USE OF AZOLIUM YLIDES IN THE SYNTHESIS OF CONDENSED HETEROCYCLIC SYSTEMS FROM 2-QUINOXALYLACETONITRILES

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The reaction of α-substituted 2-quinoxalylacetonitriles with 1-alkyl(aryl)imidazoles, -benzimidazoles, -1,2,4-triazoles and 5,6-dihydroimidazo[i,j]quinoline was studied. It was found that during the course of the reaction an unusually easy dealkylation of the azole ring takes place, while the aryl substituent is not split off. A reaction mechanism has been proposed including the formation of an ylide intermediate, followed by subsequent electrophilic attack on the $C_{(2)}$ position of the azolium ring. The applicability boundaries of the reaction studied and the spectral characteristics of the synthesized compounds were investigated.

In recent years the attention of research workers working in the field of heterocyclic compounds had been drawn to the so-called "ylide" mechanism of electrophilic substitution [1, 2]. In contrast to the classical mechanism of the "addition–splitting off" type, in the ylide substitution both basic and the acidic properties of the heterocyclic ring play an equally substantial role. This opens wide prospects for a directed synthesis of new derivatives of heterocyclic compounds, since in this case the least active during the usual electrophilic substitution positions of the heterocyclic ring become the reaction centers. In the present work the possibilities were studied of the ylide electrophilic substitution reaction of azoles for the synthesis of condensed heterocyclic systems from α-substituted 2-(3-chloro)quinoxalylacetonitriles (I-IV) [3, 4].

The reaction of compounds I-IV with N–H-azoles leading eventually to the derivatives of (benz)imidazo[1′,2′:1,6]-pyrido[2,3-b]quinoxaline has been described earlier in [5]. In the present work, we studied the reaction of these chloro derivatives with N-substituted azoles.

On heating compounds I, III, IV with an excess of 1-methylimidazole ($R^2 = CH_3$) in DMFA or on direct fusion of the reagents, the formation of compounds V-VII takes place, which is accompanied by demethylation of the nitrogen atom. We propose the following mechanism of this reaction (Scheme 1).

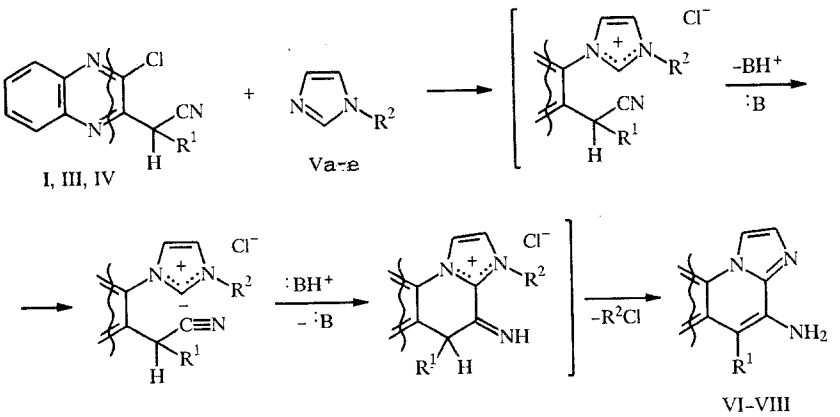
At the first stage of the reaction the formation of a quaternary imidazolium salt takes place. The excess of Va present in the reaction medium acts as a base and promotes the deprotonation of 2-position of the imidazole ring (it is known that the quaternary salts of azoles very easily form similar ylides [6]). The presence of a negative charge causes high activity of the $C_{(2)}$ atom under the electrophilic attack conditions: The carbon atom of the nitrile group is the electrophile in this case. The subsequent imino–amine isomerization ends with the formation of a conjugated system of compounds VI-VIII.

The identity of the synthesized products with cyclic compounds obtained previously from N–H azoles is confirmed by the full correspondence of all their physical, spectral, and chromatographic characteristics. The most characteristic feature of the PMR spectra of compounds VI-VIII recorded in DMSO-D_6 is the presence of a weak-field doublet in the 8.6-8.7 ppm region [$J_{(1,2)}$ = 2 Hz], corresponding to the 1H proton (see Table 1). The paramagnetic shift of this signal is explained by the falling of this proton into the region of the descreening action of the unshared pair of the $N_{(11)}$ nitrogen atom (this is especially evident on building steric models of the cyclic structures of VI-VIII). The proton signals of the amino group are in the form of two broadened one-proton singlets, which disappear on treatment of the sample with D_2O. This splitting of the signal is readily explainable if we take into account the possibility of formation of an intramolecular hydrogen bond by one of the protons with the $N_{(3)}$ nitrogen atom; in this case, the weak field signal corresponds to a proton bound by this bond.

Kiev Technological Institute of Food Industry, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 224-229, February, 1993. Original article submitted February 5, 1992.

 0009-3122/93/2902-0194$12.50

Scheme 1



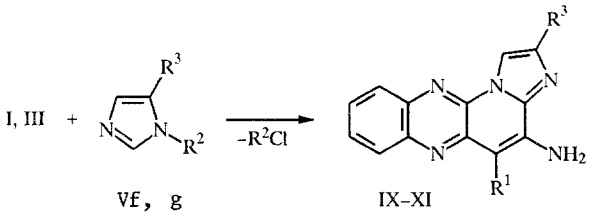
I, III, IV

Va-e

VI-VIII

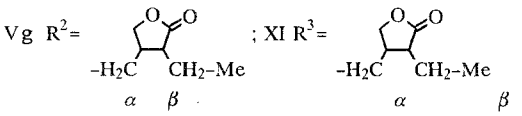
I $R^1 = CH_3—SO_2$; II $R^1 = C_6H_5—SO_2$; III R^1 = 4-Cl-C_6H_4-SO_2; IV R^1 = CN; V a $R^2 = CH_3$, b $R^2 = C_2H_5$, c $R^2 = C_6H_5CH_2$, d $R^2 = C_{18}H_{37}$, e $R^2 = (C_6H_5)_3C$; VI $R^1 = CH_3—SO_2$; VII R^1 = 4-Cl-$C_6H_4—SO_2$; VIII R^1 = CN; :B = 1-R^2-imidazole

Scheme 2



Vf, g

IX-XI



Vg R^2 = ; XI R^3 =

α β α β

Vf $R^2 = CH_3$, R^3 = Cl; g $R^2 = CH_3$, IX $R^1 = CH_3—SO_2$, R^3 = Cl; X R^1 = 4-Cl—$C_6H_4—SO_2$, R^3 = Cl; XI R1 = $CH_3—SO_2$

The reaction of compound I with various 1-alkylimidazoles Va-e in all cases, irrespective of the structure of the alkyl radical, leads to one and the same product — 4-amino-5-methyl-sulfonylimidazo[1′,2′:1,6]pyrido[2,3-b]quinoxaline VI.

We found that the duration of the reaction (monitoring by the TLC method) and the yield of the end product V are determined by the nature of the substituent R^2 in V. According to the influence on the ease of the occurrence of the reaction of I with imidazoles Va-e, the substituents studied can be arranged into the following series (in brackets are given the times of boiling of I with the corresponding imidazole in DMFA and the yield of product VI): CH_3 (1.95%) < $C_6H_5CH_2$ (1.5, 95%) < C_2H_5 (2.5, 80%) < $C_{18}H_{37}$ (3, 65%) < $(C_6H_5)_3C$ (5, 60%).

The above order of substituents correlates well with the previously studied relative ease of thermal dealkylation of imidazolium salts [6]. The position of triphenylmethyl as last in this series can be explained by the lower basicity of the 1-triphenylmethylimidazole ring in comparison with other alkylimidazoles, and correspondingly by hindrances during its quaternization.

The reaction of compounds I, III with substituted 1-methylimidazoles — 1-methyl-5-chloroimidazole Vf and the alkaloid pilocarpine Vg proceeds in the similar way. The corresponding cyclic derivatives IX-XI were isolated with preparative yields in all cases (Scheme 2).

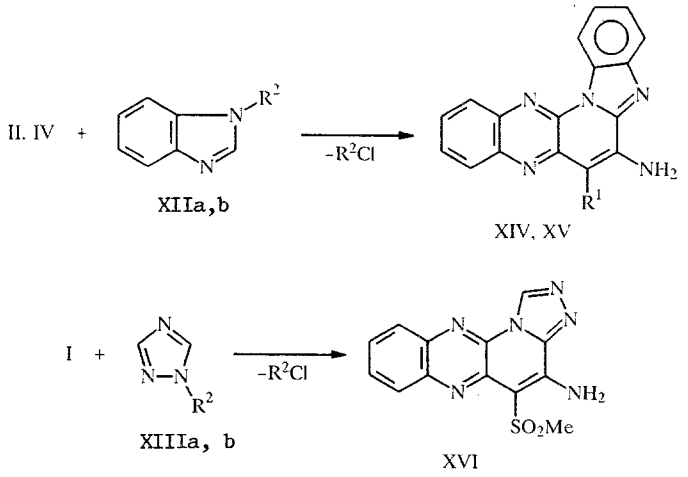
TABLE 1. Characteristics of Synthesized Compounds*

Compound	Empirical formula	PMR spectrum, ppm (SSCC, J, Hz)**	Yield, %
VI	$C_{14}H_{11}N_5O_2S$	3,36 (3H, s, CH_3); 7,74 (1H, d, 2-H, J_{12} = 2); 7,81...8,20 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,21 (1H, s, NH); 8,24 (1H, s, NH); 8,65 (1H, d, 1-H, J_{12} = 2)	98
VII	$C_{19}H_{12}ClN_5O_2S$	7,64 (2H, d, protons in the o-positions to , J = 7); 7,75 (1H, d, 2-H, J_{12} = 2); 7,8...8,11 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,29 (2H, d, protons in the o-positions -SO_2, J = 7); 8,41 (1H, s, NH); 8,46 (1H, s, NH); 8,65 (1H, d, 1-H, J_{12} = 2)	95
VIII	$C_{14}H_8N_6$	7,75 (1H, d, 2-H, J_{12} = 2); 7,81...8,14 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,31 (2H, s, NH_2); 8,67 (1H, d, 1-H, J_{12} = 2)	89
IX	$C_{14}H_{10}ClN_5O_2S$	3,66 (3H, s, CH_3); 7,80...8,12 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,22 (2H, s, NH_2); 8,80 (1H, s, 1-H)	92
X	$C_{19}H_{11}Cl_2N_5O_2S$	7,63 (2H, d, protons in the o-positions to J = 9); 7,72...8,13 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,26 (2H, d, protons in the o-positions to the-SO_2 , 8,41 (1H, s, NH); 8,51 (1H, s, NH); 8,76 (1H, s, 1-H)	95
XI	$C_{21}H_{21}N_5O_4S$	1,05 (3H, t, $\underline{CH_3}-CH_2$); 1,68 (1H, m, $\underline{CH}-C_2H_5$); 2,7...3,1 (3H, m, α-CH_2, $\underline{CH}-CH_2$); 3,73 (2H, m, β-CH_2); 4,23 (2H, d, J = 3,7, O-$\underline{CH_2}$); 7,84...8,16 (4H, m, 7-H, 8-H, 9-H, 10-H); 8,20 (2H, s, NH_2); 8,56 (1H, s, 1-H)	80
XIV	$C_{23}H_{15}N_5O_2S$	7,41...8,11 (11H, 2-H, 3-H, 4-H, C_6H_5, 9-H, 10-H, 11-H, 12-H); 8,48 (1H, s, NH); 8,53 (1H, s, NH); 9,09 (1H, d, 1-H, J_{12} = 8)	74
XV	$C_{18}H_{10}N_4$	7,62...8,31 (7H, m, 2-H, 3-H, 4-H, 9-H, 10-H, 11-H, 12-H); 8,48 (22H, s, NH_2); 9,16 (1H, d, 1-H, J_{12} = 8)	79
XVI	$C_{13}H_{10}N_6O_2S$	3,63 (3H, s, CH_3); 7,94...8,81 (4H, m, 7-H, 8-H, 9-H, 10-H); 10,4 (1H, s, 1-H)	55
XVIII	$C_{27}H_{22}ClN_5O_2S$	2,35 (2H, m, $-CH_2-\underline{CH_2}-CH_2Cl$); 3,33 (2H, t, $-\underline{CH_2}-CH_2-CH_2Cl$); 3,63 (2H, t, $-CH_2-CH_2-\underline{CH_2}Cl$); 3,74 (3H, s, CH_3); 6,99 (1H, s, NH); 7,34...8,23 (6H, m, 2-H, 3-H, 9-H, 10-H, 11-H, 12-H); 8,54 (1H, s, NH); 9,01 (1H, d, 1-H, J_{12} = 8)	58
XIX	$C_{22}H_{15}N_5O_2S$	3,59 (3H, s, CH_3); 7,56 (5H, m, C_6H_5); 7,76...8,14 (4H, m, 7-H, 8-H, 9-H, 10-H)	61
XX	$C_{24}H_{17}N_5O_2S$	3,72 (3H, s, CH_3); 7,59 (1H, d, 4-H, 7,8); 7,94 (5H, s, C_6H_5); 7,96...8,58 (7H, m, 2-H, 3-H, 4-H, 9-H, 10-H, 11-H, 12-H); 9,80 (1H, d, 7,8)	60

*Compound XVIII was recrystallized from toluene, the remaining compounds from DMFA. Melting point of compounds XVIII — 299°C, XI — 261°C, the remaining compounds melt above 300°C.

**The spectra of compounds VI-XI, XIV, XV, and XIX were run in DMSO-D_6, of compounds XVI and XX in CF_3COOD, XVIII in $CDCl_3$.

Scheme 3



XII a $R^2 = CH_3$, b $R^2 = C_2H_5$; XIII a $R^2 = CH_3$, b $R^2 = C_2H_5$; XIV $R^1 = C_6H_5SO_2$, XV $R^1 = CN$

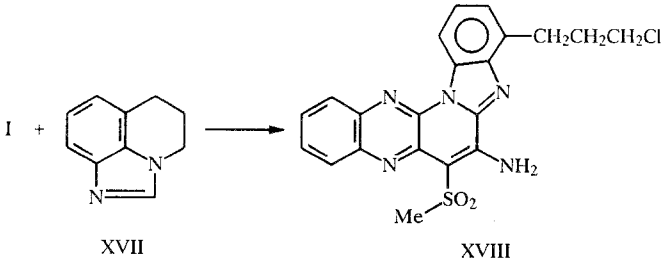
For the determination of applicability limits of this reaction, we studied the reaction of compounds I, II, IV with 1-alkylbenzimidazoles XIIa, b and 4-alkyltriazoles XIIIa, b. In all cases the reaction proceeds unequivocally and the expected cyclic products XIV-XVI are formed (Scheme 3).

In comparison with 1-methylimidazole, these reactions proceed much more slowly. The synthesis of compounds XIV and XV requires 3-4 h of boiling the reagents in DMFA, while for the preparation of product XVI still more rigorous conditions are necessary — a direct fusion of I with a large excess of azole XIII at 180-200°C for 5-6 h.

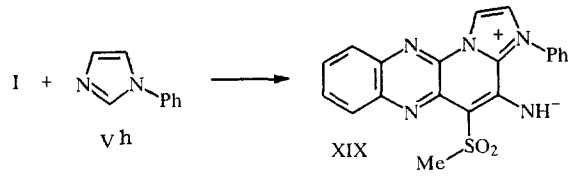
We explain the retardation of the reaction with 1-methylbenzimidazole XIIa in comparison with 1-methylimidazole Va by the presence of steric hindrances [the $C_{(7)}H$ group in the benzimidazole ring] arising at the stage of formation of the quaternary azolium salt. However, in the case of triazole XIIIa, the decisive factor is the considerably lower basicity of the heterocyclic ring (approximately by a factor of 10,000 [6]), which also hinders its primary quaternization.

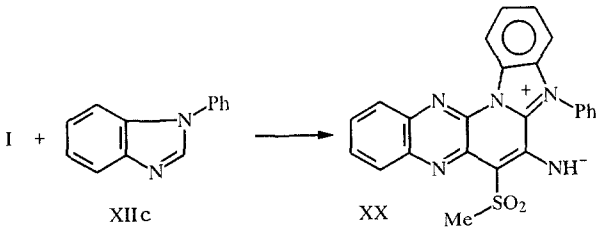
We determined the fate of the split off alkyl group from the results of the reaction of I with 1-octadecyl- and 1-triphenylmethyl substituted imidazoles Vd and Ve. At the end of the process together with product VI, the corresponding R^2Cl products — 1-octadecyl chloride and triphenylchloromethane — were isolated from the reaction mixture and identified by comparison with authentic samples.

We also obtained a direct proof for the splitting off of the alkyl group from the nitrogen atom in the form of alkyl chloride by studying the reaction of compound I with 5,6-dihydroimidazo(i,j)quinoline XVII. As a result of this reaction 4-(1-chloropropyl)-6-amino-7-mesylbenzimidazo[1′,2′:1,6]pyrido[2,3-b]quinoxaline XVIII was obtained (Scheme 4):



As known, in contrast to 1-alkyl-substituted derivatives, the quaternary salts of 1-aryl-substituted imidazoles do not undergo thermal dearylation [6]. Introduction of 1-phenylimidazole Vh and 1-phenylbenzimidazole XIIc into the reaction studied leads eventually to pseudo-cross-conjugated mesomeric betaines XIX, XX [7-9] (Scheme 5):





The singlet of the NH^- group in the PMR spectrum of compound XIX is present in the 7.4 ppm region. The fact of the mutual disposition of the doublets of the 1-H and 4-H protons in the PMR spectrum of compound XX is noteworthy. The 1-H proton is observed in the form of a doublet at 9.80 ppm [a paramagnetic shift under the influence of the unshared pair of electrons of the $N_{(13)}$ nitrogen atom], while the 4-H proton, falling into the screening cone of the N-phenyl ring undergoes a diamagnetic shift to the 7.59 ppm region.

EXPERIMENTAL

The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates, using a chloroform—methanol (9:1) mixture as eluent. The IR spectra were recorded on a Pye Unicam SP3-300 spectrophotometer in KBr tablets. The PMR spectra were recorded on a Bruker WP-100 Fourier spectrometer, using TMS as internal standard.

4-Amino-5-R^1-sulfonylimidazo[1′,2′:1,6]pyrido[2,3-b]quinoxalines (VI, VII). A solution of 0.03 mole of quinoxalylacetonitrile I or II and 0.061 mole of one of the azoles Va-e was boiled in dry DMFA for 1-6 h. The solvent was then evaporated in vacuo, 30 ml of water was added to the residue, and the precipitate of the product was filtered off.

Compounds IX-XI, XIV, XV, XIX, and XX were obtained in a similar way.

4-Amino-5-cyanoimidazo[1′,2′:1,6]pyrido[2,3-b]quinoxaline (VIII). A 0.01 mole portion of dinitrile IV was fused with 2 g of azole Va at 130°C for 1 h. Then 10 ml of cold methanol was added to the cooled melt, and the precipitate of the product that separated out was filtered off.

4-Amino-5-methylsulfonyl-1,2,4-triazolo[3′,4′:1,6]pyrido[2,3-b]quinoxaline (XVI). Compound XVI was synthesized in a similar way as quinoxaline VIII by fusing I and XIII at 160°C for 6 h.

4-(1-Chloropropyl)-6-amino-7-methylsulfonylbenzimidazo-[1′,2′:1,6]pyrido[2,3-b]quinoxaline (XVIII). A solution of 0.17 g (0.002 mole) of nitrile I and 0.64 g (0.004 mole) of quinoline XVII in 15 ml of o-dichlorobenzene was boiled for 4 h. The solvent was then evaporated in vacuo, the residue was dissolved in a minimal amount of chloroform and the solution was chromatographed on a column with silica gel, the product was eluted with chloroform, and recrystallized from toluene.

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