New Method for the Preparation of Carboxylic Esters

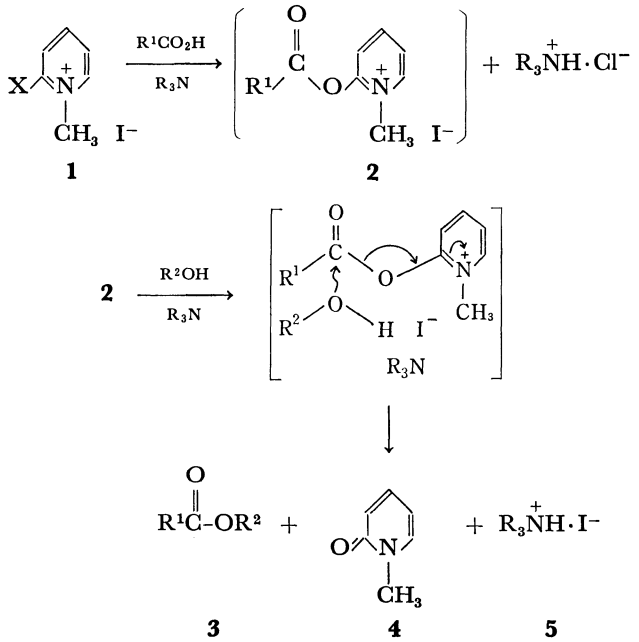
Kazuhiko SAIGO,[1] Masahiro USUI, Kazunori KIKUCHI,
Eiichiro SHIMADA, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113
(Received February 4, 1977)

Various carboxylic esters including functionalized ones are prepared in good yields from equimolar amounts of free carboxylic acids and alcohols under mild conditions by the use of 2-chloro- or 2-bromopyridinium salt, a new and efficient coupling reagent.

The ester formation is one of the most fundamental reactions in organic synthesis and a number of methods have been presented. However, relatively little work has been reported on the successful preparation of carboxylic esters by the equimolar reaction of free carboxylic acids and alcohols except when *p*-toluenesulfonyl chloride,[2] trifluoroacetic anhydride,[3] polyphosphate ester,[4] dicyclohexylcarbodiimide,[5] and graphite hydrogensulfate[6] were employed as coupling reagents.

This prompted us to develop a new and efficient coupling reagent, and 2-chloro- and 2-bromopyridinium salts were found to be efficient for the preparation of carboxylic esters from equimolar amounts of free carboxylic acids and alcohols as briefly reported in the previous communications.[7]

The work was undertaken based on the following considerations; 2-acyloxy-1-methylpyridinium iodide (**2**), an active acylating intermediate, would be produced easily and rapidly by a nucleophilic attack of the carboxylate ion on 2-chloro- or 2-bromo-1-methylpyridinium iodide (**1**) since the halogen atom at 2-position of **1** is facile to be displaced by the attack of nucleophiles. The intermediate, **2**, is in turn converted into stable molecules, *i.e.*, carboxylic esters (**3**), 1-methyl-2-pyridone (**4**) and ammonium salt (**5**) by the nucleophilic attack of alcohol to carbonyl carbon of **2** in the presence of tertiary amine, a hydrogen iodide captor.

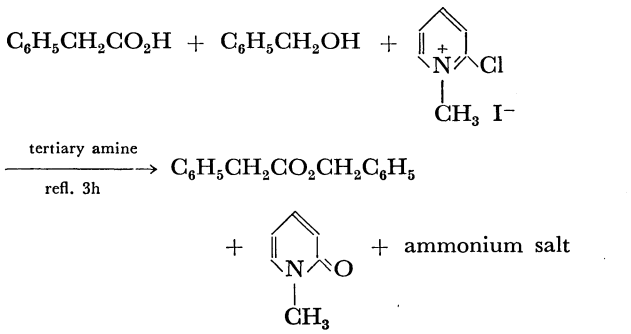


In the first place, the effective hydrogen halide captors in the ester forming reaction were examined using equimolar amounts of phenylacetic acid and benzyl alcohol. Several runs were carried out in the presence of 2.4 molar amounts of tertiary amines, such as triethylamine, tributylamine, 2,6-lutidine, α-picoline, pyridine, and *N,N*-diethylaniline, by the use of 2-chloro-1-methylpyridinium iodide. Of the amines employed, triethylamine, tributylamine, and 2,6-lutidine gave good results (see Table 1). These results indicate that the basicity of tertiary amine influences on the yield of benzyl phenylacetate, namely, the yield decreases with lowering basicity of the amine.

Next, the effect of the solvent on the reaction of phenylacetic acid and benzyl alcohol was examined using 2-chloro-1-methylpyridinium iodide in the presence of tributylamine. As listed in Table 1, no remarkable solvent effect was observed, that is, benzyl phenylacetate was obtained in almost quantitative yield in all of the solvents used.

Based on these results, several equimolar reactions of free carboxylic acids and alcohols were carried out in dichloromethane by the use of 2-chloro-1-methyl-

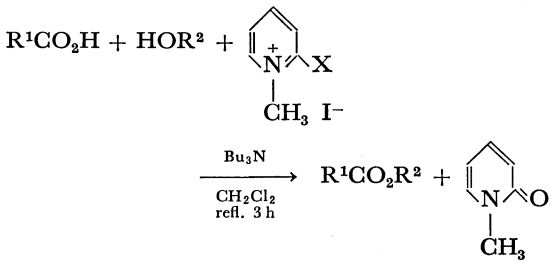
TABLE 1. EFFECTS OF TERTIARY AMINE AND SOLVENT



Tertiary amine	Solvent	Temp (°C)	Yield (%)
Triethylamine	CH_2Cl_2	refl.	98
Tributylamine	CH_2Cl_2	refl.	99
2,6-Lutidine	CH_2Cl_2	refl.	97
α-Picoline	CH_2Cl_2	refl.	77
Pyridine	CH_2Cl_2	refl.	62
N,N-Diethylaniline	CH_2Cl_2	refl.	43
Tributylamine	$(C_2H_5)_2O$	refl.	97
	CH_2Cl_2	refl.	99
	THF[a]	45—50	97
	CH_3CN	45—50	98
	DME[b]	45—50	98
	C_5H_5N	45—50	98
	CH_3-C_6H_5	45—50	99

a) Tetrahydrofuran. b) 1,2-Dimethoxyethane.

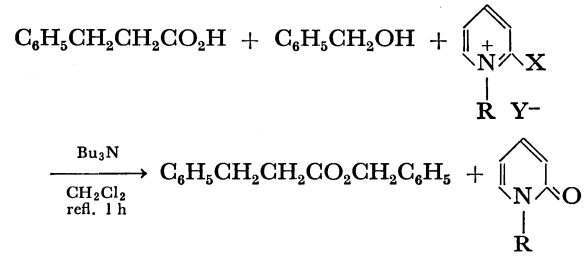
Table 2. Esterification using 2-chloro- or 2-bromo-1-methylpyridinium iodide as a coupling reagent



X	R^1	R^2	Yield (%)
Br	C_6H_5	$C_6H_5CH_2$	80
	$C_6H_5CH_2$	CH_3CH_2	92
	$C_6H_5CH_2$	$C_6H_5CH_2$	97
	$C_6H_5CH_2$	$(CH_3)_3C$	70 (82)
	CH_3	$C_6H_5CH_2$	80
	CH_3	$C_6H_5CH=CHCH_2$	80
Cl	$C_6H_5CH_2$	C_6H_5	90
	$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	93
	$C_6H_5CH_2$	$(CH_3)_3C$	81 (84)
	$C_6H_5CH_2$	$C_6H_5(CH_3)CH$	85 (88)
	CH_3	$C_6H_5CH_2CH_2$	74
	$(CH_3)_3C$	$C_6H_5CH_2$	31 (62)

Values in parentheses indicate the yields when the esterification was carried out in toluene under refluxing for 3 h.

Table 3. Examination of pyridinium salts

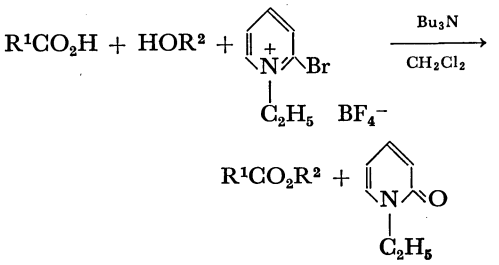


R	X	Y	Yield (%)
CH_3	Cl	I	69
CH_3	Br	I	61
C_2H_5	Cl	BF_4	73
C_2H_5	Br	BF_4	82

pyridinium iodide and tributylamine, and good results were obtained. 2-Bromo-1-methylpyridinium iodide was also found to be as effective as 2-chloro-1-methylpyridinium iodide in the esterification. An improvement in the yields was rarely recognized except for the case of the condensation of pivalic acid, a bulky carboxylic acid, with benzyl alcohol when the esterifications were carried out at an elevated temperature, that is, in refluxing toluene (see Table 2).

The consideration that both the counter ion and halogen atom attached to 2-position of the pyridinium salt would influence on the yield of carboxylic esters urged us to look for more effective pyridinium salt. The equimolar reaction of 3-phenylpropionic acid with benzyl alcohol was undertaken by the use of 2-halo-

Table 4. Esterification employing 2-bromo-1-ethylpyridinium tetrafluoroborate



R^1	R^2	Conditions: refl. 3 h Yield (%)	Conditions: r.t. overnight Yield (%)
$C_6H_5CH_2CH_2$	C_2H_5	73 (59)	
$C_6H_5CH_2CH_2$	C_6H_5	57	61
CH_3CH_2	$C_6H_5CH_2$	62 (39)	71
CH_3CH_2	$C_6H_5CH_2CH_2$	60 (48)	
$C_6H_5CH=CH$	$C_6H_5CH_2$	71 (62)	
$C_6H_5CH=CH$	C_2H_5	43 (27)	78
$(CH_3)_3C$	$(CH_3)_3C$	21[a]	54[a]
$C_6H_5CH_2$	$(CH_3)_3C$		78
Cl_3C	$C_6H_5CH_2$	40	62
$ClCH_2$	$C_6H_5CH_2$	88	
$ClCH_2$	$C_6H_5CH_2CH_2$	80	
	$C_6H_5CH_2$		97
$C_6H_5C\equiv C-$	$C_6H_5CH_2$		85
$C_6H_5COCH_2$	$C_6H_5CH_2$		87
$CH_3COCH_2CH_2$	$C_6H_5CH_2$		45[b]
	$C_6H_5CH_2$		62
$CH_3CH=CH-CH=CH$	$C_6H_5CH_2$		59[c]

Values in parentheses indicate the yields when the reactions were carried out in dichloromethane under refluxing for 3 h using 2-chloro-1-methylpyridinium iodide as a coupling reagent.
a) Yields determined by GLC. b) As a by-product, 4-benzyloxy-4-methyl-4-butanolide was obtained in 13% yield. c) Sorbic anhydride was obtained in 21% yield.

pyridinium iodide or tetrafluoroborate to determine the influence on the yield. As shown in Table 3, 2-bromo-1-ethylpyridinium tetrafluoroborate gave the best result.

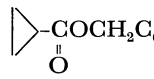
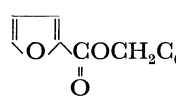
Based on the above results, the reaction of several free carboxylic acids, including functionalized ones, with equimolar amounts of alcohols was carried out employing 2-bromo-1-ethylpyridinium tetrafluoroborate as the coupling reagent, and favorable results were obtained especially when the esterification was undertaken at room temperature (see Table 4).

In conclusion, it is noted that various carboxylic esters are conveniently prepared in good yields from equimolar amounts of free carboxylic acids and alcohols under mild conditions by the use of 2-chloro- or 2-bromo-1-methylpyridinium iodide or 2-bromo-1-ethylpyridinium tetrafluoroborate, as a coupling reagent, in the presence of tributylamine. The present method is also successfully applied to the carboxylic ester synthesis

TABLE 5. PHYSICAL DATA OF PRODUCTS

Compound	IR $\nu_{C=O}$ (cm^{-1})	NMR (δ)	Elemental analysis (%)
$C_6H_5CH_2COC_2H_5$ (O)	1740	1.15(t, 3H), 3.45(s, 2H), 4.05(q, 2H), 7.20(s, 5H)	—
$C_6H_5CH_2COCH_2C_6H_5$ (O)	1740	3.50(s, 2H), 5.00(s, 2H), 7.15(s, 10H)	—
$C_6H_5CH_2COC(CH_3)_3$ (O)	1735	1.35(s, 9H), 3.40(s, 2H), 7.15(s, 5H)	Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.57.
$C_6H_5CH_2COCH(CH_3)C_6H_5$ (O)	1740	1.40(d, 3H), 3.50(s, 2H), 5.85(q, 1H), 7.25(s, 10H)	Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.85; H, 6.65.
$C_6H_5CH_2COC_6H_5$ (O)	1740	3.45(s, 2H), 7.20(s, 5H), 7.25(s, 5H)	—
$C_6H_5CH_2COCH_2CH_2C_6H_5$ (O)	1740	2.75(t, 2H), 3.40(s, 2H), 4.15(t, 2H), 7.05(s, 5H), 7.15(s, 5H)	—
$CH_3COCH_2C_6H_5$ (O)	1745	1.95(s, 3H), 5.00(s, 2H), 7.25(s, 5H)	—
$CH_3COCH_2CH=CHC_6H_5$ (O)	1745	2.00(s, 3H), 4.65(d, 2H), 6.15(d-t, 1H), 6.60(d, 1H), 7.25(s, 5H)	—
$CH_3COCH_2CH_2C_6H_5$ (O)	1720	1.90(s, 3H), 2.85(t, 2H), 4.20(t, 2H), 7.20(s, 5H)	—
$C_6H_5CH_2CH_2COC_2H_5$ (O)	1735	1.10(t, 3H), 2.4—3.4(m, 4H), 4.05(q, 2H), 7.10(s, 5H)	—
$C_6H_5CH_2CH_2COC_6H_5$ (O)	1740	2.6—3.1(m, 4H), 6.8—7.4(m, 10H)	—
$CH_3CH_2COCH_2CH_2C_5H_5$ (O)	1740	1.05(t, 3H), 2.20(q, 2H), 2.90(t, 2H), 4.25(t, 2H), 7.10(s, 5H)	—
$CH_3CH_2COCH_2C_6H_5$ (O)	1735	1.10(t, 3H), 2.25(q, 2H), 5.00(s, 2H), 7.20(s, 5H)	—
$(CH)_3CCOCH_2C_6H_5$ (O)	1735	1.20(s, 9H), 5.05(s, 2H), 7.25(s, 5H)	Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.02; H, 8.53.
$(CH_3)_3CCOC(CH_3)_3$ (O)	1710	—	Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.45; H, 11.51.
$C_6H_5COCH_2C_6H_5$ (O)	1730	5.30(s, 2H), 7.1—7.5(m, 8H) 8.0—8.3(m, 2H)	—
$C_6H_5CH=CHCOC_2H_5$ (O)	1720	1.30(t, 3H), 4.20(q, 2H), 6.40(d, 1H), 7.40(s, 5H), 7.65(d, 1H),	Calcd for $C_9H_{18}O_2$: C, 74.97; H, 6.86. Found: C, 75.12; H, 7.08.
$C_6H_5CH=CHCOCH_2C_6H_5$ (O)	1720	5.15(s, 2H), 6.40(d, 1H), 7.25(s, 10H), 7.65(d, 1H)	—
$Cl_3CCOCH_2C_6H_5$ (O)	1760	5.30(s, 2H), 7.35(s, 5H)	Calcd for $C_8H_7O_2Cl_3$: C, 42.64; H, 2.79; Cl, 41.95. Found: C, 42.67; H, 2.72; Cl, 41.88.
$ClCH_2COCH_2C_6H_5$ (O)	1730	3.55(s, 2H), 5.20(s, 2H)	—
$ClCH_2COCH_2CH_2C_6H_5$ (O)	1730	2.50(t, 2H), 3.50(s, 2H) 3.90(t, 2H), 6.85(s, 5H)	—
$CH_3CH=CH-CH=CHCOCH_2C_6H_5$ (O)	1705	1.80(d, 3H), 5.10(s, 2H), 5.75(d, 1H), 6.05(m, 2H), 7.25(d-d, 1H), 7.25(s, 5H)	Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.00; H, 7.06.
$C_6H_5C\equiv CCOCH_2C_6H_5$ (O)	1700 2200 (C≡C)	5.15(s, 2H), 7.1—7.5(m, 10H)	Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.50; H, 5.41.

Table 5. (Countinued)

Compound	IR $\nu_{C=O}$, (cm^{-1})	NMR (δ)	Element analysis (%)
$C_6H_5CCH_2COCH_2C_6H_5$ (O O)	1760 1680	3.85(s, 4/3H), 5.05(s, 4/3H), 5.15(s, 2/3H), 5.65(s, 2/3H), 7.1—7.9(m, 10H)	Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.70; H, 5.41.
$CH_3CCH_2CH_2COCH_2C_6H_5$ (O O)	1700	2.00(s, 3H), 2.50(qusi s, 4H), 5.00(s, 2H), 7.25(s, 5H)	Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62; H, 6.87.
	1780	0.8—1.1(m, 4H), 1.3—1.7(m, 1H), 5.00(s, 2H), 7.25(s, 5H)	Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.67; H, 6.88.
	1700	5.20(s, 2H), 6.30(d-d, 1H), 7.05(d, 1H), 7.25(s, 5H), 7.45(d, 1H)	Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.12; H, 4.90.

starting from free carboxylic acids or alcohols having bulky alkyl group or having functional group sensitive toward acid or base.

Experimental

Spectra. Proton NMR were obtained on Hitachi R-24 spectrometer. Chemical shifts are reported on the δ scale relative to tetramethylsilane as an internal standard. Infrared spectra were taken using Hitachi EPI-G2 spectrophotometer. Products were identified by NMR and IR spectra and elemental analyses.

Materials. All solvents used here were distilled according to the general methods and were stored over molecular sieves or sodium metal as a drying agent. Carboxylic acids and alcohols were recrystallized or distilled before use.

2-Chloro-1-methylpyridinium Iodide. To a solution of 2-chloropyridine (10.0 g, 88 mmol) in acetone (3 ml) was added methyl iodide (15.0 g, 106 mmol) at 0 °C and the mixture was stirred for 3 days at room temperature. Precipitate appeared was filtered and washed with dry ether (50 ml). After drying under reduced pressure, 2-chloro-1-methylpyridinium iodide (18.0 g, 80%) was obtained and used for the esterification without recrystallization.

2-Bromo-1-ethylpyridinium Tetrafluoroborate. A solution of 2-bromopyridine (2.88 g, 18 mmol) was added to triethyloxonium tetrafluoroborate (4.00 g, 21 mmol) at room temperature under an argon atmosphere. The solution became clear in a few minutes and white precipitate appeared gradually. After the suspension was warmed at 50—60 °C for 1 h, the mixture was cooled with ice-water bath. The precipitate was filtered and washed with dry ether (15 ml). Drying under reduced pressure at room temperature gave 2-bromo-1-ethylpyridinium tetrafluoroborate (4.07 g, 83%) which was employed for condensation without recrystallization.

General Procedure for Carboxylic Ester Synthesis by the Use of 2-Chloro- or 2-Bromo-1-methylpyridinium Iodide. To a suspension of 2-chloro-1-methylpyridinium iodide (612 mg, 2.4 mmol) or 2-bromo-1-methylpyridinium iodide (720 mg, 2.4 mmol) in dichloromethane or toluene (2 ml) was added a solution of free carboxylic acid (2.0 mmol), alcohol (2.0 mmol), and tributylamine (888 mg, 4.8 mmol), in the solvent (2 ml) under an argon atmosphere and the mixture was stirred for 3 h under refluxing. The solution became clear in accordance to progress of the reaction. After evaporation of the solvent, the residue was separated by silica gel column chromatography to give carboxylic ester.

General Procedure Utilizing 2-Bromo-1-ethylpyridinium Tetrafluoroborate. To a solution of 2-bromo-1-ethylpyridinium tetrafluoroborate (329 mg, 1.2 mmol) in dichloromethane (2 ml) was added a mixture of free carboxylic acid (1.0 mmol), alcohol (1.0 mmol), and tributylamine (444 mg, 2.4 mmol) at room temperature under an argon atmosphere. After stirring overnight at room temperature, the solvent was evaporated and the residue was chromatographed on silica gel to give carboxylic ester. The NMR and IR spectra and elemental analysis data of products were listed in Table 5.

References

1) Present Address: Department of Applied Chemistry, Faculty of Engineering, Saitama University, Shimo-okubo, Urawa, Saitama, 338.

2) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

3) R. C. Parish and L. M. Stock, *Tetrahedron Lett.*, **1964**, 1258; *J. Org. Chem.*, **30**, 927 (1965).

4) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, K. Matsuzaki, and Y. Ban, *Chem. Ind. (London)*, **1964**, 2102.

5) A. Buzas, C. Egnell, and P. Freon, *C. R. Acad. Sci.*, **256**, 1804 (1963); S. Neelakuntan, R. Padmasani, and T. R. Seshadri, *Tetrahedron*, **21**, 3531 (1965).

6) J. Bertin, H. B. Kagan, and J. J. Luche, *J. Am. Chem. Soc.*, **96**, 8113 (1974).

7) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, **1975**, 1045; T. Mukaiyama, H. Toda, and S. Kobayashi, *Chem. Lett.*, **1976**, 13.