# HETEROCUMULENES IN HETEROARYLATION

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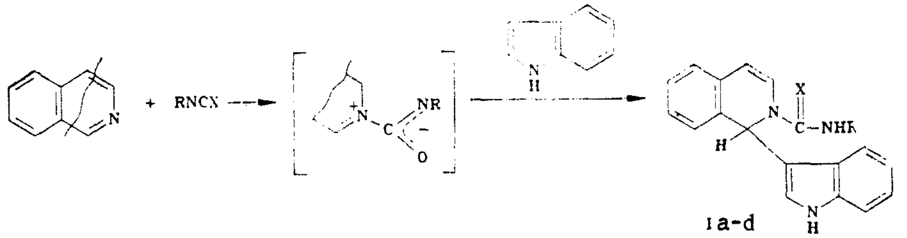
*It was discovered that certain heterocumulenes, such as isocyanates, chloroalkyl isocyanates, and isothiocyanates, can be used as activation agents for the isoquinoline series in the heteroarylation of indole and trinitrotoluene.*

The direct heteroarylation of nucleophilic organic compounds by N-heteroaromatic bases (azines, azoles) in the presence of acylating agents is based on the intermediate formation of sufficiently electrophilic N-acyl heteroaromatic cations [1]. As a rule similarly constructed N-alkyl heteroaromatic cations do not enter into this reaction under the same conditions by virtue of the significantly lower electrophilicity but form salts, in which the initial N-alkyl heteroaromatic cations and nucleophiles in the form of anions are not linked by a $\sigma$ bond or the $\sigma$ adducts undergo heterolysis in solutions, and the equilibrium is strongly shifted toward the formation of ion pairs and not $\sigma$ adducts [2,3].

In view of the numerous reactions of heterocumulenes with nucleophiles in the presence of tertiary amines [4,5] we supposed that isocyanates or isothiocyanates could be used instead of carbamoyl chlorides in heteroarylation reactions [6]. In fact, in the reaction of isoquinoline with indole in the presence of isocyanates we obtained the heteroarylation products (Ia, b):



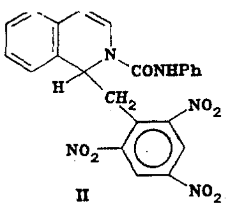
I a-d

I a $R=C_6H_5$, b $R=C_6H_4$—Cl-p, c $R=C_6H_5$, d $R=$ –α-naphthyl; a, b $X=O$, c, d $X=S$

The UV spectra of compounds (I) were identical with the absorption spectra of 1-(3-indolyl)-2-carbamoyl-1,2-dihydroisoquinolines [6] (three characteristic absorption bands in the regions of 219, 259, and 308 nm).

In the $^{13}C$ NMR spectrum of compound (Ia) there are 22 signals for the magnetically nonequivalent carbon nuclei. Seven of these signals belong to quaternary carbon atoms, and 15 to methine carbon atoms. The doublet-multiplet signal in the upfield region of the spectrum belongs to the methine atom $C_{(1)}$ of the isoquinoline fragment. The chemical shift (51.6 ppm) and spin—spin coupling constant (142 Hz) indicate that the signal belongs to the methine carbon atom in the $sp^3$-hybridization state linked to one nitrogen atom [7].

Isoquinoline reacts similarly with indole in the presence of isothiocyanates with the formation of the corresponding derivatives of dihydroisoquinolines (Ic-d). The heteroarylation of trinitrotoluene by isoquinoline and isocyanate (II) takes place in the same way (Table 1).



II

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TABLE 1. Characteristics of the Obtained Compounds

| Compound | Molecular formula | mp, °C | PMR spectrum (in DMSO), δ, ppm (SSCC, J, Hz)* | Yield, % |
|---|---|---|---|---|
| Ia | $C_{24}H_{19}N_3O$ | 163...165 | 7,12 (1H, s, 1-H); 7,14 (1H, d, 3-H, J′=7,6); 6,11 (1H, d, 4-H, J′=7,6); 6,8...7,6 (9H, m, pr, isr.); 10,82 (1H, s, NH) | 53 |
| Ib | $C_{24}H_{18}ClN_3O$ | 170...171 | 6,77 (1H, d, 3-H, J=7,6); 6,11 (1H, d 4-H, J=7,6); 7,1...8,1 (9H, m, p-Cl—$C_6H_4$, isr); 6,85 (1H, s, 2′-H) | 55 |
| Ic | $C_{24}H_{19}N_3S$ | 130...132 | 8,32 (1H, s, 1-H); 7,26 (1H, d, 3-H, J=1,3); 7,26 (1H, d, 4-H, J=1,3); 7,2...8,5 (9H, m, $C_6H_5$, isr); 8,32 (1H, s, 2′-H) | 25 |
| Id | $C_{28}H_{21}N_3S$ | 176...177 | — | 21 |
| II | $C_{23}H_{17}N_5O_7$ | 128...129 | 5,88 (1H, d, 1-H, J=8,0); 6,14 (1H, d, 3-H, J=8,0); 6,76 (1H, d, 4-H, J=8,0); 8,96 (2H, s, m-$C_6H_2(NO_2)_3$); 6,9...8,6 (9H, m, pr., isr.) | 33 |
| IIIa | $C_{31}H_{23}N_3O$ | 173...174 | 6,04 (1H, d., 1-H, J=3,3); 6,64 (1H, d, 3-H, J=7,6); 6,02 (1H, d., 4-H, J=7,6); 6,78 (1H, s, 2-H); 6,79...7,76 (19H, pr, isr, inr) | 95 |
| IIIb | $C_{29}H_{27}N_3O$ | 100...102 | 5,96 (1H, d, 1-H, J=5,2); 6,58 (1H, d, 3-H, J=7,6); 6,06 (1H, d, 4-H, J=7,3); 6,84 (1H, s, 2′-H); 6,92....7,90 (11H, m, pr, isr); 1,26 (9H, s, $CH_3$) | 66 |
| IIIc | $C_{27}H_{20}F_3N_3O$ | 143...145 | 6,08 (1H, d, 3-H, J=7,4); 6,38 (1H, d, 4-H, J=7,4); 6,89 (1H, s, 2′-H); 2,24 (3H, s, $CH_3$); 6,7...8,0 (13H, m, pr, isr, inr) | 40 |
| IIId | $C_{30}H_{21}N_5O$ | 58...59 | 5,93 (1H, d, 1-H, J=1,3); 6,61 (1H, d, 3-H, J=7,8); 6,02 (1H, d, 4-H, J=7,8); 7,1...7,8 (15H, m, pr, isr); 8,86 (2H, s, m-$C_6H_2(NO_2)_3$) | 35 |
| IIIe | $C_{28}H_{23}N_5O_7$ | 149...150 | — | 38 |

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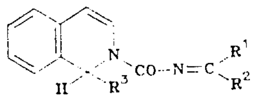
*Here pr = phenyl ring, isr = isoquinoline ring, and inr = indole ring.

The IR spectra of compounds (Ia-d) contain characteristic bands for the vibrations of the NH group in the region of 3200, the CO group in the regions of 1630-1650 (amide I) and 1580-1590 (amide II), and [for compounds (Ic, d)] also for the C=S group in the region of 1352 $cm^{-1}$.

In the reaction of the isocyanates with pyridine and quinoline we obtained the respective disubstituted ureas. This was due to the inadequate electrophilicity of the heteroaromatic ring in the intermediately formed pyridinium and quinolinium ylides, to attack on their exocyclic nitrogen atom by traces of moisture present in the reaction medium, and to hydrolysis with the release of $CO_2$, as in other reactions of isocyanates [8].

In the heteroarylation of indole and trinitrotoluene it was also possible to use 1-chloroalkyl isocyanates. It is known that these compounds have dual reactivity (alkylating and acylating), e.g., in reactions with tertiary alkylamides [9], and this is due to their chlorotropic isomerism [10].



III a-e

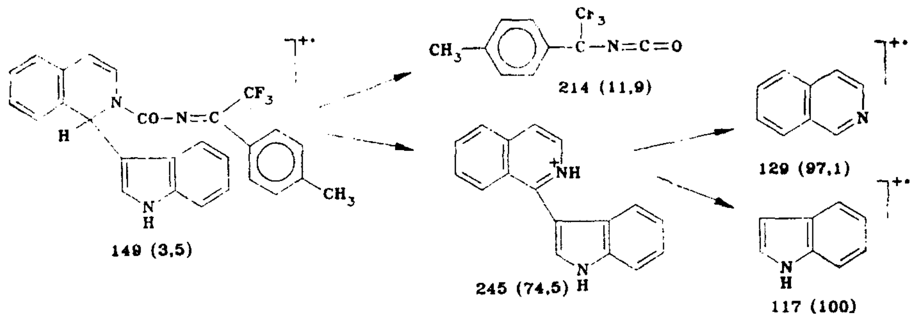
IIIa,b,d,e $R^1$=Ph, c $R^1$=$CF_3$; a—c $R^2$=Ind, d, e $R^2$=2,4,6-Trinitrobenzyl; a, d $R^3$=Ph, b, e $R^3$=t-Bu, c $R^3$= p-tolyl

As found, the corresponding N-carbonimidoyl derivatives of 1,2-dihydroisoquinolinium (IIIa-e) are formed in all cases (Table 1). The mass spectrum of 1-(3-indolyl)-N-(1-tolyl-2-trifluoroethylidenecarbamoyl)-1,2-dihydroisoquinoline (IIIa) is typical of dihydro structures and reflects the initial removal of the acyl residue and subsequent dissociation of compound (IIIa) into the initial reagents. (See scheme, top of the next page.)

Thus, we found that it is possible to increase the electrophilicity of the azinium ring in reactions with certain nucleophiles by means of the isocyanates. This makes it possible to conduct heteroarylation in their presence.

## EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer in tablets with potassium bromide or in Vaseline oil. The electronic spectra were obtained on a Specord UV-Vis spectrophotometer in acetonitrile. The PMR



spectra were obtained on a Bruker WH-90 instrument in DMSO-$d_6$, acetone, or chloroform. The mass spectrum was obtained with direct injection of the samples into the ion source on an LKB-2091 and MAT-111 Gnom spectrometer.

The elemental analyses of all the synthesized compounds agreed with the calculated data.

**Compounds (I-III).** To 0.01 mole of the isocyanate or isothiocyanate in 10 ml of benzene we added 0.01 mole of isoquinoline. A solution of 0.01 mole of indole (trinitrotoluene) in benzene was added drop by drop. The reaction mixture was kept at 60°C for 2 h. After cooling the solvent was distilled, the residue was washed with ether (3 × 20 ml), and the product was filtered off and recrystallized from ethanol.

## LITERATURE CITED

1. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, 3 (1974).
2. T. N. Nezdiiminoga, T. S. Chmilenko, and A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 3, 412 (1984).
3. A. K. Sheinkman, T. S. Chmilenko, and T. N.Nezdiiminoga, Khim. Geterotsikl. Soedin., No. 9, 1214 (1984).
4. S. Ozaki, Chem. Rev., **72**, 475 (1972).
5. D. H. Saunders and K. K. Frisch, Chemistry of Polyurethanes [Russian translation], Khimiya, Moscow (1968), p. 470.
6. A. K. Sheinkman, E. V. Fedash, T. S. Chmilenko, and S. I. Orlov, Khim. Geterotsikl. Soedin., No. 4, 502 (1990).
7. E. Breitmair and W. Voelter, $^{13}C$ NMR Spectroscopy, Verlag Chemie, Weinheim, New York (1978), pp. 78, 93.
8. A. A. Blagonravova and G. A. Levkovich, Usp. Khim., No. 1, 93 (1955).
9. V. A. Shokol, B. N. Kozhushko, and A. V. Gumenyuk, Zh. Obshch. Khim., **47**, No. 5, 1110 (1977).
10. V. I. Gorbatenko and L. I. Samaray, Synthesis, No. 2, 85 (1980).