Environmentally Friendly Esterification of Carboxylic Acids with Triethyl Orthoacetate in Ionic Liquid

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Abstract: An operationally simple, inexpensive, efficient, and environmentally friendly esterification of carboxylic acids with triethyl orthoacetate under neutral conditions in a typical room temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate, was carried out to provide the corresponding ethyl esters in high yields.

Key words: carboxylic acid, ethyl ester, triethyl orthoacetate, ionic liquid, environmentally friendly

Esterification of carboxylic acids is one of the most important functional group conversions in organic synthesis. Therefore, since the first esterification method with the Fischer ester synthesis,[1] a number of useful esterification methods catalyzed by Brønsted acids, Lewis acids, ion exchange regins, zeolite, etc., have been reported.[2] Today, environmentally friendly organic synthesis has become much more important and popular, aiming toward green chemistry. Especially, room temperature ionic liquids attracts great interest as environmentally friendly reaction media and reaction promotion media for organic synthesis.[3] Thus, these solvents possesses interesting and useful advantages such as negligible vapor pressure, nonflammability, high thermal stability at a wide range of temperature, and easy reusability. Therefore, these solvents have been successfully used in Friedel–Crafts reaction,[4] hydrogenation,[5] Diels–Alder reactions,[6] Heck, Suzuki, Sonogashira, and olefin metathesis reactions,[7] Michael addition,[8] oxidation,[9] condensation such as Knoevenagel and Robinson annulation reactions,[10] 1,2-rearrangement,[11] esterification of carboxylic acids and carboxylates,[12] nucleophilic substitution such as the Williamson ether synthesis,[13] etc. Here, as a part of our study on environmentally friendly organic synthesis with ionic liquid,[14] we would like to report an operationally simple, inexpensive, efficient, and environmental friendly esterification of carboxylic acids with triethyl orthoacetate under neutral conditions in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), which is a typical room temperature ionic liquid. It is well known that generally triethyl orthoformate and triethyl orthoacetate are used for the conversion of carbonyl groups to their acetals and ketals.[15] Additionally, triethyl orthoacetate can be used for the esterification of sulfonic acids[16] and carboxylic acids.[16b] However, generally, esterification of carboxylic acids with triethyl orthoacetate requires high temperatures and long reaction times. For example, 1-naphthoic acid was converted to the desired ethyl ester in 89% yield with triethyl orthoacetate (3 equiv) under refluxing conditions in toluene for 24 hours. In our present study, when a mixture of 1-naphthoic acid with triethyl orthoacetate (2.0 equiv) in [bmim]PF_6 (2 mL) was heated at 80 °C for 100 minutes without any additive, the desired ethyl ester was smoothly obtained in 98% yield, this reaction gave rise to low yields under the same conditions in toluene, DMF, DMSO, and even in solvent-free conditions. Several examples of esterification by use of our protocol are shown in Table 1, and the formation of the corresponding ethyl esters was much accelerated except for more acidic carboxylic acid such as 3,5-dinitrobenzoic acid. Thus, the present system is highly effective, especially for less acidic carboxylic acids. Here, room temperature ionic liquid [bmim]PF_6 can be recycled and reused without loss of chemical yield of ester.

Another interesting advantage of this esterification is the use for sterically hindered carboxylic acids such as 2,4,6-triisopropylbenzoic acid, and for amino acid without any racemization as shown in Table 2. Here, ethyl 2,4,6-triisopropylbenzoate cannot be obtained by typical esterification processes such as the Fischer method or the DCC method. Moreover, when competitive esterification reactions of 3,5-dinitrobenzoic and palmitic acids, and 3,5-dinitrobenzoic and 3,4,5-trimethoxybenzoic acids were carried out, the corresponding ethyl 3,5-dinitrobenzoate together with recovered palmitic acid, and ethyl 3,5-dinitrobenzoate together with recovered 3,4,5-trimethoxybenzoic acid were selectively obtained, respectively (Scheme 1). When 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), instead of [bmim]PF_6, was used as an ionic liquid, the same results were obtained. Trimethyl orthoacetate can be also used for the same esterification reaction, methylation of carboxylic acids, and shows the same reactivity as with triethyl orthoacetate.

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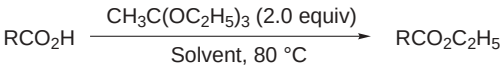
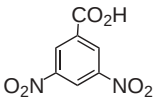
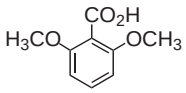
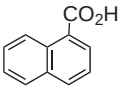
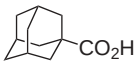
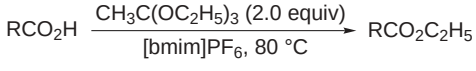
Table 1 Solvent Effects in the Esterification of Carboxylic Acids with Triethyl Orthoacetate

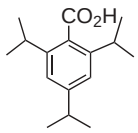
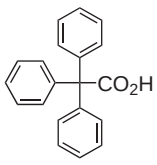
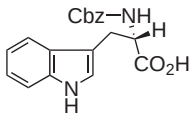


Carboxylic Acid	Time	Yields (%)				
		[bmim]PF_6	Toluene	Solvent-free	DMF	DMSO
	30 min	97	90	98	88	62 (27)[a]
	2.5 h	94	19 (78)[a]	5 (94)[a]	15 (82)[a]	23 (68)[a]
	100 min	98 95[c] 92[d] 97[e] 94[f]	39 (47)[a]	66 (28)[a]	23 (64)[a]	19 (75)[a]
$CH_3(CH_2)_{14}CO_2H$	3.5 h[b]	95	66 (32)[a]	70 (30)[a]	30 (70)[a]	28 (72)[a]
	5 h[b]	94	79 (20)[a]	73 (14)[a]	39 (54)[a]	47 (53)[a]
	5 h[b]	91	42 (48)[a]	22 (74)[a]	21 (76)[a]	18 (80)[a]

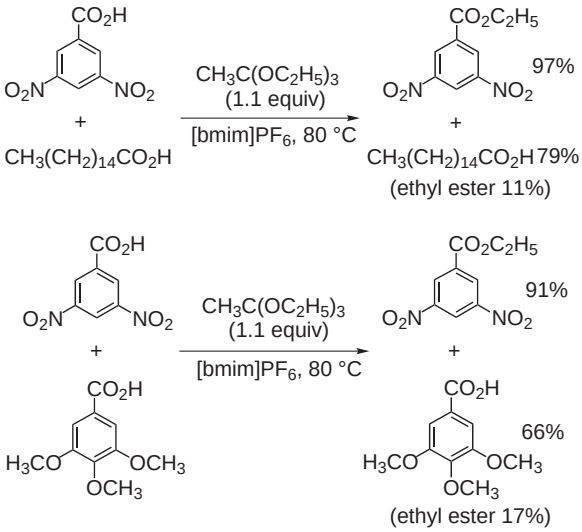
[a] Yields in parentheses refer to recovered carboxylic acid.
[b] Reaction temperature was 100 ºC.
[c] With the first regenerated [bmim]PF_6.
[d] With the second regenerated [bmim]PF_6.
[e] With the third regenerated [bmim]PF_6.
[f] With the fourth regenerated [bmim]PF_6.

Table 2 Esterification of Carboxylic Acids in [bmim]PF_6



Carboxylic Acid	Time (h)	Yield (%)
	3	97
	3	96
	12	96[a]

[a] Optically pure (Daicel Chiralcel OD-H; eluent: hexane–*i*-PrOH, 4:1).



Scheme 1

Thus, the present method is an operationally simple, inexpensive, efficient, and environmentally friendly esterification of carboxylic acids with triethyl orthoacetate under neutral conditions in [bmim]PF_6, and it can be used for various kinds of carboxylic acids, even those that are sterically hindered.[17]

Typical Experimental Procedure

A flask containing 1-butyl-3-methyl imidazolium hexafluorophosphate ([bmim]PF_6, 2.0 mL) as a solvent was dried under reduced pressure with a vacuum pump for 2 h at 80 °C. Then, 1-naphthoic acid (1.0 mmol) and triethyl orthoacetate (2.0 mmol) were added in the ionic liquid and the obtained mixture was heated at 80 °C under an argon atmosphere. The reaction was monitored by TLC until the starting 1-naphthoic acid disappeared. After 100 min., the mixture was extracted with Et_2O (5 × 5 mL). The combined Et_2O extract was purified by short column chromatography on silica gel (eluent: hexane–EtOAc, 9:1) to give pure ethyl 1-naphthalenecarboxylate in 98% yield (bp 120 °C/1 mmHg, lit.[15b] 100 °C/0.45 mmHg).

The recovered ionic liquid was washed with distilled water (5 mL) once and then dried under reduced pressure with a vacuum pump at 80 °C for 2 h, and the ionic liquid was repeatedly used for the same reaction.

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(17) Most ethyl esters were identified by comparison with authentic commercially available materials, or with spectroscopic and microanalytical data.