CHEMISTRY LETTERS, pp. 13-14, 1976. Published by the Chemical Society of Japan

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

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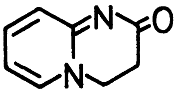
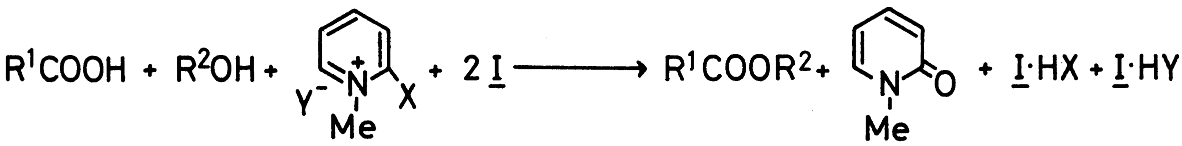
The equimolar reactions of carboxylic acids and alcohols with 1-methyl-2-fluoro or -2-chloropyridinium salt in the presence of a betaine, (3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one(I)), afforded the corresponding carboxylic esters in good yields.

A convenient method for the preparation of carboxylic esters by the equimolar reactions of carboxylic acids and alcohols with 1.2 mol of 1-methyl-2-fluoro or -2-chloropyridinium salt and 2.4 mol of tri-n-butylamine has been reported in the previous paper.1)

Recently such reactions as to proceed under mild and almost neutral conditions are required for the effective application to the synthesis of complex molecules having a base or an acid sensitive functional group. Therefore we investigated the development of a suitable acid captor in place of a base as tri-n-butylamine employed in the above mentioned experiment in order to keep the reaction medium almost neutral during the reaction. It was thought that a betaine would be one of the most promising acid captor since a betaine itself is an almost neutral substance and is readily converted to a salt by the interaction with an acid.

After a number of experiments based on the above consideration, 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one,  (I), prepared easily from 2-aminopyridine and ethyl acrylate,2) was found to be effective as the acid captor . In this communication, the usefulness of the betaine I in the synthesis of carboxylic esters according to the reaction shown in the following equation is described.



The effect of solvent was examined using phenylacetic acid and benzyl alcohol as model substrates, and methylene chloride or acetonitrile was found to be the most profitable solvent. In the other solvents such as benzene, ethyl acetate, pyridine and dimethoxyethane, benzyl phenylacetate was obtained in more than 90% yield, but the ester forming reaction was slightly slower than in the former solvent such as methylene chloride or acetonitrile.

The typical procedure is described for the preparation of benzyl phenylacetate; to a mixture of 1-methyl-2-chloropyridinium iodide (308 mg, 1.2 mmol) and betaine I (355 mg, 2.4 mmol) was added a methylene chloride solution (10 ml) of phenylacetic acid (137 mg, 1.0 mmol) and benzyl alcohol (109 mg, 1.0 mmol) at room temperature under an argon atmosphere, and the resulting mixture was stirred at room temperature for 3 hr. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel, and benzyl phenylacetate was isolated (220 mg, 96% yield).

In a similar manner various carboxylic esters were prepared in good yields as summarized in the following Table.

Table. The Synthesis of Carboxylic Esters

Acid^a	Alcohol^b	Pyridinium Salt^c		Reaction Time (hr)	Volume of Solvent (ml)	Isolated Yield (%)$^{3)}$
R^1	R^2	X	Y			
$PhCH_2$	$PhCH_2$	Cl	I	3	10	96^d
$PhCH_2$	Ph	Cl	I	3	10	78^d
$PhCH_2$	$PhCH{=}CHCH_2$	Cl	I	3	10	97^d
$PhCH_2$	$CH_3CH{=}CHCH_2$	Cl	I	3	10	94^d
$PhCH_2$	$CH_3(CH_2)_3$	Cl	I	3	10	89^d
$PhCH_2$	$CH_3CH_2CH(CH_3)$	Cl	I	3	10	72^d
$PhCH_2$	$(CH_3)_3C$	Cl	I	8	4	72^e
$PhCH_2CH_2$	$PhCH_2$	F	TsO	6	4	74^e
CH_3CH_2	$PhCH{=}CHCH_2$	F	TsO	7.5	4	60^e
$CH_3(CH_2)_3$	$PhCH_2$	F	TsO	46	4	74^e
$CH_3(CH_2)_{10}$	$PhCH_2$	F	TsO	——^{f}	10^g	42^d

Condition; in CH_2Cl_2 at r.t. a. 1.0 mmol, b. 1.0 mmol, c. 1.2 mmol, d. betaine 2.4 mmol, e. betaine 4.8 mmol, f. at r.t. for 1 hr, and then reflux for 5 hr, g. in $ClCH_2CH_2Cl$.

It should be noted that the betaine I is an effective acid captor in various condensation reactions and the present method would be successfully applied to the preparation of various carboxylic esters or lactones with base sensitive functional group in the same molecule. Further works on the utility of the betaine I are now in progress.

REFERENCES

1) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1045 (1975).
2) R. Adams and I. J. Pachter, J. Amer. Chem. Soc., 74, 5491 (1952).
3) All compounds exhibited correct ir and nmr spectral data.

(Received October 24, 1975)