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C_3-ACYLATION OF INDOLES *VIA* C_3-LITHIATION DIRECTED BY THE C_2-CARBOXYL GROUP[1]

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Abstract - N-Protected indole-2-carboxylic acid (1) was lithiated at the 3-position using *sec*-BuLi in the presence of an additive (HMPA) in THF, and then acylated at that position regioselectively by subsequent treatment with ester or DMF in moderate yields.

As C_3-acylation is one of the most important reactions in indole chemistry, we have continuously studied[2,3] it using ethyl indole-2-carboxylate in acidic condition. However, these methods have some limitations that strongly electronegative acyl groups, such as chloroacetyl one, were introduced at 3-position in only poor yields[2] or substituted preferentially in the benzene moiety.[3] Thus, we have further examined regioselective C_3-acylation and now report the first regioselective C_3-acylation of indole *via* C_3-lithiation directed by the C_2-carboxyl group. A solution of 1-methoxymethylindole-2-carboxylic acid (1, 0.5 mmol) and HMPA (1.3 mmol) in THF was treated with *sec*-BuLi (1.3 mmol) at -78°C for 20 min. To the solution containing resulting intermediate 2 was added electrophile (1.5 mmol), and then the whole was allowed to react at room temperature for the period shown in the Table. After usual work-up procedure the resulting carboxylic acid was converted to corresponding methyl ester (3) with CH_2N_2 for purification. The result is shown in the Table. The yield of the deuteration (run 1) was calculated by multiplication of chemical yield (84%) and D% (76%) measured by the mass spec-

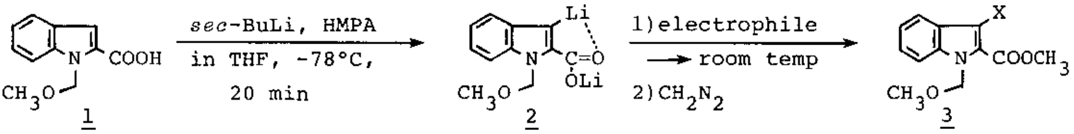

Table. C_3-Acylation of Indole *via* C_3-Lithiation ($\underline{1} \longrightarrow \underline{3}$)

Run	electrophile	Reaction time	Product ($\underline{3}$) X=	Yield (from $\underline{1}$)	S.M.[a] ($\underline{3}$, X=H) Recovery
1	D_2O	30 min	-D	64%	20%[b]
2	DMF	60 min	-CHO	60%	17%
3	$C_2H_5COOC_2H_5$	30 min	$-COC_2H_5$	48%	35%
4	$ClCH_2COOC_2H_5$	60 min	$-COCH_2Cl$	41%	43%

a) A methyl ester of starting material ($\underline{1}$)

b) Estimated by the chemical yield and the product yield

trum. All reactions proceeded at the 3-position exclusively.
There have been only limited reports[4,5,6] on C_3-lithiation of indoles, while the C_2-lithiation and its application have been studied extensively.[7] Present C_3-acylation of indole is based on the first C_3-lithiation directed by C_2-carboxyl group, being developed on the basis of two directed lithiations, C_3-carboxylation in benzofuran-2-carboxylic acid[8] and C_2-acylation in indole-1-carboxylic acid.[9] The method is complementary with our previous method[3] in regioselectivity and is superior to the C_3-acylation *via* lithiation directed by C_2-carboxamide[4] in wide applicability. Therefore it can be applied to syntheses of various kinds of C_3-substituted indoles hardly prepared by other methods.

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