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BETAINE AS AN EFFECTIVE ACID CAPTOR: A CONVENIENT METHOD FOR THE SYNTHESIS OF CARBOXAMIDES

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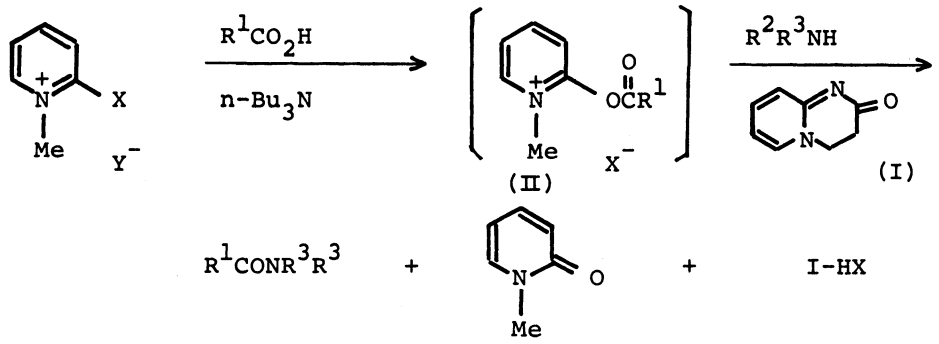
The equimolar reactions of carboxylic acids and amines with 1-methyl-2-fluoro or 2-chloropyridinium salt by the successive use of 1 mol of tri-n-butylamine and the betaine, (3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (I)), afforded the corresponding carboxamides in good yields.

In the course of our continuing investigations[1)] on the development of new synthetic method by utilizing 2-halopyridinium salts, it has recently been found that the betaine, 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (I)[1d)], can act as an effective hydrogen halide captor in the formation of an ester by the equimolar reaction of a carboxylic acid and an alcohol. Then we investigated the carboxamide formation using the pyridinium salt in the presence of the betaine (I) as a hydrogen halide captor instead of tri-n-butylamine employed in the previous experiment[1b)] in order to make the reaction medium almost neutral during the coupling reaction.

In the first place, the reaction of equimolar amounts of a carboxylic acid and an amine with 1.2 mol of the pyridinium salt and 2.4 mol of the betaine (I) was examined under various conditions. However, the corresponding carboxamide resulted only in a poor yield.

This result would be probably due to the consumption of 1 mol of the amine as the amine-hydrogen halide in the stage of forming a key intermediate, 2-acyloxypyridinium salt (II). After a number of examinations, it was found that the treatment of a carboxylic acid with the pyridinium salt and tri-n-butylamine leading to the initial in situ formation of the 2-acyloxypyridinium salt, and the

successive addition of an amine and the betaine (I) affords a high yield of carboxamide as illustrated in the following equation.



The typical procedure is described for the preparation of N-n-butylphenylacetamide; to 1-methyl-2-fluoropyridinium tosylate (300 mg, 1.06 mmol) was added a methylene chloride solution (6 ml) of phenylacetic acid (136 mg, 1.0 mmol) and tri-n-butylamine (185 mg, 1.0 mmol) at 0°C under argon atmosphere, and the resulting mixture was stirred for 1 hr at 0°C. After the addition of 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (I) (178 mg, 1.2 mmol) and a methylene chloride solution (4 ml) of n-butylamine (73 mg, 1.0 mmol) at 0°C, stirring was continued for an additional 2 hr at 0°C. The reaction mixture was quenched with water and the product was extracted with methylene chloride. The methylene chloride layer was successively washed with aqueous $NaHCO_3$ solution, 0.5% aqueous HCl solution, water, and brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was separated by silica gel thin layer chromatography to afford N-n-butylphenylacetamide (191 mg) in a quantitative yield.

In a similar manner, various carboxamides were prepared in high yields as summarized in the Table.

Table. The Preparation of Carboxamides

Acid	Amine		Halogen	Isolated Yield[2)]
R^1	R^2	R^3	X	(%)
$C_6H_5CH_2CH_2$	n-C_4H_9	H	F	96
$C_6H_5CH_2CH_2$	n-C_4H_9	n-C_4H_9	F	89
$C_6H_5CH_2CH_2$	t-C_4H_9	H	F	70
$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	H	F	93
$C_6H_5CH_2CH_2$	C_6H_5	H	F	82
$C_6H_5CH_2$	n-C_4H_9	H	F	quant.
$C_6H_5CH_2$	n-C_4H_9	n-C_4H_9	F	96
$C_6H_5CH_2$	t-C_4H_9	H	F	88
$C_6H_5CH_2$	C_6H_5	H	F	90
$C_6H_5CH_2$	C_6H_5	H	F	82
C_6H_5	n-C_4H_9	H	Cl	83*
C_6H_5	n-C_4H_9	n-C_4H_9	Cl	90*
C_6H_5	t-C_4H_9	H	Cl	78*
C_6H_5	$C_6H_5CH_2$	H	Cl	78*
CH_3CH_2	$C_6H_5CH_2$	H	F	76
CH_3CH_2	$C_6H_5CH_2$	CH_3	F	82
$(CH_3)_3C$	$C_6H_5CH_2$	H	F	84

* The methylene chloride solution of benzoic acid, an amine, tri-n-butylamine, the pyridinium salt, and the betaine (I) was refluxed for 3 hr.

It should be noted that the use of the betaine (I) as an acid captor afforded various carboxamides including hindered ones in high yields under almost neutral condition in coupling reaction of acids and amines with 2-halopyridinium salts. Further applications of the utility of the betaine (I) are now in progress.

REFERENCES

1) (a) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1045 (1975).
(b) E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1163 (1975).
(c) T. Mukaiyama, S. Ikeda, and S. Kobayashi, Chem. Lett., 1159 (1975).
(d) T. Mukaiyama, H. Toda, and S. Kobayashi, Chem. Lett., 13 (1976).
2) All compounds exhibited correct ir and nmr spectral data.

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