2, 31.8, 34.7, 67.3, 173.5 (The one signal in ^{13}C NMR might be overlapping. See also the supporting information of ref 33); LRMS (APCI) m/z 201 (M^+ + H); HRMS (APCI) calcd for $\text{C}_{12}\text{H}_{25}\text{O}_2$ (M^+ + H) 201.1849, found 201.1848.

Isopropyl cinnamate (**12**)

^1H NMR (400 MHz, CDCl_3) δ 1.32 (d, J = 6.3 Hz, 6H), 5.14 (septet, J = 6.3 Hz, 1H), 6.41 (d, J = 16.1 Hz, 1H), 7.35–7.41 (m, 3H), 7.48–7.55 (m, 2H), 7.66 (d, J = 16.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 67.8, 118.8, 128.0, 128.8, 130.1, 134.5, 144.3, 166.5; LRMS (EI) m/z 190 (M^+), 131 (M^+ – $\text{C}_3\text{H}_7\text{O}$); HRMS (EI) calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ (M^+) 190.0994, found 190.0999.

(*E*)-Isopropyl 3-(4-methoxyphenyl)acrylate (**15**)

^1H NMR (400 MHz, CDCl_3) δ 1.30 (d, J = 6.3 Hz, 6H), 5.13 (septet, J = 6.3 Hz, 1H), 6.28 (d, J = 15.9 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 55.3, 67.5, 114.3, 116.3, 127.3, 129.6, 143.9, 161.3, 166.8; LRMS (EI) m/z 220 (M^+), 161 (M^+ – $\text{C}_3\text{H}_7\text{O}$); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ (M^+) 220.1099, found 220.1103.

(*E*)-Isopropyl 3-(3-methoxyphenyl)acrylate (**17**)

^1H NMR (400 MHz, CDCl_3) δ 1.31 (d, J = 6.3 Hz, 6H), 5.14 (septet, J = 6.3 Hz, 1H), 6.40 (d, J = 16.1 Hz, 1H), 6.92 (dd, J = 8.3, 2.0 Hz, 1H), 7.04 (t, J = 2.0 Hz, 1H), 7.11 (dd, J = 8.3, 0.5 Hz, 1H), 7.29 (t, J = 8.3 Hz, 1H), 7.63 (d, J = 16.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9, 55.2, 67.8, 112.8, 116.0, 119.1, 120.7, 129.8, 135.9, 144.2, 159.9, 166.4; LRMS (EI) m/z 220 (M^+), 161 (M^+ – $\text{C}_3\text{H}_7\text{O}$); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ (M^+) 220.1099, found 220.1094.

Isopropyl 1-naphthoate (**19**)

^1H NMR (400 MHz, CDCl_3) δ 1.44 (d, J = 6.3 Hz, 6H), 5.37 (septet, J = 6.3 Hz, 1H), 7.48 (t, J = 7.1 Hz, 1H), 7.51 (t, J = 7.1 Hz, 1H), 7.60 (t, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 7.1 Hz, 1H), 8.88 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.0, 68.5, 124.5, 125.8, 126.1, 127.6, 128.0, 128.5, 129.8, 131.3, 133.0,

133.8, 167.2; LRMS (EI) m/z 214 (M^+), 155 ($M^+ - C_3H_7O$); HRMS (EI) calcd for $C_{14}H_{14}O_2$ (M^+) 214.0994, found 214.0995.

Isopropyl 2-(4-methylbenzoyl) benzoate (**21**)

1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, $J=6.1$ Hz, 6H), 2.40 (s, 3H), 4.99 (septet, $J=6.1$ Hz, 1H), 7.22 (d, $J=8.0$ Hz, 2H), 7.35 (d, $J=7.6$ Hz, 1H), 7.54 (t, $J=7.6$ Hz, 1H), 7.61 (t, $J=7.6$ Hz, 1H), 7.66 (d, $J=8.0$ Hz, 1H), 8.06 (d, $J=7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.6, 69.4, 127.5, 129.1, 129.3, 129.6, 129.7, 130.1, 132.1, 134.8, 141.8, 143.9, 165.4, 196.6; LRMS (EI) m/z 282 (M^+), 223 ($M^+ - C_3H_7O$); HRMS (EI) calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256, found 282.1252.

(*E*)-Diphenethyl hex-3-enedioate (**23**)

1H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, $J=7.1$ Hz, 4H), 3.05 (d, $J=5.1$ Hz, 4H), 4.30 (t, $J=7.1$ Hz, 4H), 5.60-5.66 (m, 2H), 7.18-7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0, 37.8, 65.1, 76.7, 125.9, 126.5, 128.5, 128.9, 137.7, 171.4; LRMS (APCI) m/z 353 ($M^+ + H$); HRMS (APCI) calcd for $C_{22}H_{26}O_4$ ($M^+ + H$) 353.1747, found 353.1736.

Other compounds such as methyl benzoate (**3**)³², *n*-octyl benzoate (**4**)³², isopropyl benzoate (**5**)³⁴, *n*-butyl 3-phenylpropanoate (**7**)³⁵, and isopropyl 3-phenylpropanoate (**8**)³⁶, were identified through the comparison of its spectral data with those of reported literatures.

3 RESULTS AND DISCUSSION

In preliminary studies, we examined the reaction of benzoic acid (**1**) with 1.5 equivalents of *n*-butyl iodide (*n*-BuI) in DMF using 1.2 equivalents of Bu_4NF (1.0 M in THF) (Table 1, condition A). The usual workup procedure and flash column chromatography afforded the corresponding ester (*n*-butyl benzoate (**2**)) in 56% yield as shown in Table 1 (only the isolated yields of esters are listed; the conversions were not determined). In contrast, in the absence of Bu_4NF , no product was obtained from the reaction of **1** and *n*-BuI, indicating that Bu_4NF is essential for the esterification of carboxylic acids with alkyl halides. Therefore, it is concluded that Bu_4NF itself plays two important roles in this esterification: first, the F^- anion derived from Bu_4NF serves as an effective base for the deprotonation of the carboxylic acid; and second, the resulting Bu_4N^+ carboxylates are partially soluble in organic media; therefore, the reaction of the carboxylates with alkyl halides via the S_N2 mechanism would be accelerated^{21, 23, 31}. Other alkyl halides such as *n*-butyl bromide (*n*-BuBr), methyl iodide (MeI), *n*-octyl iodide (*n*-OctI), and isopropyl iodide (*i*-PrI) were also used for the esterification of benzoic acid to afford the corresponding products (**2**, **3**, **4**, and **5**) in 42%, 44%, 68%, and 32% yields, respectively.

The esterification reactions of other carboxylic acids

were also examined under condition A. As shown in Table 1, 3-phenylpropanoic acid (**6**) was treated with *n*-BuI and *i*-PrI to form **7** and **8**, respectively. In addition, nonanoic acid (**9**), cinnamic acid (**11**), (*E*)-3-(4-methoxyphenyl) acrylic acid (**14**), (*E*)-3-(3-methoxyphenyl) acrylic acid (**16**), and 1-naphthoic acid (**18**) afforded the corresponding esters **10**, **12**, **15**, **17**, and **19**, respectively, in moderate yields; however, the reaction of **11** with 2-chlorobutane did not proceed at all, presumably because of the low reactivity of 2-chlorobutane. It is noteworthy that the reaction of 2-(4-methylbenzoyl) benzoic acid (**20**) afforded the corresponding ester **21** in 55% yield, and that the fluoride ion did not attack the carbonyl group.

We suspected that the first step of this esterification, that is, the deprotonation of the acid, would be rate-controlling, because the longer reaction time of **1** afforded a higher yield of **2** (74% yield, Table 1, condition A). Therefore, we modified the reaction conditions in order to accelerate the reactions, and used two equivalents of Bu_4NF (1.0 M in THF) and three equivalents of the alkyl halide (Table 1, condition B). The reaction of **1** and *n*-BuI for 60 min afforded the product in 95% yield (quantitative yield from 1H NMR of crude product). For the reaction of the carboxylate ions with alkyl halides, we also examined the effect of reaction time. The reactions for 5 and 10 min with *n*-BuI afforded the products in 76% and 94% yields (1H NMR yields of crude products), respectively, indicating that the reaction proceeded more rapidly than under condition A. Furthermore, as seen in Table 1, the reactions proceeded smoothly and afforded the corresponding products in good yields in all other cases. In view of the successful results obtained here, esterification reactions using THF as the solvent instead of DMF under condition B were also examined (Table 1, condition C). This protocol was also found to be effective for the synthesis of esters from carboxylic acids and alkyl halides. However, in some cases, the reaction yields decreased. For example, the reaction of **18** and *i*-PrI afforded the product in 22% yield, together with the recovery of **18** in approximately 75% yield. These results might be caused by the low solubility of the carboxylic acids of starting materials in THF.

Finally, this method was successfully applied to the diesterification reaction (Scheme 2). Bu_4NF (1.0 M in THF, 4.0 mL, 4.0 mmol) was added to a solution of (*E*)-hex-3-enedioic acid (**22**) (1.0 mmol) in DMF (1.0 mL) or THF (1.0 mL). Then, the resulting solution was allowed to react with (2-bromoethyl) benzene (6.0 mmol) for 60 min, and the corresponding product **23** was obtained in 45% yield in DMF and 36% yield in THF³⁷.

4 CONCLUSION

In summary, the reaction of carboxylic acids with the

Table 1 Reaction of carboxylic acids and alkyl halides using Bu₄NF as the base.

carboxylic acid	R'-X	product	condition A % yield ^{a,b}	condition B % yield ^{b,c}	condition C % yield ^{b,d}
1	<i>n</i> Bu-I	2	56 (56) ^e 74 (75) ^{e,f}	95 (quant) ^e (76) ^{e,g} (94) ^{e,h}	89
	<i>n</i> Bu-I	2	n.r. ^{ij}	n.r. ^{ij}	n.r. ^{ij}
	<i>n</i> Bu-Br	2	42	88	59
	Me-I	3	44	52	45
	<i>n</i> Oct-I	4	68	99	51
	5	32	57	38
6	<i>n</i> Bu-I	7	69	97	94
	8	44	80	63
9		10	46	68	58
11		12	49	74	50
	13	n.r. ^j	n.r. ^j	n.r. ^j
14		15	47	73	57
16		17	42	78	54
18		19	43	84	22 ^k
20		21	55	97	75

^a Typical procedure (condition A): Bu₄NF (1.0 M in THF, 1.2 mL, 1.2 mmol) was added at room temperature to a solution of carboxylic acid (1.0 mmol) in DMF (1.0 mL), and the mixture was stirred for 20 min. Then, the solution was allowed to react with R'-X (1.5 mmol) for 60 min at the same temperature. Subsequently, water (5.0 mL) was added to the resulting solution. ^b Isolated yields. ^c Condition B: DMF (1.0 mL) as the solvent, Bu₄NF (1.0 M in THF, 2.0 mL, 2.0 mmol) and R'-X (3.0 mmol) were used. The reaction time was same. ^d Condition C: THF (1.0 mL) as the solvent, Bu₄NF (1.0 M in THF, 2.0 mL, 2.0 mmol) and R'-X (3.0 mmol) were used. The reaction time was same. ^e Yield in parenthesis is ¹H NMR yield of the crude product. ^f The reaction time of **1** and Bu₄NF was 20 min, and the reaction time with *n*-BuI was 120 min. ^g The reaction time of **1** and Bu₄NF was 20 min, and the reaction time with *n*-BuI was 5 min. ^h The reaction time of **1** and Bu₄NF was 20 min, and the reaction time with *n*-BuI was 10 min. ⁱ Reaction of benzoic acid (**1**) and *n*-BuI without Bu₄NF. ^j n.r. = no reaction. ^k Approximately 75% of **18** was recovered.

Scheme 2 Diesterification of (*E*)-hex-3-enedioic acid (**22**).

$\text{Bu}_4\text{NF/THF}$ reagent proceeded smoothly to generate ammonium carboxylates, which reacted with alkyl halides to afford the corresponding esters in moderate to good yields. In some cases, on the basis of the product yields, DMF seemed to be a better solvent than THF; this might be because of the difference in the solubility of the carboxylic acids in DMF and THF. Diesterification was also demonstrated by using this procedure. The success of this method seems to be due to the high reactivity of carboxylate ions, which might be increased by the bulky tetrabutylammonium counteranion^{21, 23, 31}. This method allows the straightforward synthesis of various esters. Further studies on other types of reactions using Bu_4NF as a base are in progress in our laboratories.

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