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A SIMPLE GENERAL METHOD FOR THE ACYLATION OF ETHYL INDOLE-2-CARBOXYLATES

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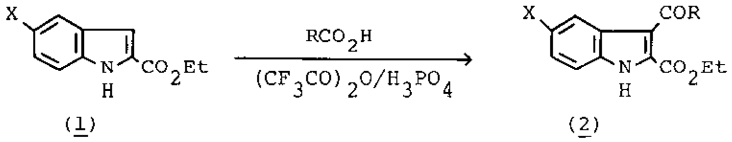
Abstract——Reaction of ethyl indole-2-carboxylates(1) with carboxylic acids in acetonitrile, using trifluoroacetic anhydride-phosphoric acid gave the ethyl 3-acylindole-2-carboxylates (2) in satisfactory yields. The present method provides a simple general method for acylation of ethyl indole-2-carboxylates.

Acylation reaction of indoles at their C-3 position is one of the important and fundamental reactions in the indole chemistry, and well documented1). On the other hand indole-2-carboxylic acids or their esters(1) are known2) to serve as stable synthon. However, acylation of them(1) has been little known except for the formylation3,4), because their reactivity at the C-3 position is decreased by carbonyl group at the C-2 position. Since we required some 3-acylindole-2-carboxylic esters during the course of our program on the synthetic indole chemistry, we investigated to develop the acylation of them(1). We now wish to report a simple general method for direct acylation of ethyl indole-2-carboxylates (1) using various carboxylic acids as acylating reagents.

Trifluoroacetic anhydride has been known as a good activating reagent of carboxylic acids for the preparation of ester5), lactone6), or ketone7). Now we found that the treatment of ethyl indole-2-carboxylates(1) and carboxylic acids with trifluoroacetic anhydride-phosphoric acid7) in acetonitrile gave 3-acylindoles(2) in satisfactory yields. The result is summarized in the Table8). The yields ranges from 21.4 to 93.2 %, which are dependent on the kind of carboxylic acids and the substituents of indoles(1). Aliphatic carboxylic acids gave somewhat better yields than aromatic ones. Main by-product was anhydride of the carboxylic

Table



Starting indole(1) X=	Carboxylic acid R=	Reaction condition time(hr)	temperature	3-Acylindole(2) yield(%)a)	mp	Recovered indole(1) %
H	Me-	5	r.t.	64.0	96-97.5°	3.8
H	n-Pro-	5	r.t.	84.4	57-58°	0
H	t-Bu-	1	r.t.	93.2	103.5-105°	0
H	Ph-	5	r.t.	62.2	135-136.5°	27.5
H	p-NO$_2$Ph-	5.5	50°	21.4	189-190.5°	31.1
H	p-MeOPh-	6.5	r.t.	73.9	134-136.5°	6.5
MeO	n-Pro	6.5	r.t.	34.8	84.5-85.5°	12.7
MeO	Ph-	5.5	r.t.	44.0	132.5-134°	28.2
Cl	n-Pro-	5.5	r.t.	65.8	126-128.5°	22.7

a) based on indole(1).

acid, (RCO)$_2$O, which was actually obtained in the cases of aromatic acid, while yields of N-acyl indoles were very minute(below 5 % or none). 3-Trifluoroacetyl indole derivative was not found. Treatment of indole itself and acetic acid with the same reagent gave a complex mixture instead of the expected 3-acetyl indole. However, this defect can be compensated, as the hydrolysis followed by decarboxylation of 3-acyl compound(2) should easily give9) 2-unsubstituted-3-acylindole.

General Procedure: Trifruoroacetic anhydride(2.4 mmoles) was added to the solution of a carboxylic acid(2.4 mmole) and phosphoric acid(0.27 mmole) in acetonitrile(1.8 ml) at room temperature under argon atmosphere, and the whole was stirred for 5 to 10 min. Then the solution of indole derivative(1)(0.8 mmole) in acetonitrile(1.7-9.0 ml) was added to the resulted solution at room temperature. After stirring for 1 to 6.5 hr at the noted temperature, with monitoring by TLC, the reaction mixture was poured into water and extracted with ether. The crude product(2) was purified by column chromatography on silica gel.

In summary the present method provides a mild and convenient procedure for acylation of ethyl indole-2-carboxylates(1). Because, usual acylating reagents for indoles have usually been carboxylic acid derivatives, while the present method involves carboxylic acids as reagent.

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9. Usually, 2-ethoxycarbonyl group of ethyl indole-2-carboxylate derivative can easily be removed.10) By this method we obtained 3-acetylindole from 3-acetyl-2-ethoxycarbonyl compound(2, X=H, R=Me) in good yield.
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