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CESIUM FLUORIDE-PROMOTED SYNTHESIS OF CARBOXYLIC ACID DERIVATIVES USING 2-FLUOROPYRIDINIUM SALT

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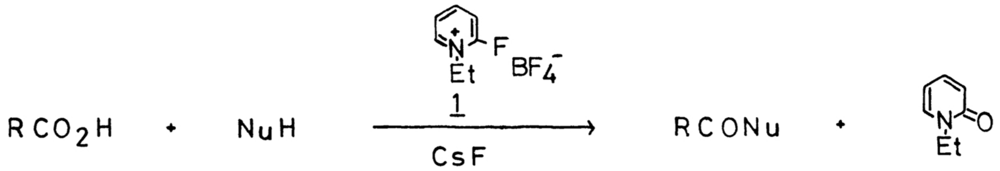
In the presence of cesium fluoride, the equimolecular reactions of carboxylic acids with alcohols, amines or thiols using 2-fluoropyridinium salt proceeded smoothly under mild conditions to afford the corresponding carboxylic acid derivatives with base sensitive groups in good yields.

Recently, much effort has been devoted to find effective acid captors in order to carry out various condensation reactions under mild conditions. On these lines, we have shown that the betaine, 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one, a rather weak base, is effectively employed as an acid captor in place of conventionally used tertiary amines for various acylation reactions using 2-halopyridinium salts.1)

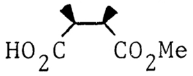
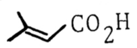
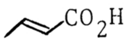
On the other hand, the fluoride ion has frequently been employed in synthetic reactions based on its characteristic property of forming a strong hydrogen bond with various protic organic compounds.2)

On the basis of these facts, the present communication describes a superior property of cesium fluoride as an acid captor over tertiary amines.3) Cesium fluoride is sparingly soluble in methylene chloride, but it activates protic organic compounds to behave as nucleophiles and it also accepts HF and HBF_4 formed during the condensation reaction. Actually, various carboxylic acid derivatives with base sensitive functional groups were obtained in good yields under essentially neutral conditions as depicted in the following equation.



The following is a typical procedure for the preparation of 3-phenyl 4-phenylbutanoate: A suspension of cesium fluoride4) (600 mg, 3.9 mmol), 1-ethyl-2-fluoropyridinium tetrafluoroborate 1 (256 mg, 1.2 mmol) and 4-phenylbutanoic acid (164 mg, 1.0 mmol) in methylene chloride (2 ml) was stirred for 30 min at room temperature. A methylene chloride (1 ml) solution of 3-phenylpropanol (163 mg, 1.2 mmol) was then added and the reaction mixture was stirred overnight at room temperature. As the reaction proceeded, the appearance of granulated cesium fluoride changed cloudy. Usual work-up and separation by TLC (silica gel) afforded 3-phenylpropyl 4-phenylbutanoate (265 mg) in 94% yield. In a similar manner, amides and thiol esters were prepared in good yields (see Table).

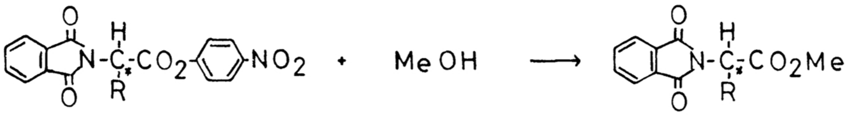
Table. Synthesis of Carboxylic Acid Derivatives[a)]

RCO_2H	NuH	Conditions Temp.	Conditions Time	Yield(%)
$Ph(CH_2)_3CO_2H$	$Ph(CH_2)_3OH$	r.t.	overnight	94
$Ph(CH_2)_3CO_2H$	3β-Cholestanol	r.t.	overnight	92
	MeOH[b)]	r.t.	1h	70[c)]
	$Ph(CH_2)_3OH$	r.t.	overnight	70
	$Ph(CH_2)_3OH$	r.t.	overnight	70
$Ph(CH_2)_3CO_2H$	$PhCH(CH_3)NH_2$	r.t.	1h	94
Z-Phe-OH	H-Gly-OEt	r.t.	1h	60
$Ph(CH_2)_3CO_2H$	PhSH	r.t.	3h	93
$Ph(CH_2)_3CO_2H$	$PhCH(CH_3)SH$	r.t.	3h	93

a) All compounds exhibited nmr and ir spectra in agreement with assigned structure.
b) Methanol was used in large excess.
c) No epimerization at α-carbon atom to carbonyl group was detected by gas chromatography.

According to the present reaction, α,β-unsaturated carboxylic esters can be prepared without isomerization of olefinic groups as shown in Table, while isomerization of the olefinic groups takes place when the same reaction is carried out in the presence of triethylamine instead of cesium fluoride.

Another excellent example indicating the usefulness of cesium fluoride was found in the formation of optically pure N-phthaloylamino acid methyl ester from the corresponding p-nitrophenyl ester and methanol in methylene chloride.[5)] In contrast, considerable racemization occurred when triethylamine was employed in the above reaction.



base \ R	O.P. (%) CH_3	O.P. (%) CH_2Ph
CsF	98	95
Et_3N	57	79

It is noted that various carboxylic acid derivatives having base sensitive functional groups can be successfully prepared under essentially neutral conditions by the employment of cesium fluoride.

References and Notes

1) E. Bald, S. Kobayashi, and T. Mukaiyama, Heterocycles, 1976, 1707, and references cited therein.
2) a) J. H. Clark and J. M. Miller, J. Am. Chem. Soc., 99, 498 (1977).
b) S. L. Beaucage and K. K. Ogilvie, Tetrahedron Lett., 1977, 1691.
3) Good results could not be obtained when other fluoride ion sources, such as potassium fluoride and tetrabutylammonium fluoride were used.
4) Cesium fluoride was thoroughly dried by heating at 130°C for few hours in vacuo.
5) Optical purity of the methyl esters were decided by comparing the optical rotations with those of methyl esters prepared from N-phthaloylamino acids and diazomethane.

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