FRIEDEL–CRAFTS ALKYLATION OF INDOLES

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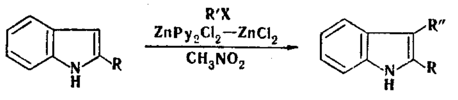
The alkylation of indole and 2-methylindole with alkyl halides in the presence of a complex catalyst – dipyridinezinc chloride – was investigated. Nitromethane was used as the solvent. 3-Alkylindoles were obtained in 30-80% yields in all cases. The reaction mechanism is discussed. Data from the PMR and mass spectra are presented.

The Friedel–Crafts alkylation of indoles has not been studied heretofore, since the acidophobic character of indoles leads to pronounced resinification of the reaction mixtures. This difficulty could be partially overcome by carrying out the reaction in ether in the presence of zinc chloride and anhydrous zinc acetate, which ties up the resulting strong acid [1, 2]. However, the low solubility of zinc acetate in ether and the increase in the concentrations of the catalyst and the overall acidity of the medium during the reaction have a negative effect on the course of the alkylation. The yields of 3-alkylindoles did not exceed 30% even with such active alkyl halides as tert-butyl chloride and allyl chloride, and a considerable amount of polyalkylation occurred, despite the presence of a large amount of uncharged indole in the reaction medium. All of this indicates the relative freedom of the "carbonium ion," and one can consequently expect isomerization processes in the alkyl group. Thus this reaction is a "classic" variant of Friedel–Crafts alkylation with all of its shortcomings.

We have developed [3] a rather efficient method for the introduction of alkyl substituents in the 3 position of the indole molecule by alkylation of indoles with alkyl halides in nitromethane in the presence of dipyridinezinc chloride (see Table 1):



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It is important that the dipyridinezinc chloride, which is responsible for tying up the acid liberated during the reaction, is soluble in nitromethane.

As expected, in the alkylation of indole with isomeric butyl halides, their activities increase in the order primary < secondary < tertiary; however, the fact that alkyl bromides are more active than alkyl chlorides is unusual for the Friedel–Crafts reaction.

A control experiment established that a catalytic reaction rather than the direct alkylation that might have been expected for the above order actually occurs in this case.

The true catalyst of the alkylation is evidently pyridinezinc chloride, since the coordination-saturated dipyridinezinc chloride cannot be an effective alkylation catalyst, and zinc chloride is less soluble in nitromethane and dissolves gradually only on contact with a solution of dipyridinezinc chloride. It should be noted that prior preparation of the dipyridinezinc chloride is not necessary: It is sufficient to add an equimolar amount of pyridine to a suspension of zinc chloride in nitromethane and to stir the mixture with heating until the solids dissolve (5-10 min).

The reaction scheme can probably be represented as follows:

$$S + ZnPy_2Cl_2 \rightleftharpoons S \ldots ZnPyCl_2 + Py \tag{1}$$

$$S + ZnCl_2 + Py \rightleftharpoons S \ldots ZnPyCl_2 \tag{2}$$

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TABLE 1. Conditions for the Alkylation of Indoles and Characteristics of the Compounds Obtained

Compound	R	R′	X	R″	Reaction time, h	Picrate, mp, °C	PMR spectrum, ppm	Mass spectrum, m/e (intensity in % of the maximum ion peak)	Yield, %
Ia	H	n-C_4H_9	Br	n-C_4H_9	8	113—114	0,87 (3H, t, J=9 Hz, CH_3), 1,50 (4H,m, CH_2CH_2), 2,70 (2H, t, J=9 Hz, CH_2), 6,57 (1H, d, J=1,5 Hz, 2-H)	173 (14,7), 143 (2,7), 130 (100), 117 (2,7), 115 (4,0)	30
Ib	H	s-C_4H_9	Br	s-C_4H_9	7	90—91	0,85 (3H, t, J=10 Hz, CH_3), 1,27 (3H, d, J=10 Hz, CH_3), 1,60 (2H, m, CH_2), 2,87 (1H, m, J=10 Hz, CH), 6,60 (1H, d, J=2 Hz, 2-H)	173 (21,4), 158 (7,1), 144 (100), 130 (5,0), 117 (13,6), 115 (6,4)	35
Ic	H	i-C_4H_9	Cl	t-C_4H_9	15	106—107 67*	1,40 (9H, s, $C(CH_3)_3$) 6,62 (1H, d, J=2 Hz, 2-H)	173 (13,0), 158 (100), 143 (13,0), 130 (24,0), 117 (14,1)	52
Ic	H	i-C_4H_9	Br	t-C_4H_9	8				78
Ic	H	t-C_4H_9	Cl	t-C_4H_9	5				85
Ic	H	t-C_4H_9	Br	t-C_4H_9	2				72
Id	H	$C_6H_5C(CH_3)C_2H_5$	Cl	$C_6H_5C(CH_3)C_2H_5$	20†	106—107*	0,70 (3H, t, J=5,5 Hz, CH_3), 1,65 (3H, s, CH_3), 2,20 (2H, m, CH_2)		78
Ie	CH_3	$C_6H_5C(CH_3)C_2H_5$	Cl	$C_6H_5C(CH_3)C_2H_5$	24†	120—121*	0,70 (3H, t, J=5,5 Hz, CH_3), 1,70 (3H, s, CH_3), 2,03 (3H, s, 2-CH_3), 2,25 (2H, q, J=5,5 Hz, CH_2)		77

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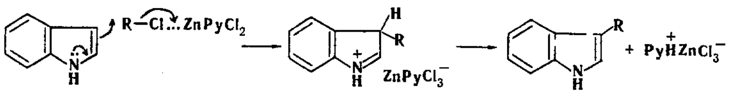
* This is the melting point of the corresponding indole.

† The reaction was carried out at room temperature.

$$R{-}Cl + S\ldots ZnPyCl_2 \rightleftharpoons \underset{II}{R{-}Cl\ldots ZnPyCl_2} + S \qquad (3)$$



(4)

$$S + 2\,ZnPyCl_3^- \rightleftharpoons S\ldots ZnPyCl_2 + ZnCl_4^{2-} + Py$$

$$S{=}CH_3NO_2 \qquad (5)$$

Pyridinium trichlorozincate rather than pyridinium tetrachlorozincate is evidently formed during the reaction [4], i.e., equilibrium (5) is shifted markedly to the left, since the yields of alkylation products depend on the amount of zinc chloride introduced into the reaction.

It was demonstrated by chromatographic mass spectrometry that isomerization of the alkyl groups does not occur in the alkylation of indole with primary and secondary butyl bromides. This is probably associated with the weakness of complex II, which is due to deactivation of the zinc chloride by complexing with pyridine. This may also explain the higher activity of bromides as compared with chlorides: the increase in the polarizability of the C–X bond on the background of weak interactions in the II complex with an excess compensates for the decrease in the effectiveness of the X...Zn interaction on passing from chlorides to bromides.

However, isomerization always occurs in the alkylation of indole with isobutyl chloride and bromide, and 3-tert-butylindole is formed. Even weak catalysis is evidently sufficient for isomerization in this case (isobutyl bromide readily undergoes rearrangement to tert-butyl bromide even when it is heated [5]).

The weakness of the II complex and the fact that the energy of cationic localization in the indole molecule is higher for the 1 position than for the 3 position [6] entail high selectivity of the alkylation (the 3-butylindole : 1-butylindole ratio in the alkylation with n-butyl bromide is greater than 10), and this leads to a decrease in polyalkylation. In conformity with the activity : selectivity ratio, the latter should increase on passing from bromides to chlorides and from tertiary alkyl halides to primary halides; this is actually observed experimentally.

Thus the investigated reaction is a convenient method for the synthesis of the previously inaccessible 3-alkylindoles, particularly those with branched groups.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source of an ionizing-electron energy of 50 eV. The chromatographic mass-spectral studies were carried out with a Varian MAT-111 spectrometer with a 2-m long column filled with 5% SE-30 on Chromosorb W at an ionizing-electron energy of 80 eV.

The alkylindoles were isolated by chromatography with columns filled with silica gel L (40-100 μ) with elution by CCl_4. Monitoring of the reactions and chromatographic separation were accomplished by thin-layer chromatography (TLC) on Silufol UV-254 plates in a hexane–benzene system (1 : 1).

Commercial analytical-grade anhydrous zinc chloride (GOST 4529-48) was used for the experiments.

Dipyridinezinc Chloride. Excess dry pyridine was added with cooling and stirring to anhydrous zinc chloride (the reaction was exothermic!), after which the mixture was cooled, transferred to a filter, and washed with dry ether. The resulting white powder was stable and nonhygroscopic.

General Method of Alkylation. A 2.20-g (7.5 mmole) sample of dipyridinezinc chloride, 1.02 g (7.5 mmole) of anhydrous zinc chloride, and 15 mmole of alkyl halide were added to a solution of 10 mmole of indole in 35 ml of dry nitromethane, and the mixture was refluxed. When alkyl halides that split out hydrogen halide on heating were used, the reaction was carried out at lower temperatures. At the end of the reaction, the bulk of the nitromethane was removed by distillation, the residue was poured into water, and the aqueous mixture was extracted with benzene. The benzene layer was dried and evaporated, and the residue was chromatographed.

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EFFECT OF PROTECTION OF AMINO GROUP ON DIRECTION OF REACTION OF 2-AMINOINDOLE WITH α,β-UNSATURATED KETONES

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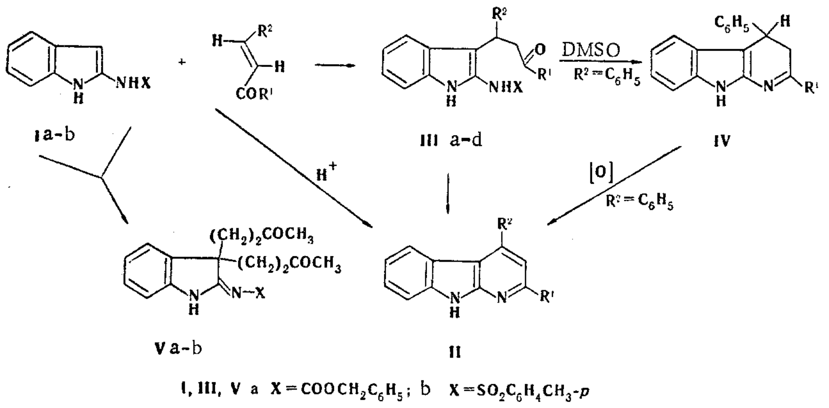
The electron-acceptor properties of arylsulfonyl and carbobenzoxy groups decrease the probability of primary electrophilic attack at the nitrogen atom. They also determine primary attack at the 3-C atom of the indole ring. Michael addition products, 3,4-dihydro-α-carbolines, and α-carbolines themselves are obtained, depending on the reaction conditions. The reaction with α,β-unsaturated ketones proceeds under milder conditions in the case of 2-benzyloxycarbonylaminoindole.

The 2-aminoindole molecule has three interrelated nucleophilic centers, and two different pairs of these centers (both nitrogen atoms or the nitrogen atom of the amino group and the 3 position of indole) consequently react with 1,3-difunctional compounds, depending on the conditions, to give pyrimidoindole or α-carboline structures [1]. However, if the amino group is protected with a tosyl or carbobenzoxy grouping, the analogous cyclization with 1,3-dioxo compounds proceeds with detachment of the protective group, and only α-carbolines are formed [2, 3]. Intermediate addition products and substances whose synthesis proceeds with involvement of the pyrrole imino group cannot be detected.

We have found that the corresponding α-carbolines (II) are also formed in the condensation of 2-carbobenzoxyaminoindole (Ia) with α,β-unsaturated ketones (in ethanol containing hydrobromic acid), although the process takes place in a considerably more complex manner in some cases. If benzalacetophenone or benzalacetone participates in the condensation, the reaction requires prolonged heating, and the carbolines are obtained in low yields; i.e., both the electrophilicity of the β-carbon atom of the double bond of the unsaturated ketone and the steric hindrance at this atom, which has a greater effect on attack at the 3-C atom, have a substantial effect on the process.



I, III, V a $X=COOCH_2C_6H_5$; b $X=SO_2C_6H_4CH_3$-*p*

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