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A CONVENIENT METHOD FOR THE SYNTHESIS OF CARBOXYLIC ESTERS

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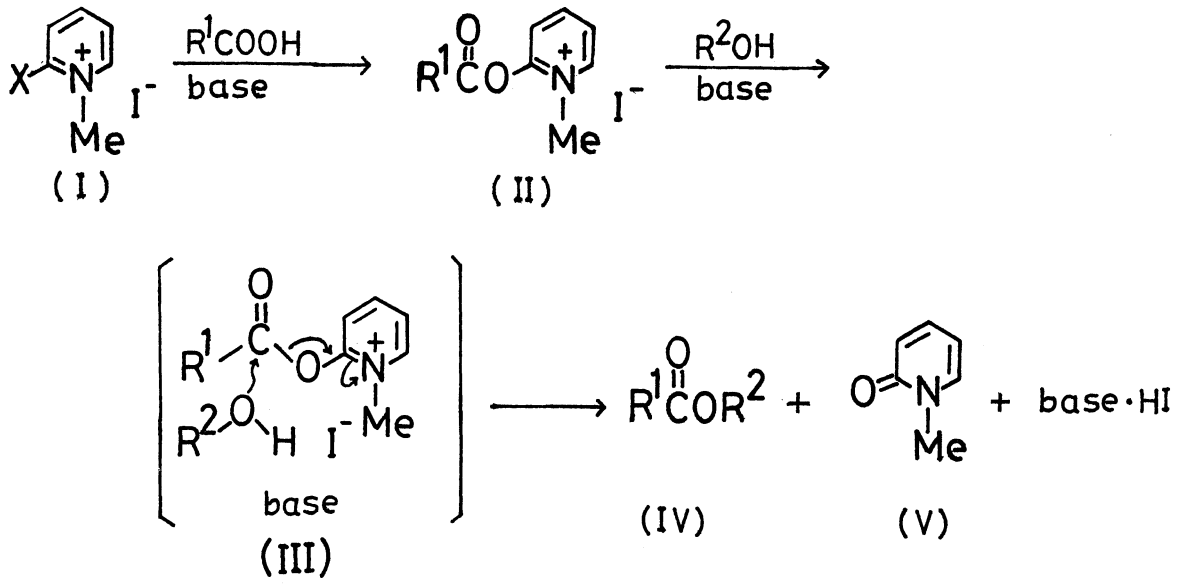
The equimolar reactions of carboxylic acids and alcohols with 1-methyl-2-halopyridinium salts in the presence of two equimolar amounts of tri-n-butylamine afforded the corresponding carboxylic esters in good yields.

The esterification reaction forming carboxylic esters is one of the most important and fundamental reactions in organic synthesis and many methods have been reported. However, relatively little work has been reported on the preparation of carboxylic esters by the equimolar reactions of free carboxylic acids and alcohols except for the esterification by using toluenesulfonyl chloride,[1] trifluoroacetic anhydride,[2] polyphosphate ester,[3] N,N'-dicyclohexylcarbodiimide[4] or graphite bisulfate[5] as a condensing reagent. In these reactions, 2-15 molar amounts of the condensing reagent are generally employed for the completion of the esterification.

In this communication, we wish to report a convenient method for the preparation of carboxylic esters by the equimolar reactions of carboxylic acids and alcohols with 1.2 moles of 1-methyl-2-halopyridinium salt and 2.4 moles of tri-n-butylamine based on the following consideration. Pyridinium salt (II) would be produced very rapidly by a nucleophilic attack of the carboxylate on 1-methyl-2-halopyridinium salt (I) because the halogen atom at the 2-position of I is facile to be displaced by the attack of nucleophiles. By the exchange of the counter anion, II is changed to a key intermediate (III), which is in turn converted into stable molecules, i.e., carboxylic ester (IV) and 1-methyl-2-pyridone (V).



As illustrated in the equation, since all the reacting species involved in this reaction would be in the close proximity of a central pyridinium salt, the condensation reaction should be entropically advantageous.

After a number of investigations on the reaction conditions, it was established that the present reaction could be carried out in a variety of solvents, such as toluene, dichloromethane, dimethoxyethane and pyridine, at the temperature ranging from room temperature to boiling point of the solvent. The optimum yield was given when the reaction was carried out in toluene or dichloromethane under refluxing by using 1.2 molar amounts of pyridinium salt and 2.4 molar amounts of tri-n-butylamine.

The typical procedure is described; to a suspended CH_2Cl_2 (2 ml) solution of 1-methyl-2-bromopyridinium iodide (720 mg, 2.4 mmol) was added a mixture of benzyl alcohol (216 mg, 2.0 mmol), phenylacetic acid (272 mg, 2.0 mmol) and tri-n-butylamine (888 mg, 4.8 mmol) in CH_2Cl_2 (2 ml) under an argon atmosphere, and the resulting mixture was refluxed for 3 hr. Dichloromethane insoluble pyridinium salt was progressively dissolved as the reaction proceeded. After evaporation of the solvent under reduced pressure, the residue was separated by silica gel column or thin layer chromatography, and benzyl phenylacetate was isolated in 97% yield.

In a similar manner, various esters were prepared in good yields as summarized in the Table. Further, it was found that the present reaction was applicable to the preparation of esters from sterically hindered carboxylic acids or alcohols.

Table. Esterification of Carboxylic Acid with Alcohol

Acid R^1	Alcohol R^2	Halogen X	Solvent	Isolated Yield[6] %
CH_3	$C_6H_5CH_2$	Br	CH_2Cl_2	80
CH_3	$C_6H_5CH{=}CHCH_2$	Br	CH_2Cl_2	80
C_6H_5	$C_6H_5CH_2$	Br	CH_2Cl_2	80 *
$C_6H_5CH_2$	CH_3CH_2	Br	CH_2Cl_2	92
$C_6H_5CH_2$	C_6H_5	Cl	CH_2Cl_2	90
$C_6H_5CH_2$	$C_6H_5CH_2$	Br	CH_2Cl_2	97
$C_6H_5CH_2$	$(CH_3)_3C$	Br	toluene	82
$C_6H_5CH_2$	$C_6H_5CH(CH_3)$	Cl	toluene	88
$C_6H_5CH{=}CH$	$C_6H_5CH_2$	Br	CH_2Cl_2	62 *
$(CH_3)_3C$	$C_6H_5CH_2$	Cl	toluene	62

* A small amount of acid anhydride was isolated as a by-product.

For instance, tert-butyl phenylacetate was successfully obtained in 82% yield from tert-butyl alcohol and phenylacetic acid and also benzyl pivalate was given in 62% yield by the reaction of benzyl alcohol with pivalic acid.

It is noted that the present reaction provides a convenient method for the preparation of various carboxylic esters including sterically hindered ones in good yields from equimolar amounts of carboxylic acids and alcohols. Further investigation on the preparation of lactones by an intramolecular cyclization of hydroxyacids is now in progress.

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