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EFFICIENT IN SITU ESTERIFICATION OF CARBOXYLIC ACIDS USING CESIUM CARBONATE

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EFFICIENT *IN SITU* ESTERIFICATION OF CARBOXYLIC ACIDS USING CESIUM CARBONATE

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The esterification of carboxylic acids is a fundamental process in organic synthesis¹ and may effected by the reaction of carboxylate anions with alkyl halides.² Compared to other alkali metal carboxylate salts, cesium salts have been shown to be especially efficient in esterification³⁻⁶ and macrocyclization reactions.⁷ However, these reactions usually required high boiling solvent (DMF) in the presence of water³⁻⁵ or cesium fluoride/DMF system⁶ which are undesirable in terms of convenience. We now report a highly effective method for the esterification of carboxylic acids in acetonitrile with readily available cesium carbonate under non-aqueous conditions.

Acetonitrile was used as a reaction medium because of its appropriate boiling point as well as high dielectric constant and polar aprotic nature. The latter two properties should provide good solubility for the cesium carboxylate salt and concomitant rate enhancement of the reaction. Reflux of the carboxylic acids with alkyl iodides (1.0-5.0 equiv.) and cesium carbonate (1.5 equiv.) in

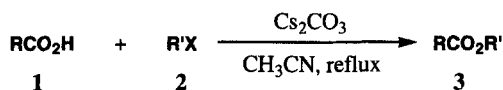


TABLE 1. Yields of Esters from Esterification Using Cesium Carbonate

Entry	RCO ₂ H (1)	R'X ^a (2)	Time ^b (hrs)	Yield of 3 ^c (%)	bp. (mp.) (°C) ^d
1	Benzoic acid	EtI	1	96	210-212
2	Benzoic acid	EtI	e,f,g		
3	Benzoic acid	i-PrI	1	93	217-218
4	Benzoic acid	CH ₂ =CHCH ₂ Br	0.5	100	240-242
5	Benzoic acid	PhCH ₂ Br ^h	0.5	96	(20-21)
6	Benzoic acid	PhCH ₂ Cl ^h	0.5	90	
7	2,4,6-Trimethylbenzoic acid	EtI	2	100	129-130
8	2,4,6-Trimethylbenzoic acid	i-PrI	2	96	135-137
9	2,4,6-Trimethylbenzoic acid	CH ₂ =CHCH ₂ Br	0.5	98	226-227
10	2,4,6-Trimethylbenzoic acid	PhCH ₂ Br ^h	0.5	97	309-311
11	<i>trans</i> -Cinnamic acid	EtI	2	100	269-271
12	<i>trans</i> -Cinnamic acid	i-PrI	2	95	268-270
13	Phenylpropionic acid	EtI	1.5	100	262-265
14	<i>trans</i> -3-(3-Pyridyl)acrylic acid	EtI	1	97	93-95
15	4-Fluorophenoxyacetic acid	EtI	1.5	99	(31-32)
16	3-Quinoline carboxylic acid	EtI	1.5	93	(68-69)
17	4-Nitrobenzoic acid	EtI	1.5	91	(55-57)
18	4-Nitrobenzoic acid	i-PrI	1.5	95	(108-109)
19	2-Chlorobenzoic acid	EtI	1.5	98	241-243
20	4-Methoxybenzoic acid	EtI	1.5	100	261-263
21	1-Naphtic acid	EtI	1.5	100	308-310
22	Phenylacetic acid	EtI	1.5	98	226-228
23	Cyanoacetic acid	EtI ^h	1.5	98	207-209
24	Eicosanoic acid	EtI ^h	2	97	(47-48)
25	<i>trans</i> -2-Hexenoic acid	PhCH ₂ Br ^h	0.5	98	231-232
26	Cyclohexanecarboxylic acid	i-PrI	1	91	130-131
27	N-Acetyl-DL-alanine	EtI	2	90	(34-35)
28	N-Acetyl-DL-alanine	i-PrI	2	93	175-176
29	N-Acetyl-L-phenylalanine	EtI	1.5	99	(88-89)
30	N-Acetyl-L-phenylalanine	i-PrI	1.5	98	(72-73)
31	(R)-(-)-2-Phenylbutyric acid	EtI	1.5	100	205-206
32	(R)-(-)-2-Phenylbutyric acid	i-PrI	1	98	207-208

a) Five equiv. were used unless otherwise indicated. b) Reaction in CH₃CN with 1.5 equiv. of Cs₂CO₃. c) Yield of isolated product. d) Uncorrected. e) Reaction in CH₃CN at reflux with 2.5 equiv. of K₂CO₃ for 4 hrs gave a 67% yield. f) Reaction in THF at reflux with 1.5 equiv. of Cs₂CO₃ for 24 hrs gave a 72% yield. g) Reaction in DMF at 80° with 1.5 equiv. of Cs₂CO₃ for 7 hrs gave a 59% yield. h) One equiv. was used.

acetonitrile for 0.5-2 hrs yielded the corresponding esters in essentially quantitative yield. The generality of this reaction was shown by use of a variety of carboxylic acids. The results are summarized in Table 1. The yields obtained in the present study were always higher than or comparable to those reported in the literature. Alkyl iodides were generally used as alkylating agents because not only their high reactivity in nucleophilic reaction but also the easy separation of precipitated cesium iodide from the esterification products.⁸ All of the reactions were completed within 2 hrs. The use of potassium carbonate instead of cesium carbonate, however, decreased the yield significantly (Entry 2). The use of either tetrahydrofuran (THF) or dimethylformamide (DMF) proved to be less effective than acetonitrile (Entry 2). These results clearly demonstrate the advantages of the present reaction conditions with respect to the yields and reaction times, there was no need to pre-form the cesium carboxylate salts which makes this method convenient for the *in situ* esterification of carboxylic acids. The procedure is also effective for the preparation of the sterically hindered esters (Entries 7-10). The mildness of the present method is illustrated with the use of base-sensitive functional groups (Entries 22, 23, 25 and 26). In addition, no racemization was observed with optically pure compounds (Entries 29-32).

In conclusion, an economical and practical method for the esterification of variety of carboxylic acids has been developed using readily available reagents under mild conditions. We believe this procedure provides an attractive alternative to the previously established methods in light of its high yield, short reaction time, and easy product isolation.

TABLE 2. Combustion Analysis Data for Compounds **9, 24, 25, 28, 30** and **32**

Cmpd.	bp. (mp.) (°C)	C (Found)	H (Found)	N (Found)
9	226-227	76.44 (76.36)	7.90 (7.80)	
24	(47-48)	77.58 (77.42)	13.02 (13.06)	
25	231-232	76.44 (76.36)	7.90 (7.79)	
28	175-176	55.47 (55.38)	8.73 (8.64)	8.09 (8.02)
30	(72-73)	67.45 (67.30)	7.68 (7.57)	5.62 (5.59)
32	207-208	75.69 (75.50)	8.80 (8.65)	

EXPERIMENTAL SECTION

¹H NMR spectra were recorded with Bruker AW 80 spectrometer. IR spectra were obtained using a Unicam Mattson FT 1000 spectrometer. Cesium carbonate (99.5%) was obtained from Janssen Chimica. HPLC grade acetonitrile was obtained from EM Science and used without purification. All other commercially available reagents were obtained in high purity. All products showed spectral data consistent with their proposed structures. Elemental analyses were performed by Korea Basic Science Institute.

Typical Procedure.- To a solution of benzoic acid (0.24 g, 2.0 mmol) and cesium carbonate (0.98 g, 3.0 mmol) in acetonitrile (20 mL) was added iodoethane (1.56 g, 10.0 mmol) and the mixture was

stirred at reflux for 1 hr. After cooling to room temperature, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform (100 mL) and washed with 20% aq. NaHCO₃ solution (3 x 30 mL). The chloroform layer was washed (brine), dried (Na₂SO₄), and evaporated under reduced pressure to give pure ethyl benzoate (0.29 g, 96%).

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8. The higher bp. of the iodides also allowed the esterification of be performed at reflux in acetonitrile.
