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CATALYTIC DEHYDROCYCLIZATION OF AZOMETHINES. SYNTHESIS OF SUBSTITUTED INDOLES AND 4(5)-AZAINDOLES

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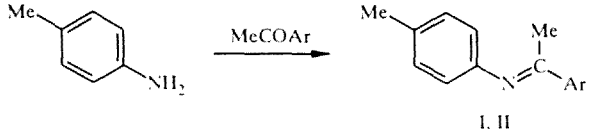
Catalytic dehydrocyclization of azomethines obtained by condensation of p-*toluidine and also 3(4)-aminopyridines with methyl aryl ketones leads to substituted indoles and pyrrolopyridine isomers with the nitrogen atom at different positions in the six-membered ring in 20-40% yield.*

The use of azomethines as starting materials for the preparation of indoles has attracted the attention of research workers for a long time. One of the first studies in this area was carried out by Pictet [1]. Pyrolysis of N-benzylidene-*o*-toluidine (by passing it through a metal tube at 800°C) gave 2-phenylindole in 30% yield.

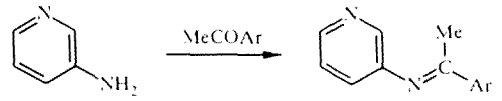
More recently [2], a similar conversion of acetophenone and propiophenone anils and *N*-benzylidene-*o*-toluidine to 2-phenylindole in 5-31% yield at 510-575°C on a chromium–copper catalyst on a carbon support was reported. 2-Phenyl-5-methylindole (7% yield) was obtained in a similar manner from acetophenone and *p*-toluidine. The application of dehydrocyclization for the synthesis of azaindoles has not been reported in the literature, since the main method for obtaining the latter is the thermal indolization of 3- and 4-pyridylhydrazones [3].

Systematic studies have been conducted in our laboratory into the synthesis of condensed nitrogen-containing heterocyclic compounds by catalytic dehydrocyclization in a suitable manner of substituted pyridine bases on K-12 and K-16 industrial dehydrogenation catalysts containing zinc oxide, chromium, iron, and aluminum, with potassium oxide as the promoter [4]. The present work is a continuation of these studies and relates to the synthesis of substituted indoles and azaindoles from azomethines.

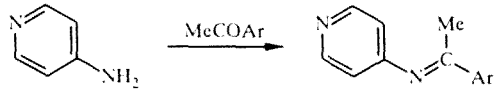


I, II

I Ar = Ph, II Ar = C_6H_4-Ph-*p*



III, IV



V–VII

III, V Ar = Ph; IV, VI Ar = α-thienyl; VII Ar = 2,2'-bithienyl

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TABLE 1. Physicochemical Properties of Azomethines I-VII

Compound	Empirical formula	mp, °C	R_f (solvent)	M^+	IR spectrum, ν, cm^{-1} (C=N)	Yield, % (from amine)
I	$C_{15}H_{15}N$	Liquid*	0,5 (ether–heptane, 1:1)	209	1645	36
II	$C_{21}H_{19}N$	164...166	0,7 (ether–heptane, 1:1)	285	1640	73
III	$C_{13}H_{12}N_2$	41...45	0,28 (ether)	196	1635	40
IV	$C_{11}H_{10}N_2S$	41...45 oily liquid	0,21 (ether)	202		43
V	$C_{13}H_{12}N_2$	97...100	0,29 (ether)	196	1655	35
VI	$C_{11}H_{10}N_2S$	83...85	0,28 (ether)	202	1648	29
VII	$C_{15}H_{12}N_2S_2$	103...106	0,48, (ethyl acetate)	284	1650	22

*bp 130-160°C/10 mm Hg; $n_D^{20} = 1.6009$

TABLE 2. Physicochemical Properties of Indoles and Azaindoles VIII-XIV

Compound	Empirical formula	mp, °C	R_f*	M^+	IR spectrum, ν, cm^{-1} (N–H)	Yield, % (from azomethine reacted)
VIII	$C_{15}H_{13}N$	205...206†	0,45	207	3425	20
IX	$C_{21}H_{17}N$	298...300	0,47	283	3420	18
X	$C_{13}H_{10}N_2$	242...243‡ (decomp.)	0,22	194	3450	40
XI	$C_{11}H_8N_2S$	245...250 (decomp.)	0,20	200	3430	22
XII	$C_{13}H_{10}N_2$	255...257 (decomp.)	0,22	194	3430	24
XIII	$C_{11}H_8N_2S$	229...232 (decomp.)	0,18	200	3400	18
XIV	$C_{15}H_{10}N_2S_2$	160...170	0,22	282	3434	11

*Compound VIII: ether–heptane, 1:1; compound IX: ethyl acetate–heptane, 1:1; compounds X-XIV: ether.

†Lit: mp 213°C (ligroin) [2].

‡Lit: mp 256-257°C [3].

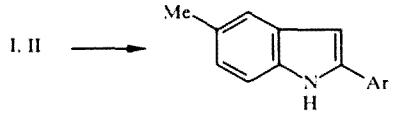
TABLE 3. Outline PMR Spectra of Indoles and Azaindoles VIII, IX (in $CDCl_3$) and X-XIII (in DMSO-d_6)

Compound	Chemical shifts, δ, ppm							
	CH_3	NH	3-H	4-H	5-H	6-H	7-H	2-Ar
VIII	2,40	11,38	6,70	7,25	—	7,08	7,60	7,37...7,70
IX	2,25	11,45	6,89	7,27	—	7,01	8,00	7,35...7,89
X	—	11,60	7,01	—	8,33	7,09	7,75	7,40...7,98
XI	—	11,35	6,80	—	8,30	7,09	7,70	7,60, 7,18, 7,56
XII		11,90	7,00	8,82	—	8,12	7,35	7,42...7,96
XIII		11,50	6,98	8,80	—	8,12	7,32	7,71, 7,62, 7,10

The initial azomethines I-VII were obtained by condensation of *p*-toluidine or 3(4)-aminopyridines with acetophenone, 4-phenylacetophenone, 2-acetylthiophene, and 5-acetyl-2,2'-thiophene. In this way, the following previously unreported ketimines were synthesized: α-methyl-*p*-phenylbenzylidene-*p*-toluidine (II), 3-(α-methyl-benzylidene) aminopyridine (III), 3-(α-thienyl-2-ethylidene)aminopyridine (IV), 4-(α-methylbenzylidene)aminopyridine (V), 4-(α-thienyl-2-ethylidene) aminopyridine (VI), and 4-{α-[5-(2,2'-bithienyl)]ethylidene}aminopyridine (VII). Azomethine I had been prepared previously [2].

The dehydrocyclization of azomethines I-VII was carried out on a K-16 catalyst (azomethine IV was reacted without being isolated in a pure form).

Azomethines I and II gave 5-methyl-2-phenylindole (VIII) and 5-methyl-2-*p*-biphenylindole (IX) respectively in 20% and 18% yield, which suggests that the K-16 catalyst is considerably more efficient than a copper-chromium catalyst [2].

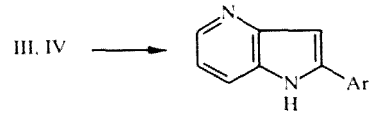


VIII, IX

VIII Ar = Ph, IX Ar = C_6H_4–Ph-*p*

In the case of azomethine III, which has an asymmetrically substituted pyridyl group, two dehydrocyclization routes are possible — on the α- and (or) γ-position of the pyridine, giving isomeric azaindoles. However, the results of TLC of the reaction mixture showed that only one compound was formed. The compound isolated in 40% yield had the structure of 2-phenyl-4-azaindole (X), as shown by the PMR spectrum, in which there were signals due to an ABC system of protons. The 5-H proton resonated at 8.33 ppm as a double doublet signal with spin-spin coupling constants of 4.6 and 1.5 Hz. The 6-H proton of the pyridine ring appeared as a quartet at 7.09 ppm. The γ-proton of the pyridine residue gave rise to a complex multiplet because of interaction not only with 5-H and 6-H but also with the two protons of the pyrrole ring (at 7.75 ppm, J = 8.0, 2.4, 1.53, and 0.9 Hz).

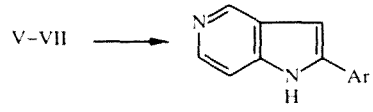
The dehydrocyclization of ketimine IV occurs in a similar manner, giving 2-thienyl-4-azaindole (XI) as the sole isomer. This compound was obtained in lower yield (22%), probably because of the instability of the azomethine containing a thienyl residue. Thus, it has been shown that the α-position of the pyridine ring in compounds III and IV is considerably more active in the thermal cyclization reaction than the γ-position.



X, XI

X Ar = Ph, XI Ar = α-thienyl

It was of interest to investigate the possibility of cyclization occurring at the β-position of the pyridine ring in symmetrically substituted azomethines V-VII.



XII–XIV

XII Ar = Ph; XIII Ar = α-thienyl; XIV Ar = 2,2′-thienyl

In this case only one isomer can be formed. In fact, 2-phenyl- (XII), 2-(α-thienyl)- (XIII), and 2-[5-(2,2′-bithienyl)]-5-azaindole (XIV) were obtained respectively from these azomethines. The yields of the final products of cyclization of the azomethines V-VII (11-24%) are appreciably lower than those from azomethines III and IV. This is most likely due to the lower activity of the β-position of the pyridine ring.

EXPERIMENTAL

The PMR spectra of the compounds synthesized were recorded on a Bruker WP-80 spectrometer (in TMS); the IR spectra were recorded on a Specord IR-75 instrument. Silufol plates were used for TLC.

Preparation of Azomethines (I, III-VII). A solution of 0.01 mole of amine, 0.01 mole of ketone, and a catalytic amount of glacial acetic acid (1-2 ml) in 50 ml of absolute toluene was refluxed with a Dean-Stark adapter for 24-30 h. The course of the reaction was monitored by TLC. The solvent was distilled off. The azomethine was isolated from the residue by vacuum distillation or fractional crystallization.

The properties of the azomethines obtained are listed in Table 1.

α-Methyl-*p*-phenylbenzylidene-*p*-toluidine (II). A solution of 2 g (0.01 mole) of *p*-toluidine, 2 g (0.01 mole) of methyl diphenyl ketone, and a catalytic amount of glacial acetic acid in 50 ml of glycerine was heated for 5 h at 190-200°. On completion of the reaction (TLC), the reaction mixture was poured into 100 ml of water. The precipitate that formed was separated, washed several times with water, and dried to constant weight (see Table 1).

2-Arylindoles (VIII, IX), 2-Aryl-4-azaindoles (X, XII), and 2-Aryl-5-azaindoles (XII-XIV). Dehydrocyclization was carried out in a continuous-flow system with a vertical reactor. The catalysis tube and packing were made of quartz. The catalyst volume was 25 ml. The temperature in the catalyst zone was 560-580°C. A solution of 0.03 mole of azomethine in 60 ml of absolute benzene was passed through at a constant rate above the catalyst for 3 h. The reactor was then cooled to room temperature and washed with 50 ml of benzene (compounds VIII and IX) or 50 ml of ethanol (compounds X-XIV). The solvent was distilled off. The residue was crystallized from heptane (for compounds VIII and IX) or from ethanol (for compounds X-XIV).

The properties of the indoles and azaindoles synthesized are listed in Tables 2 and 3.

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