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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Jong Chan Lee & Youngsup Choi (1998) An Improved Method for Preparation of Carboxylic Esters Using CsF-Celite/Alkyl Halide/Ch<sub>3</sub>Cn Combination, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:11, 2021-2026, DOI: <u>10.1080/00397919808007177</u>

To link to this article: http://dx.doi.org/10.1080/00397919808007177

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## AN IMPROVED METHOD FOR PREPARATION OF CARBOXYLIC ESTERS USING CsF-CELITE/ALKYL HALIDE/CH<sub>3</sub>CN COMBINATION

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**ABSTRACT:** A new method for efficient and chemoselective esterification of carboxylic acids in CsF-Celite/alkyl halide/CH<sub>3</sub>CN reaction system is described.

Alkylation of cesium carboxylate salts with alkyl halide is very useful tool for the preparation of carboxylic esters.<sup>1-7</sup> Among other cesium salts, cesium fluoride proved as an excellent base for converting carboxylic acids into their corresponding esters with alkyl halides.<sup>6, 7</sup> However, these methods are limited in terms of using high boiling N,N-dimethylformamide (DMF) as a reaction solvent and very low chemoselectivity. It is apparently desirable to use low boiling solvent such as acetonitrile that can be used with operational simplicity for practical applications.

Although considerable attention has been paid to the esterification of carboxylate salts with alkyl halides,<sup>8</sup> only a few examples have been reported for chemose-lective esterification of phenolic carboxylic acids in basic conditions. For

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example, chemoselective esterification of phenolic carboxylic acids with alkyl halides has been accomplished by employing Li<sub>2</sub>CO<sub>3</sub>/alkyl halide/DMF reaction system.<sup>9-10</sup> But this method was only applicable to the esterification of phenolic acetic acids which limits its utilization.

We report herein a convenient and efficient method for esterification of carboxylic acid based on use of CsF-Celite<sup>11</sup> as a solid base in acetonitrile.

Examples are summarized in Table 1. Present method is generally being equally applicable to aromatic, aliphatic, and heteroaromatic carboxylic acids and provided the corresponding carboxylic esters in excellent yields. In all cases examined, the esterification reactions were very clean and leading to essentially pure esters in short reaction times. The work-up simply consists of filtration of inorganic salts and did not require aqueous alkaline wash. These results are compatible or better than those of existing methods in terms of yields and reaction times. No problems associated with base sensitive carboxylic acids were encountered (entries 8 - 10). Esterification of chiral  $\alpha$ -substituted carboxylic acid proceeded in excellent yields with retention of configurations (entries 17 - 19). Replacing CH<sub>3</sub>CN by THF, the esterification yields were reduced to 10% on average after prolonged reaction times (24 h). The effectiveness of KF-Celite<sup>12</sup> was compared against the CsF-Celite for the esterification of benzoic acid with EtI in CH<sub>3</sub>CN but gave substantially reduced yield (60 % after 24 h).

In order to test the differentiating ability of CsF-Celite/CH<sub>3</sub>CN system for the alkylation between carboxylic -COOH and phenolic -OH, esterification of phenolic

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Entry	RCOOH	R'X <sup>a</sup>	RCOOR'	Time (h)	Yield (%) <sup>b</sup>
1	PhCOOH	A	PhCOOEt	2	96
2	PhCOOH	В	PhCOO <i>i</i> Pr	2.5	95
3	PhCOOH	С	PhCOOCH <sub>2</sub> CH=CH <sub>2</sub>	1.5	99
4	PhCOOH	D	PhCOOCH <sub>2</sub> Ph	2	98
5	4-AcOC <sub>6</sub> H <sub>4</sub> COOH	Α	4-AcOC <sub>6</sub> H <sub>4</sub> COOEt <sup>c</sup>	2	88
6	2-PhCOC <sub>6</sub> H <sub>4</sub> COOH	Α	2-PhCOC <sub>6</sub> H <sub>4</sub> COOEt	2	95
7	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> COOH	Α	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> COOEt	1	99
8	PhCH <sub>2</sub> COOH	Α	PhCH <sub>2</sub> COOEt	1.5	99
9	PhCOCH <sub>2</sub> CH <sub>2</sub> COOH	Α	PhCOCH <sub>2</sub> CH <sub>2</sub> COOEt	1.5	98
10	PhOCH <sub>2</sub> COOH	Α	PhOCH <sub>2</sub> COOEt	1.5	94
11	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>18</sub> COOH	Α	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>18</sub> COOEt	1.5	96
12	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOH	С	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOCH <sub>2</sub> CH=CH	2 2	93
13	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOH	D	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOCH <sub>2</sub> Ph	2.5	93
14	trans-Cinnamic acid	Α	Ethyl trans-cinnamate	1.5	98
15	2-Thiophenecarboxylic aci	d A	Ethyl 2-thiophenecarboxylate	2.5	93
16	Nicotinic acid	Α	Ethyl nicotinate	2	92
	OH		ОН		
17	с-С <sub>6</sub> H <sub>11</sub> / СООН	Α	c-C <sub>6</sub> H <sub>11</sub> COOEt	2.5	93
18	Ph CH <sub>3</sub> CH <sub>2</sub> H	A	Ph CH <sub>3</sub> CH <sub>2</sub> H	1.5	94
19	CH <sub>3</sub> CONH COOH	А		1.5	95

Table 1. Esterification of Carboxylic Acids Using CsF-Celite in CH<sub>3</sub>CN.

<sup>a</sup> A: EtI, B: *i*PrI, C: CH<sub>2</sub>=CHCH<sub>2</sub>Br, D: PhCH<sub>2</sub>Br. <sup>b</sup> Isolated yields of pure product. <sup>c</sup> Purified by column chromatography.

carboxylic acids at present reaction conditions were conducted. The results are shown in Table 2. In all cases, the monoalkylation to the more acidic carboxylic group were occurred predominantly with slight amounts of dialkylated product which were easily separated by flash column chromatography.

In summary, the CsF-Celite/alkyl halide/CH<sub>3</sub>CN combination provides a clean and practical method for the esterification of carboxylic acids in high yields without

RCOOH	R'X <sup>a</sup>	RCOOR'	Time (h)	Yield (%) <sup>b</sup>
4-HOC <sub>6</sub> H₄COOH	Α	4-HOC <sub>6</sub> H₄COOEt	5	87
4-HOC <sub>6</sub> H <sub>4</sub> COOH	С	4-HOC <sub>6</sub> H <sub>4</sub> COOCH <sub>2</sub> CH=CH <sub>2</sub>	3	85
4-HOC <sub>6</sub> H <sub>4</sub> COOH	D	4-HOC <sub>6</sub> H <sub>4</sub> COOCH <sub>2</sub> Ph	3	90
2-HOC <sub>6</sub> H <sub>4</sub> COOH	Α	2-HOC <sub>6</sub> H <sub>4</sub> COOEt	3	90
4-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> COOH	Α	4-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> COOEt	4	91
CH <sub>3</sub> O HO	A	CH <sub>3</sub> O HO	9	76
но С	Α	HO CI	6	82
	A	H COOEt H OH	9	78

 Table 2. CsF-Celite Mediated Chemoselective Esterification of Phenolic Carboxylic Acids.

<sup>a</sup> A: EtI, C: CH<sub>2</sub>=CHCH<sub>2</sub>Br, D: PhCH<sub>2</sub>Br. <sup>b</sup> Isolated yields of pure products.

using operationally inconvenient DMF solvent. Moreover, we have demonstrated the utility of present method for the high yielding chemoselective esterification of phenolic carboxylic acids under basic conditions.

#### **Experimental Section**

**Preparation of CsF-Celite:** To a stirred solution of Celite 521 (10.0 g) in water (300 mL) was added 1.0 mol of cesium fluoride (15.2 g). After 20 min the water was removed at 60 °C with rotary evaporator under vacuo. The solid residue was shaken in CH<sub>3</sub>CN (100 mL), filtered, washed with CH<sub>3</sub>CN (2 x 50 mL), and dried in a dessicator at room temperature.

General Esterification Procedure: To a stirred solution of carboxylic acid (1.0 mmol) and CsF-Celite (1.5 mmol) in 100 mL of CH<sub>3</sub>CN was added iodoethane (2.0 mmol). After stirring at reflux for indicated time in the Tables, the solvent was evaporated and the residue was dissolved in EtOAc. The precipitates was filtered off, washed with EtOAc (20 mL), and evaporation of the filtrate gave pure carboxylic esters. In the cases of chemoselective esterifications, the desired products were readily isolated by flash column chromatography (EtOAc/hexane 1:3). All products showed spectral data consistent with the assigned structures.

Acknowledgment: This paper was supported by Non Directed Research Fund, Korea Research Foundation, 1996.

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(Received in Japan 8 December 1997)