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NUCLEOPHILE-INDUCED TRANSFORMATIONS OF 1,2,4-TRIAZINES.* 3.** ANRORC CONSTRICTION OF THE RING IN THE REACTION OF 6-ARYL-3-DIMETHYLAMINO-1,2,4-TRIAZINE 4-OXIDES WITH KCN

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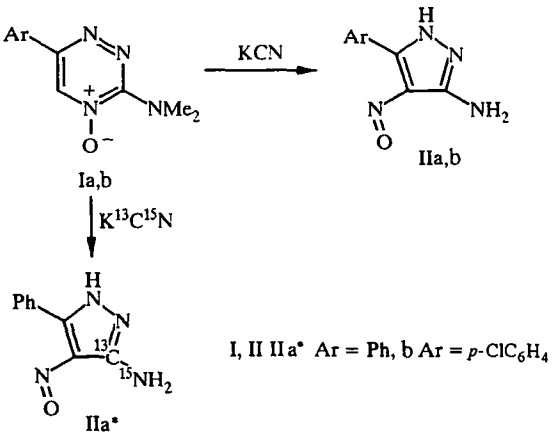
Reaction of 6-aryl-3-dimethylamino-1,2,4-triazine 4-oxides with KCN results in constriction of the heterocycle and formation of 3-amino-5-aryl-4-nitrosopyrazoles. Several methods including labelled $K^{13}C^{15}N$ are used to demonstrate that the reaction proceeds through the ANRORC mechanism.

Facile addition of nucleophiles is a characteristic trait of π-deficient azine systems, including 1,2,4-triazine N-oxides. Further transformations of the adducts depend on the site of attack and the nature of the reagents and include aromatization due to oxidation or autoaromatization with *ipso-* or *tele*-elimination of a leaving group [2]. In addition, nucleophilic attack on an unsubstituted carbon atom is rather frequently accompanied by opening of the azine ring or its transformation. If in the latter instance the new heterocycle contains a fragment of nucleophile, reactions occur through the so-called ANRORC mechanism [3]. Transformations of this type can be accompanied by elimination of not only the leaving group but also whole fragments of the heterocycle [4].

Namely this transformation occurs during the reaction of 6-aryl-3-dimethylamino-1,2,4-triazine 4-oxides Ia and b with cyanide. Heating Ia and Ib with KCN in methanol produces 3-amino-5-aryl-4-nitrosopyrazoles IIa and Ib in 50-60% yield (Scheme 1).

Scheme 1



* Dedicated to Professor Henk van der Plas on his 70th birthday.

** For No. 2, see [1].

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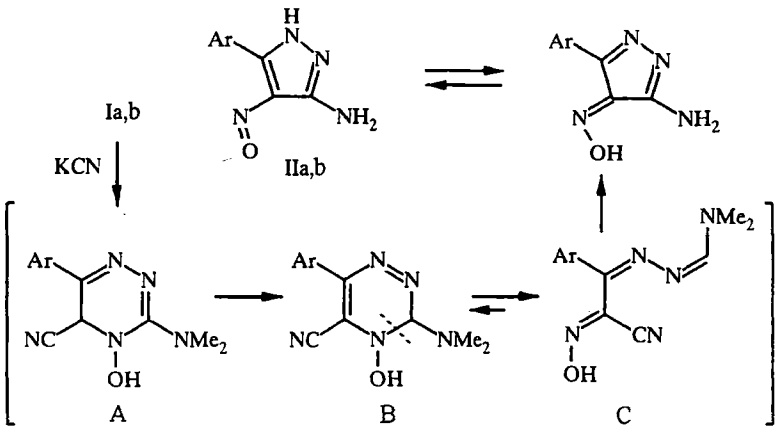
The ^{1}H NMR spectra of IIa and b contain proton signals of the aromatic substituent and broadened singlets for protons of the NH and NH_2 groups near 12.3 and 6.2 ppm, respectively (Table 2). The ^{13}C NMR spectrum of IIa contains, in addition to signals for the phenyl carbon atoms, signals for pyrazole atoms bonded to the amino group (137.49 ppm), the phenyl moiety (148.70 ppm), and the nitroso group (150.59 ppm) (Table 2). The IR spectrum data of IIa can be assigned to stretching vibrations of the C=N, N=O (dimer), and NH_2 groups (Table 1). The presence of the nitroso group is also confirmed by the fact that pyrazoles II, which are orange in the solid state, turn deep green in solution.

The observed transformation occurs through the ANRORC mechanism. Addition of the nucleophile to the 5-position of 1,2,4-triazine is followed by rearrangement of the adduct A *via* a [1,5]-sigmatropic hydride shift. A similar hydride shift was found for *tele*-substitution of the dialkylamino group during amination of 3-dialkylamino-1,2,4-triazine 4-oxides [5]. Further opening of 3,4-dihydrotriazine B ring *via* cleavage of the $C_{(3)}$–$N_{(4)}$ bond, which is typical of such systems [1, 6], and ring closure of the intermediate C with loss of the $C_{(3)}$–NMe_2 moiety of the 1,2,4-triazine ring produces 3-amino-5-aryl-4-hydroxyliminopyrazoles, existing as the nitrosoisomers IIa, b.

This mechanism was confirmed for the reaction of 3-dimethylamino-6-phenyl-1,2,4-triazine 4-oxide Ia by using KCN labelled with ^{13}C (60%) and ^{15}N (80%). In the ^{1}H NMR spectrum of the product IIa*, the signal of the amino group appears as a two-proton doublet owing to spin–spin coupling between the protons and the ^{15}N atom of the amino group. The spin–spin coupling constant (SSCC) is J^1 = 91 Hz (Table 2). All signals of carbon atoms of the labelled pyrazole ring appear in the ^{13}C NMR spectrum as doublets (Table 2): $C_{(3)}$, SSCC of the ^{15}N atom of the amino group $J_{(CN)}$ = 17.8 Hz; $C_{(4)}$, SSCC of $^{13}C_{(3)}$ $J_{(CC)}$ = 56.3 Hz; $C_{(5)}$, SSCC of $^{13}C_{(3)}$ $J_{(CCC)}$ = 13.1 Hz (Table 2). The signal of the ^{15}N atom of the amino group in the ^{15}N NMR appears as a doublet with chemical shift relative to liquid ammonia of 62.74 ppm and SSCC to $^{13}C_{(3)}$ $J_{(CN)}$ = 17.8 Hz and as a singlet for the sample without ^{13}C enrichment. The C=N stretching vibrations in the IR spectrum of pyrazole IIa enriched in ^{13}C and ^{15}N are shifted by 40 cm^{-1} (Table 1). These facts suggest that the reaction of Ia with $K^{13}C^{15}N$ formed 3-^{15}N-amino-4-nitroso-5-phenylpyrazole-3-^{13}C, IIa*, i.e., the carbon atom of the nitrile group was incorporated into the pyrazole ring whereas the nitrogen atom was incorporated into the amino group. Such positioning of the isotopic labels in IIa* is possible only if the reaction occurs through the ANRORC mechanism (Scheme 2).

Scheme 2



Two facts should be mentioned concerning the reasons of the 1,2,4-triazine ring transformation. On one hand, it is known [7] that the reaction of 3-unsubstituted or 3-alkyl-1,2,4-triazine 4-oxides with cyanide occurs *via* nucleophilic substitution of hydrogen atom to form 3-cyano-1,2,4-triazines. The presence of a dimethylamino group in the 3-position of 1,2,4-triazine 4-oxides I causes the ring transformation after addition of the nucleophile to occur more quickly than the autoaromatization of σ-adducts A with loss of water. On the other hand, it has been demonstrated [8] that the reaction of 3-chloro-1,2,4-triazine, which does not have an N-oxide group, with the phenylacetonitrile anion occurs through opening of the heterocycle with cleavage of the $N_{(4)}$–$C_{(5)}$ bond and further

TABLE 1. Characteristics of Compounds IIa, b, and IIa*

Compound	Empirical formula	mp, °C	IR spectrum, (ν, cm^{-1})				Mass spectrum, *m/z*, (I_{rel}, %)	Yield, %
			NH_2	NH	C=N	N=O		
IIa	$C_9H_8N_4O$	275...276 (dec.)	3400	3250	1640	1210	51 (13), 77 (28), 91 (7), 103 (17), 104 (26), 118 (10) 119 (7), 128 (32), 129 (17), 130 (15), 188 (100), 189 (11)	57
IIb	$C_9H_7ClN_4O$	272...273 (dec.)					75 (13), 102 (11), 111 (14), 137 (19), 138 (23), 162 (28) 163 (13), 164 (18), 222 (100), 223 (13), 224 (34)	62
IIa*	$C_9H_8N_4O$	275...276 (dec.)	3400	3250	1600	1210	51 (17), 77 (44), 91 (11), 103 (24), 104 (42), 118 (17) 119 (11), 129 (28), 130 (32), 131 (12), 188 (25), 189 (77) 190 (100)	52

TABLE 2. ^1H and ^{13}C NMR Spectral Characteristics of Compounds IIa, b, and IIa*

Compound	^1H NMR spectrum (DMSO-D_6), δ, ppm			^{13}C NMR spectrum (DMSO-d_6), δ, ppm			
	Ar	NH_2 (2H)	NH (1H, br. s)	C–NO	C–Ph	C–NH_2	Ph
IIa	7,4...7,6 (2H, m) 8,1...8,3 (3H, m)	8,09 br. s	12,29	150,67	148,68	137,49	131,71; 128,97 128,42; 127,78
IIb	7,56 (2H, d) 8,28 (2H, d)	8,20 br. s	12,36				
IIa*	7,4...7,6 (2H, m) 8,1...8,3 (3H, m)	8,09 br. d $J_{(NH)}$ = 91 Hz	12,29	150,68* d $J_{(CC)}$ = 56,3 Hz	148,68* d $J_{(CCC)}$ = 13,1 Hz	137,74* d $J_{(CN)}$ = 17,8 Hz	131,61; 129,06 128,49; 127,82

* Only signals of the ^{13}C-enriched isomer are given.

recyclization to 3-amino-4-phenylpyridazine with loss of two atoms ($C_{(3)}$–$N_{(4)}$) of the 1,2,4-triazine. The presence of an N-oxide group changes the nature of the ring opening and caused retention of the $N_{(4)}$ atom in the transformation product 1,2,4-triazine 4-oxides Ia, b, although it is located in the exocyclic nitroso group. Thus, combination of the dimethylamino group in the 3-position and the N-oxide in the 1,2,4-triazine ring directs the σ-adducts to ring transformation and not to aromatization of the nucleophilic substitution products.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WM-250 (250.1 MHz) spectrometer with TMS as internal standard; ^{13}C NMR spectra, on a Bruker DRX-500 (125.8 MHz) with TMS as internal standard; ^{15}N NMR spectra, on a Bruker DRX-500 (50.7 MHz) with NH_3 as internal standard. Mass spectra were obtained on a Varian MAT-311A instrument (electron-impact ionization) at accelerating potential 3 kV, cathode emission current 1 A, ionizing electron energy 70 eV, and direct-probe sample introduction. IR spectra were recorded on a Specord IR-75 instrument in KBr pellets. The purity of the products was monitored by TLC on Silufol UV-245 plates with ethylacetate eluent and visualization by UV light.

General Method for Preparation of 3-Amino-4-nitroso-5-phenyl- or 5-(4-Chlorophenyl)pyrazoles IIa, b, and IIa*. A mixture of 3-dimethylamino-6-phenyl- or 6-*p*-chlorophenyl-1,2,4-triazine 4-oxide (1 mmol) and KCN or K^{13}C^{15}N (75 mg, 1.5 mmol) in methanol (2 ml) was stirred for 1 h at room temperature. After the reaction was finished water (2 ml) and acetic acid (0.2 ml) were subsequently added. The solid was filtered off, washed with water, and recrystallized from ethanol. IIa: Found, %: C 57.28; H 4.19; N 29.80. $C_9H_8N_4O$. Calculated, %: C 57.44; H 4.28; N 29.77. IIb: Found, %: C 48.37; H 3.29; N 25.29. $C_9H_7ClN_4O$. Calculated, %: C 48.55; H 3.17; N 25.17. IIa*: Found, %: C 57.39; H 4.12; N 29.87. $C_9H_8N_4O$. Calculated, %: C 57.31; H 4.25; N 29.99.

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