A Convenient Procedure for Esterification of Carboxylic Acids

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A variety of carboxylic acids including simple acids, sterically hindered acids, thermally unstable acids and N-protected amino acids react with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene to give esters in good yields. The reaction is simple, affording a general method for esterification of carboxylic acids.

Esterification is an important reaction widely used in various fields of chemistry. Although a simple reaction, it often involves unexpected difficulties. For example, other functional groups in the molecule may be sensitive to the acidic or basic conditions, or the reaction may proceed very slowly as is frequently the case with sterically hindered acids. Many useful processes to avoid such difficulties have been reported. Boron trifluoride etherate–alcohol,[1] trialkyloxonium tetrafluoroborate,[2] dialkyl sulfate,[3] and 2-halopyridinum salt–alcohol[4] have been recommended as esterification reagents for a number of cases. Alkyl halides are also useful when the reaction is carried out with use of alkali metal salts of carboxylic acids in dipolar aprotic solvents.[5,6] Caesium salt as an alkali metal salt[5] and hexamethylphosphoric triamide (HMPA)[6] as a solvent are specially effective for esterification with alkyl halides. However, some of these methods are restricted by inconvenience in procedure or expense and inaccessibility of reagents or solvents.[6]

In this paper we wish to report an alternative simple procedure for esterification of carboxylic acids which is based on the reaction of carboxylic acids with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). The reaction proceeds in a non-polar solvent such as benzene under mild conditions to give esters in good yields. Since alkyl halides are used as the esterification reagent, various esters are easily prepared. Thus, carboxylic acids including sterically hindered acids, thermally unstable acids, heterocyclic carboxylic acids and *N*-protected amino acids are readily converted into the corresponding esters. This new esterification process is noteworthy for converting *N*-protected amino acids into the corresponding esters without observable racemization.

Results and Discussion

Esterification was carried out as follows. A mixture of carboxylic acids, DBU and alkyl halides in benzene was refluxed or kept at room temperature for an appropriate period, after which the DBU-hydrohalides (DBU·HX) were either filtered off or washed out with water from the reaction mixture. The product was purified by distillation or recrystallization. The yields were excellent. Results obtained with various carboxylic acids and alkyl halides are given in Table 1. The esterification is shown by

$$R^1COOH + R^2X \xrightarrow[\text{benzene}]{\text{DBU}} R^1COOR^2 + DBU\cdot HX \quad (1)$$

No difficulties were encountered in the preparation of phenacyl esters,[7] methylthiomethyl esters,[8] esters of sterically hindered acids,[9] or esters of heterocyclic acids,[10] some of which are difficult to prepare by the usual esterification method.[7–10] Thermally unstable carboxylic acids such as malonic or cyanoacetic acid were also esterified by this procedure without decarboxylation. Active methylene compounds are carboxylated by using the reagent of DBU and carbon dioxide,[11] so the reagent system of DBU, carbon dioxide and alkyl halides may afford a new means for introduction of alkoxycarbonyl function to active methylene compounds.

Carboxylic acids having functional groups such as hydroxyl or amino group are esterified without protection of these groups. For example, *p*-aminobenzoic acid, *p*-hydroxybenzoic acid or *N*-benzyloxycarbonyl(*Z*)-threonine were converted into their esters in good yields with alkyl halides and DBU (Tables 1 and 2).

The new method has advantages over the conventional procedure. First, a wide variety of esters can be prepared under mild conditions. Secondly, the procedure is simple and easily scaled up. Thirdly, the reaction proceeds in benzene, making the work-up very simple; for instance, products can be obtained in sufficiently pure form only by removal of DBU·HX and benzene. Furthermore, DBU can be easily recovered by treatment of DBU·HX with a strong base such as sodium hydroxide. Thus, the troublesome preparation of anhydrous alkali metal salts of carboxylic acids or the use of expensive dipolar aprotic solvents becomes unnecessary. In general, it is difficult to carry out the alkylation reaction of carboxylate ions with alkyl halides in a non-polar solvent such as benzene, since few carboxylate ions are soluble in benzene. Recently, alkylation of carboxylate ions with alkyl halides in a non-polar solvent was reported, where the crown ether was used as a catalyst[12] or quarternary ammonium carboxylate was used instead of alkali metal salts.[13] The present method is superior to these methods in the following points. No prior preparation of carboxylate ions is necessary. No competing side reaction of dehydrohalogenation often encountered in the reaction of alkali metal salts of carboxylic acids with *s*-alkyl halides is observed. For example, the reaction of dry potassium acetate with 2-bromooctane in the presence of 18-

Table 1. Esterification of carboxylic acids using alkyl halides and DBU in benzene

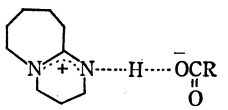
$R^1COOH + R^2X \longrightarrow R^1COOR^2$

R^1	R^2X (eq)	Conditions		Yield (%)[a]	Bp or (Mp) °C
		Temp (°C)	Time (h)		
C_6H_5	C_2H_5I(1.0)	25 (room temp)	1.5	95	95/30 mmHg
C_6H_5	CH_3SCH_2Cl(1.2)	80 (refl.)	2.0	81	106—108/2 mmHg
Mesitoic[b]	C_2H_5I(1.0)	25	2.0	80	98/3 mmHg
Mesitoic	*p*-Br–$C_6H_4CCH_2Br$(1.0) (O)	80	2.0	70	(98—99)
Mesitoic	*s*-C_4H_9Br(1.5)	80	6.0	91	115/2 mmHg
p-Me_2N–C_6H_4	C_2H_5Br(1.5)	80	3.0	85	(60—62)
p-H_2N–C_6H_4	C_2H_5Br(1.5)	80	4.0	70	(86—88)
p-HO–C_6H_4	C_2H_5Br(2.0)	80	5.0	81	(114—116)
	C_2H_5Br(1.5)	80	3.0	90	(34)
CH_3	$C_6H_5CH_2CH_2Br$(0.67)	80	3.0	86[c]	120/20 mmHg
CH_3	$CH_3(CH_2)_5CHCH_3$(0.67) (Br)	80	10.0	91[c]	87/20 mmHg
CH_3	*p*-Br–$C_6H_4CCH_2Br$(1.0) (O)	80	1.0	89	(85—86)
$(CH_3)_3C$	*n*-C_4H_9Br(1.2)	80	2.0	81	67/20 mmHg
$(CH_3)_3C$	*s*-C_4H_9Br(1.2)	80	3.0	86	55/13 mmHg
$(CH_3)_3C$	$CH_3(CH_2)_5CHCH_3$(0.67) (Br)	80	3.0	80[c]	114/20 mmHg
$(CH_3)_3C$	$C_6H_5CH_2CH_2Br$(0.67)	80	3.0	90[c]	137/20 mmHg
$(CH_3)_2C{=}CH$	C_2H_5Br(1.5)	80	2.0	80	60/30 mmHg
NC–CH_2	*n*-C_4H_9Br(1.2)	80	2.0	91	110/20 mmHg
HOOC–CH_2	C_2H_5I(2.0)	25	10.0	84[d]	85/20 mmHg

a) Based on carboxylic acids unless otherwise mentioned. b) 2,4,6-Trimethylbenzoic acid. c) Based on alkyl halides. d) Diethyl malonate produced.

crown-6 in dry acetonitrile or benzene produces the corresponding acetate along with 10—15% yield of octenes in about 20 h at reflux temperature.[12] On the other hand, the reaction of acetic acid with 2-bromooctane in the presence of DBU in benzene gave 1-methylheptyl acetate in 91% yield without formation of octenes. No alkene products could also be detected by NMR or VPC technique from the reaction mixture of mesitoic acid or pivalic acid with 2-bromobutane, 2-bromooctane or phenethyl bromide in the presence of DBU. It should be noted that alkenes were produced in good yields in these reactions in the absence of carboxylic acids;[14] *e.g.*, the reaction of 2-bromooctane or phenethyl bromide with DBU gave octenes or styrene in 87 or 60% yield, respectively. The results clearly show that the carboxylate ions formed by the reaction of carboxylic acids with DBU in benzene are sufficiently reactive to alkyl halides to give esters in good yields, but they have not enough basicity to induce the elimination reaction from *s*-alkyl halides or phenethyl bromide. Namely, basicity of both DBU and carboxylate ions is greatly reduced by protonation.

The reaction of carboxylic acids with alkyl halides in the presence of usual amines such as triethylamine is too slow to be useful for the esterification reaction. For example, the reaction of benzoic acid with ethyl iodide in the presence of DBU at room temperature for one hour gave ethyl benzoate in 95% yield, but the same reaction using triethylamine as a base gave only 1% yield of ethyl benzoate under the same conditions. High temperature (*ca.* 150 °C) and long reaction time are usually required for esterification of carboxylic acids by means of alkyl halides and triethylamine.[15] The difference in reactivity between DBU salt and triethylamine salt of carboxylic acids can be attributed to the difference in dissociation of these salts in benzene. DBU or triethylamine reacts with carboxylic acids to form complex I or II, respectively. Complex I is more soluble in benzene than complex II, complex I having a larger and more delocalized cation than complex II.



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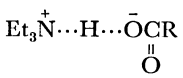

II

The principle of the present esterification reaction using DBU in benzene resembles that of the ion pair extractive alkylation or the method using crown ether. The biggest difference of the present reaction from the others is that the complex is not a free ion pair but is hydrogen-bonded between DBU and the carboxyl protons. The hydrogen bond plays an important role in the control of the reactivity of carboxylate ions. Namely, the free carboxylate ions can attack both the carbon and the hydrogen of alkyl halides, but the hydrogen-bonded complex I attacks carbon rather than hydrogen.

Table 2. Esterification of *N*-protected amino acids using alkyl haides and DBU in benzene

Z-AA-OH[a]	RX (eq)	Reflux time (h)	Yield (%)	Mp (°C)	$[\alpha]_D^{20}$	Lit Mp (°C)	Lit $[\alpha]_D^{20}$	Ref.
Z-Ala-OH	CH_3I(2)	2	92.0	45—46	−36.9° [b]	45—46	−36.0° [b]	19
Z-Pro-OH	CH_3I(2)	2	90.4	oil	−59.1° [b]		−57.3° [b]	20
Z-Val-OH	C_2H_5Br(2)	1	94.6	oil	−22.2° [b]		−19.6° [b]	21
Z-Val-OH	C_2H_5Br(2)	2	98.8	oil	−23.2° [b]			
Z-Val-OH	C_2H_5Br(2)	3	99.2	oil	−23.0° [b]			
Z-Phe-OH	C_2H_5Br(2)	2	99.0	oil	−12.1° [c]		−10.1° [c]	20
Z-Leu-OH	C_2H_5Br(2)	2	94.9	oil	−28.8° [b]		−27.5° [b]	20
Z-Ser-OH	BzlBr(1.2)[d]	2	92.9	83—84	+5.1° [e]	83.5—84.5	+6.1° [f]	22
Z-Thr-OH	BzlBr(1.2)	2	92.3	80—80.5	−13.8° [g]	80—81	−13.3° [g]	23
Z-Ser-OH	NBzlBr(1.2)[h]	2	95.7	116—117	−11.0° [b]	115.5—116.5	−11.87° [i]	24
Z-Thr-OH	NBzlBr(1.2)	2	100	114—115	−14.4° [j]	114—115	−14.01° [j]	24
Boc-Asn-OH	BzlBr(1.2)	2	81.4	120—121	−17.4° [k]	120—122	−17.29° [k]	5
Boc-Gln-OH	BzlBr(1.2)	2	80.1	109—110	−23.5° [k]	108—110	−22.67° [k]	5

a) Of the L-configuration. b) *c* 1, CH_3OH. c) *c* 1.4, C_2H_5OH. d) Benzyl bromide. e) *c* 2.95, $CHCl_3$, 24 °C. f) *c* 7, $CHCl_3$, 24 °C. g) *c* 2.5, $CHCl_3$. h) *p*-Nitrobenzyl bromide. i) *c* 0.9, CH_3OH. j) *c* 2, CH_3OH. k) *c* 1, DMF.

Recently, reports were given on the selective monoalkylation of methyl cyanoacetate[16] or tosylacetonitrile[17] using DBU in benzene as a base. The selectivity of monoalkylation in these reactions using DBU in benzene is much higher than that in the reaction using the ion pair extraction or phase transfer technique. In this case also the selectivity of monoalkylation is mainly controlled by the hydrogen bond between DBU and the active methylene compounds. Another good example of the importance of the hydrogen bonding in organic synthesis was recently demonstrated by Clark and Miller.[18] They showed that the hydrogen-bonded complex between a fluoride anion and carboxylic acids is a mild fluorinating agent but a strong acyloxylating agent.

Since the complex of DBU and carboxylic acids is a strong nucleophile but a weak base, it is expected that the optically active amino acids can be esterified without loss of the optical activities by the present procedure. Esterification of some *N*-*Z*-amino and *N*-*t*-butoxylcarbonyl(Boc)-amino acids was carried out by the use of DBU and alkyl halides in benzene in a similar way to that for the esterification of simple carboxylic acids. From the results of esterification of *N*-*Z*-valine, the standard reaction time, reflux for 2 h, was applied in all cases. The results are summarized in Table 2. Various *N*-protected amino acids were cleanly esterified in excellent yields without observable racemization. They have been esterified by other methods.[19-24] Recently, facile esterification of *N*-protected amino acids and peptides using their caesium salts and alkyl halides in *N*,*N*-dimethylformamide (DMF) was reported.[5] However, the present procedure for esterification of *N*-protected amino acids is superior to those methods as mentioned in esterification of simple carboxylic acids.

Experimental

Solvents and DBU were purified by distillation. Other commercial products were used without purification. Some typical examples of the procedure for esterification of carboxylic acids and the general procedure for esterification ot *N*-protected amino acids are described below. The reaction conditions and the physical properties of esters are summarized in Tables 1 and 2.

Ethyl 2,4,6-Trimethylbenzoate. A solution of ethyl iodide (1.56 g, 0.01 mol) in 5 ml of benzene was added to a solution of 2,4,6-trimethylbenzoic acid (1.64 g, 0.01 mol) and DBU (1.52 g, 0.01 mol) in 15 ml of benzene and the mixture was stirred at room temperature for 2 h. The reaction mixture was then washed with water, dried over anhydrous magnesium sulfate, and distilled. Ethyl 2,4,6-trimethylbenzoate; bp 98 °C/3 mmHg, 1.53 g (80% yield) was obtained. NMR (CCl_4) δ=1.31 (t, 3), 2.21 (s, 6), 4.28 (q, 2), 6.72 (s, 2); IR (neat) 1710 cm^{-1} (C=O).

s-*Butyl 2,4,6-Trimethylbenzoate.* A mixture of *s*-buytlbromide (2.0 g, 0.15 mol), 2,4,6-trimethylbenzoic acid (1.64 g, 0.01 mol), DBU (1.52 g, 0.01 mol), and 20 ml of benzene was refluxed for 6 h. The reaction mixture was then washed with water, dried over anhydrous magensium sulfate, and distilled. *s*-Butyl 2,4,6-trimethylbenzoate, bp 115 °C/2 mmHg, 1.90 g (91% yield) was obtained. NMR (CCl_4) δ= 0.99 (t, 3), 1.30 (d, 3), 1.60 (m, 2), 2.22 (s, 9), 4.99 (m, 1), 6.70 (s, 2); IR (neat) 1710 cm^{-1} (C=O).

1-Methylheptyl Acetate. A mixture of 2-bromooctane (3.86 g, 0.02 mol), acetic acid (1.8 g, 0.03 mol), DBU (4.56 g, 0.03 mol), and 40 ml of benzene was refluxed for 10 h. The reaction mixture was then washed with water, dried over anhydrous magnesium sulfate, and distilled. 1-Methylheptyl acetate, bp 87 °C/20 mmHg, 3.1 g (91% yield), was obtained. NMR (CCl_4) δ=0.9—1.3 (m, 16), 1.98 (s, 3), 4.8 (m, 1); IR (neat) 1730 cm^{-1} (C=O).

Phenethyl Pivalate. A mixture of phenethyl bromide (1.9 g, 0.01 mol), pivalic acid (2.05 g, 0.02 mol), DBU (3.04 g, 0.02 mol), and 20 ml of benzene was refluxed for 3 h. The reaction mixture was then washed with water, dried over anhydrous magnesium sulfate, and distilled. Phenethyl pivalate, bp 137 °C/20 mmHg, 1.9 g (90% yield), was obtained. NMR (CCl_4) δ=1.12 (s, 9), 2.90 (t, 2), 4.20 (t, 2), 7.15 (s, 5); IR (neat) 1740 cm^{-1} (C=O).

n-*Butyl Cyanoacetate.* A mixture of *n*-butyl bromide (1.37 g, 0.01 mol), cyanoacetic acid (0.85 g, 0.01 mol), DBU (1.52 g, 0.01 mol), and 20 ml of benzene was refluxed. The reaction mixture was then washed with water, dried over an-

hydrous magnesium sulfate, and distilled. *n*-Butyl cyanoacetate, bp 110 °C/20 mmHg, 1.28 g (91% yield) was obtained. NMR (CCl_4) δ= 1.0(t, 3), 1.55 (m, 4), 3.52 (s, 2), 4.16 (t, 2); IR (neat) 1730 cm^{-1} (C=O).

Reaction of Phenethyl Bromide with DBU. A mixture of DBU (1.6 g, 0.11 mol), phenethyl bromide (1.9 g, 0.01 mol), and benzene (20 ml) was refluxed for 5 h. The reaction mixture was then washed with water, dried over anhydrous magnesium sulfate, and distilled. Styrene, bp 145 °C, 0.64 g (60% yield) was obtained.

General Procedure for Esterification of N-Protected Amino Acids. Alkyl halide (1.2 or 2 mmol) in benzene (1—2 ml) was added to a solution of *N*-protected amino acid (1 mmol) and DBU (152 mg, 1 mmol) in benzene (4 ml; 9 ml in the case of Z-Ser-OH, Boc-Asn-OH and Boc-Gln-OH), and the mixture was refluxed with stirring for 2 h. After cooling, the mixture was was diluted with diethyl ether (20 ml), and the precipitate (BDU·HX) was filtered and washed with diethyl ether or ethyl acetate. The filtrate and the washing were combined, washed with water, 1 M HCl (0.5 M citric acid in the case of N-Boc derivatives), 1 M $NaHCO_3$, and water again, and dried over sodium sulfate. The ester obtained after removal of solvent was treated as follows. In the case of ethyl ester, the product itself was satisfactorily pure, while methyl ester was treated with active carbon for removal of a trace of iodine. Benzyl ester and *p*-nitrobenzyl ester were recrystallized from ethyl acetate–petroleum ethrer or diethyl ether–petroreum ether. The results are summarized in Table 2.

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