# SYNTHESIS AND NMR STUDY OF 7-ARYL-1,2,4-TRIAZOLO-[1,5-a]-1,3,5-TRIAZINES

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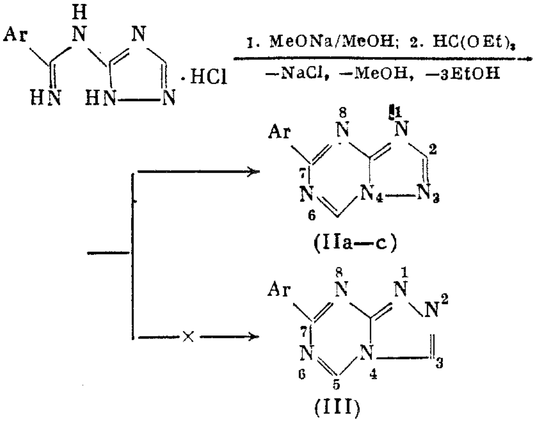
UDC 542.91:543.422.25:547.792.9:547.872.3

*The reaction of N-(1,2,4)-triazol-5-yl)amidines with ethyl orthoformate is a convenient method for the fusion of a triazine ring to the triazole ring. An NMR study showed that the heterocyclic compounds obtained are 7-aryl-1,2,4-triazolo-[1,5-a]-1,3,5-triazines.*

We have recently proposed a method for the preparation of the hydrochloride salts of N-(1,2,4-triazol-5-yl)amidines (I) from 5-amino-1,2,4-triazole and nitriles through boron chelate complexes [1]. Amidines (I) may be seen as interesting potential reagents for heterocyclic synthesis and we now report the use of these compounds for the fusion of a triazine ring to a triazole ring.

The free bases obtained in situ from salts (Ia)-(Ic) react with ethyl orthoformate to give 7-aryl-1,2,4-triazolo-[1,5-a]-1,3,5-triazines (IIa)-(IIc) in 64-71% yield



$Ar = Ph$ (a); $Ar = o\text{-}MeC_6H_4$ (b) $Ar = p\text{-}MeC_6H_4$ (c).

Products (IIa)-(IIc) are colorless, crystalline compounds with good solubility in ethanol, acetonitrile, and DMSO but only limited solubility in benzene. Their IR spectra lack absorption in the $\nu$NH region, while their mass spectra display strong peaks for $M^{+\cdot}$ ions, whose subsequent fragmentation involves the elimination of HCN. The PMR spectra of (IIa)-(IIc) in DMSO-$d_6$ have singlets at 8.77-8.81 and 10.09-10.14 ppm in addition to the aryl proton signals, while the $^{13}C$ NMR spectrum of (IIa) has four signals for the carbon atoms of the triazolo-triazine system in addition to the signals for the phenyl group carbon atoms.

These results do not exclude the alternative structure of 7-aryl-1,2,4-triazolo-[4,3-a]-1,3,5-triazines (III) which is exhibited by isomer (II). We should consider (II) as the more probable structure since the $N^1$ atom in 5-amino-1,2,4-triazoles usually is presumed to participate in condensation reactions leading to fusion of the six-membered ring [2-5]. Specific proof for structure (II) was obtained by $^{15}N$ NMR spectroscopy.

Thus, the spectrum of the compound synthesized from (Ia) with complete proton decoupling has five singlets from all the nitrogen atoms, while the INEPT spectrum with polarization transfer from all the protons has four doublets (see Table 1).

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N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2386-2388, October, 1989. Original article submitted April 27, 1988.

0568-5230/89/3810-2197$12.50

TABLE 1. $^{15}N$ NMR Spectral Indices of (IIa)

| Parameter | $N^1$ | $N^3$ | $N^4$ | $N^6$ | $N^8$ |
|---|---|---|---|---|---|
| δ, ppm | –149,66 | –108,64 | –153,73 | –135,30 | –137,45 |
| $J_{^{15}N, ^1H}$, Hz | 13.6 s ($H^2$) | 15,3 s ($H^2$) | 11,0 s ($H^2$) | 12,7 s ($H^5$) | – |

The SPTCW spectrum with polarization transfer from the proton at 8.80 ppm shows doublets at (δ, ppm): -108.64 (J = 15.3 Hz), -149.66 (J = 13.6 Hz), and -153.73 (J = 11.0 Hz). The finding of three doublets with such coupling constants is possible only for structure (IIa) and the assignment of the signal at 8.80 ppm to $C^2$-H. Indeed, the magnitude of the $^2J_{^{15}N,^1H}$ coupling constant for the pyridine ring nitrogen atoms in azoles exceeds 10 Hz, while the $^3J$ coupling constants for these atoms are not more than 1-3 Hz [6-9]. The $^3J_{^{15}N,^1H}$ coupling constants for the pyrrole nitrogen atoms in azoles may also reach 10.5 Hz [6]. Thus, the three doublets with the constants found in the range from 11 to 15 Hz may be assigned to $N^1$, $N^3$, and $N^4$ of the triazole ring (coupling with $C^2$-H). If the compound had structure (III), more than two doublets with such constants could not be observed in the SPTCW experiments (coupling of $N^2$ and $N^4$ with $C^3$-H or of $N^4$ and $N^6$ with $C^5$-H).

The signal in the PMR spectrum of (IIa) at 10.14 ppm is assigned to $C^5$-H. One doublet is found in the SPTCW spectrum with polarization transfer from this proton at δ = -135.30 ppm (J = 12.7 Hz), which should be assigned to $N^6$ (the possibility of coupling with $N^4$ is less likely since the $^2J_{^{15}N,^1H}$ coupling constant for pyrrole atoms usually does not exceed 9 Hz [6-9]).

The signal at -137.45 ppm apparently belongs to $N^8$, which is not coupled with protons, the closest of which are separated from this atom by four bonds. A regular decrease in shielding is observed for azole nitrogen atoms: $N_{pyrr}$ > C=N-C > C=N-N [8, 10, 11]. Thus, the signals at -153.73, -149.66, and -108.64 ppm may be assigned to $N^4$, $N^1$, and $N^3$, respectively.

Products (IIa)-(IIc) may be seen as analogs of azapurine. The reported methods for the synthesis of 5-azapurines lead exclusively to the corresponding amino, oxo, or thio derivatives. Thus, various workers have described the reactions of 5-amino-1,2,4-triazole with ethoxymethylenecyanamide [5] and of bis(1,2,4-triazol-5-yl)formamidine with potassium cyanamide [3], transformations of derivatives of 1-aminocarbonyl— and 1-aminothiocarbonyl-5-amino-1,2,4-triazoles [3, 4], intramolecular cyclization of N-ethoxycarbonyl-N'-(1,2,4-triazol-5-yl)-thiourea [4], and the condensation of 4-hydrazino—(1H)—1,3,5-triazin-2-one with diethoxymethyl acetate [12].

The use of the reactions of amidines (I) with various one-carbon synthones is a simple and efficient method for the construction of the 5-azapurine system.

## EXPERIMENTAL

Starting (Ia)-(Ic) were obtained according to our previous procedure [1]. The IR spectra were obtained on a UR-20 spectrometer using KBr pellets (ν, $cm^{-1}$). The mass spectra were taken on a Varian MAT CH-6 mass spectrometer with direct sample inlet into the ion source at 100-150°C (the m/z values are given).

The $^{15}N$ NMR spectra were taken at 55°C on a Bruker AM-300 spectrometer at 30.42 MHz with the natural isotope content. The chemical shifts were determined from the $^{15}N-\{^1H\}$ spectra with complete proton decoupling and measured relative to $CH_3NO_2$ as the external standard. The $J_{^{15}N,^1H}$ coupling constants were determined from the INEPT spectra (nonselective polarization transfer from $^1H$ to $^{15}N$) and SPTCW spectra (selective population transfer with selective decoupling). The $^{13}C$ NMR spectra were taken on the same spectrometer at 75.43 MHz with complete proton decoupling, selective $^{13}C-\{^1H\}$ double heteronuclear resonance, and gated decoupling. The signals were assigned on the basis of their chemical shifts, coupling constants, and multiplicity. The PMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz. A solution of the sample in DMSO-$d_6$ was placed in an NMR tube with 10 mm diameter for the $^{15}N$ and $^{13}C$ NMR spectra and 5 mm for the PMR spectra. $Cr(acac)_3$ was added in taking the $^{15}N$ NMR spectra in order to decrease the time of the experiment for determining the chemical shifts in the DMSO-$d_6$ solution in amounts of 0.01 M for each nitrogen atom with 0.5 M sample concentration.

**7-Aryl-1,2,4-triazolo-[1,5-a]-1,3,5-triazine (IIa)-(IIc).** An equivalent amount of 0.6 M MeONa in methanol was added to 0.005-0.015 mole (Ia)-(Ic). After stirring for 15 min, methanol was removed in vacuum. The residue was heated at reflux with 2-6 ml $HC(OEt)_3$ for 3-

5 h. The reaction mixture was evaporated to dryness. The products were separated from the residue by extraction with hot ethyl acetate [(IIa) and (IIb)] or acetonitrile [(IIc)].

**7-Phenyl-1,2,4-triazolo-[1,5-a]-1,3,5-triazine (IIa)** was obtained in 68% yield, mp 182°C (dec., from benzene). Found: C, 60.79; H, 3.66; N, 35.50%. Calculated for $C_{10}H_7N_5$: C, 60.90; H, 3.58; N, 35.52%. Mass spectrum: 197 $[M]^{+\cdot}$. PMR spectrum (δ, ppm): 10.14 s ($C^5$-H), 8.80 s ($C^2$-H), 8.63-8.30 m and 7.75-7.38 m (Ph). $^{13}C$ NMR spectrum (δ, ppm, J, Hz): 162.88 (2.6) ($C^7$), 157.45 (208.9) ($C^2$), 155.96 (2.5) ($C^3$), 148.85 (219.5) ($C^5$), 134.52, 132.18, 128.56, 128.45 (Ph). IR spectrum: 1490, 1600, 1614 (C=C, C=N).

**7-o-Tolyl-1,2,4-triazolo-[1,5-a]-1,3,5-triazine (IIb)** was obtained in 71% yield. An analytical sample was purified by column chromatography on silica gel L 100/160 with ethyl acetate as the eluent, $R_f \approx 0.8$, mp 69°C. Found: C, 62.60; H, 4.42; N, 32.83%. Calculated for $C_{11}H_9N_5$: C, 62.54; H, 4.30; N, 33.16%. Mass spectrum: 211 $[M]^{+\cdot}$. PMR spectrum (δ, ppm): 10.14 s ($C^5$-H), 8.81 s ($C^2$-H), 8.11-8.00 m and 7.53-7.25 m ($C_6H_4$), 2.64 s (Me). IR spectrum: 1490, 1600, 1615 (C=C, C=N).

**7-p-Tolyl-1,2,4-triazolo-[1,5-a]-1,3,5-triazine (IIc)** was obtained in 64% yield, mp 239-241°C (from acetonitrile). Found: C, 62.04; H, 4.33; N, 33.01%. Calculated for $C_{11}H_9N_5$: C, 62.54; H, 4.30; N, 33.16%. Mass spectrum: 211 $[M]^{+\cdot}$. PMR spectrum (δ, ppm): 10.09 s ($C^5$-H), 8.77 ($C^2$-H), 8.38 d and 7.41 d ($C_6H_4$), 2.42 s (Me). IR spectrum: 1490, 1600, 1620 (C=C, C=N).

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