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FORMATION OF 6-ACYLINDOLES FROM 1-ACYLINDOLES

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Abstract : 1-Acylindoles react regioselectively with α-halogenoacyl chloride in the presence of aluminum chloride to produce 1-acyl-6-halogenoacylindoles in excellent yields.

Regioselective substitution on indole is one of the most important problems in indole chemistry and many substitution methods have been developed for many years. Acylations are the best known of a family of substitution reactions, of which the Friedel-Crafts acylations are also commonly used members. These reactions have achieved special importance for the preparation of pharmacologically active indole derivatives. A number of 6-substituted indole derivatives are significant because of biological activity. Increasing importance of substitution reaction at the 6-position of indole prompted us to challenge a new possibility to develop a simple and efficient method starting from easily available indole.

The acylation of indoles has been a rather widely used synthetic method for some time. The 2- and 3-positions of the indole ring are the normal sites of attack. The direct acylations at the 6-position of 2,3-unsubstituted indole have been studied, however, the acylations take place not at the desired 6-position but only at the 2- and 3-position, because of its much more nucleophylic activity of the 2- and 3-positions than benzene part of indole ring. Indoles which have a substituent at the benzene part have usually been prepared from the benzene derivatives which are already carrying the substituent.

In the presence of reactive acylating agents, 2,3-dialkylated indoles can be acylated in the benzene part.[1, 2] The acetylation of 3-acetylindole and alkyl 3-indolecarboxylate with acetyl chloride - aluminum chloride has been reported to give 5-, 6- or 7-acetyl derivatives.[3, 4] 1-Acetyl-2,3-dialkylindoles are acetylated in good yield at the 6-position under Friedel-Crafts conditions.[5, 6] It is pointed out there that the 6-position of 1-acylindoles is more reactive than other positions of the benzene part of indole ring. Based on the results, a new possibility was considered that 3-unsubstituted 1-acylindoles might afford regioselective acylations at the 6-position under especial conditions.

In this paper, we would like to report highly regioselective Friedel-Crafts acylations at 6-position of 2,3-unsubstituted indole derivatives by using α-halogenoacyl chloride - aluminum chloride. In the initial approach, acetyl chloride and aluminum chloride as acetylation agents were employed for the acetylation of various 1-acylindoles (**1a~d**), prepared from indole and the corresponding alkanoyl chlorides (NaH / DMF). While 1-acetylindole (**1a**) was acetylated in good yield, the acetylated products were 1,3-diacetylindole (40% yield) and the desired 1,6-diacetylindole (30% yield) as shown in Table 1 (Entry 1). 1-Pivaloylindole (**1b**), 1-methoxycarbonylindole (**1c**) and 1-chloroacetylindole (**1d**) were acetylated only at the 3-position of indole ring in 80 ~ 90% yields (Entry 2 ~ 4). Subsequently, it was found that treatment of 1-acylindole (**1a~d**) with excess α-halogenoacyl chlorides in 1,2-dichloroethane in the presence of excess aluminum chloride gave regioselectively 6-acylindoles in 16 ~ 83% yields. Table 1 (Entry 5 ~ 14) details the results.

A typical experimental procedure is as follows ; to a stirred suspension of aluminum chloride (89 g, 0.67 mol), in 1,2-dichloroethane (600 ml), was added dropwise chloroacetyl chloride (56 ml, 0.70 mol) at 0 °C. After completion of addition, the mixture was kept at ambient temperature for 15 min, after which time 1-pivaloylindole (30 g, 0.15 mol) was added over 3 h. After completion of addition, the resulting mixture was stirred for 15 min at ambient temperature, then poured into ice-cooled water, and extracted

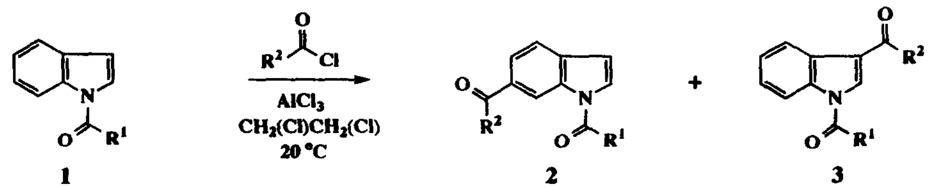

Table 1 Friedel-Crafts acylations of 1-acylindoles with alkanoyl chlorides [a]

Entry	Substrate (1)	Alkanoyl chloride	Position of acylation and yield(%) [b]	
	R^1	R^2	C-6 (**2**)	C-3 (**3**)
1	CH_3 (**1a**)	CH_3 [c]	30	40
2	$(CH_3)_3C$ (**1b**)	CH_3	0	80
3	CH_3O (**1c**)	CH_3	0	88
4	$ClCH_2$ (**1d**)	CH_3	0	90
5	CH_3 (**1a**)	$ClCH_2$	80	0
6	$(CH_3)_3C$ (**1b**)	$ClCH_2$	73	0
7	CH_3O (**1c**)	$ClCH_2$	60	25
8	$ClCH_2$ (**1d**)	$ClCH_2$	80	0
9	$(CH_3)_3C$ (**1b**)	$BrCH_2$ [d]	58	0
10	$(CH_3)_3C$ (**1b**)	$CH_3CH(Cl)$	83	0
11	$(CH_3)_3C$ (**1b**)	$CH_3CH(Br)$	78	0
12	$(CH_3)_3C$ (**1b**)	$CH_3CH_2CH(Cl)$ [e]	50	0
13	$(CH_3)_3C$ (**1b**)	$(CH_3)_2CHCH(Cl)$ [f]	39	0
14	$(CH_3)_3C$ (**1b**)	$(CH_3)_3CCH(Cl)$ [g]	16	0

[a] With 4.5 equiv. alkanoyl chloride and 4.7 equiv. aluminum chloride in 1,2-dichloroethane at 20 °C. [b] Isolated yield after purification by silica gel chromatography. [c] This reaction was performed at 50 °C. [d] Fresh bromoacetyl chloride prepared by bromoacetic acid and thionyl chloride was used. [e] 2-Chlorobutyryl chloride was prepared by butyryl chloride and sulfuryl chloride. [f] 2-Chloroisovaleryl chloride was prepared by isovaleryl chloride and sulfuryl chloride. [g] 2-Chloro-3,3-dimethylbutyryl chloride was prepared by 3,3-dimethylbutyryl chloride and sulfuryl chloride.

with 1,2-dichloroethane. The 1,2-dichloroethane extract was thoroughly washed with water three times and 5% $NaHCO_3$ aqueous three times, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was crystallized from methyl alcohol to give 6-chloroacetyl-1-pivaloylindole (25 g, 60% yield) as white needles. The second crop (5.4 g, 13% yield) and 4-chloroacetyl-1-pivaloylindole (1.7 g, 4% yield) were obtained from the mother liquor by silica gel column chromatography.

In summary, this work has first demonstrated that the regioselective Friedel-Crafts acylations at 6-position of 1-acyl indoles are realized by using α-halogenoacyl chloride and aluminum chloride. The applications of these 6-α-halogenoacylindoles are under investigation.

References and Notes

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