N-ALKYLATION OF 4-CHLORO-5-CYANO-1,2,3-TRIAZOLE WITH ORTHOFORMIC ACID DERIVATIVES

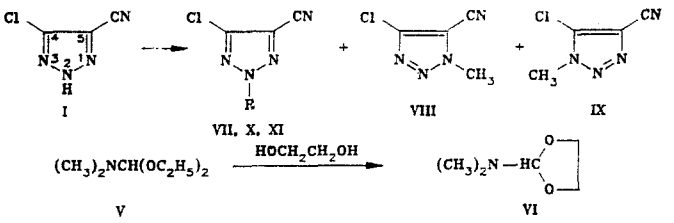
Yu. N. Bulychev, M. N. Preobrazhenskaya, A. I. Chernyshev, and S. E. Esipov

UDC 547.791.1.04:543.422.25

The N-alkylation of 4-chloro-5-cyano-1,2,3-triazole with methyl and ethyl orthoformate, and the dimethyl, diethyl and ethylene acetals of DMF has been examined. Methylation gives all three N-methyl isomers, whereas ethylation and hydroxyethylation gives the 2-N-alkyl derivatives only. It has been shown for the first time that it is possible to use DMF ethylene acetal to obtain N-hydroxyethylazoles. The structures of the products were established by ^{13}C NMR spectroscopy.

Continuing an examination of the N-alkylation of nitrogen heterocycles by derivatives of orthoacids [1], we have carried out the N-alkylation of 4-chloro-5-cyano-1,2,3-triazole (I) by orthoformic acid derivatives. Interest in alkyl derivatives of this heterocycle arises for two reasons. Firstly, they can be used as model compounds in structural studies of more complex compounds of this type, and secondly, in accordance with our suggestion of the existence of a correlation between the NH acidity of the azole and the ease of formation of N-alkyl derivatives, it was of interest to commence a study of the alkylation of polynitrogen heterocycles. These are clearly stronger NH acids than pyrazoles, the reactivity of which towards alkylation by orthoacid derivatives we have previously studied [1, 2].

The alkylating agents used were methyl and ethyl orthoformates (II and III), DMF dimethyl and diethyl acetals (IV and V), and DMF cyclic ethylene acetal (VI). We found no fundamental differences between the alkylation of the triazole (I) with DMF acetals or the corresponding orthoesters. Unlike the previously-studied pyrazoles, and condensed pyrazoles [1, 2], towards which (V) is a more reactive alkylating agent than ethyl orthoformate (III), the triazole (I) is alkylated with equal ease by orthoesters (II) and (III), and by acetals (IV) and (V). Methylation of (I) with the orthoester (II) or the acetal (IV) gave all three methyl isomers, but in both instances it was possible to isolate in the pure state only N-2-methyl-4-chloro-5'-cyano-1,2,3-triazole (VII), in 55 and 57% yield respectively. The 1- and 3-methyl derivatives of (I) (VIII and IX) were obtained as mixtures in overall yields of 29 and 30% respectively. According to the ^1H and ^{13}C NMR spectra, the ratio of isomers (VIII) and (IX) (in both cases!) was 3:2. It was not possible to separate the N-methyl compounds (VIII) and (IX), either by preparative chromatography on silica gel plates, or by HPLC. Ethylation of (I) with the ester (III) or the acetal (V) gave in both instances N-2-ethyl-4-chloro-5-cyano-1,2,3-triazole (X) only.



VII R=CH_3; X R=CH_2CH_3; XI R=CH_2CH_2OH

The acetal (VI) was obtained by transacetalization of DMF diethyl acetal (V) with ethylene glycol, by a method similar to that described in [3]. Following heating the triazole (I) in an excess of the acetal (VI), chromatography on silica gel gave N-2-(2-hydroxyethyl)-4-chloro-5-cyano-1,2,3-triazole (XI) in 74% yield. The reaction appears to involve opening of the

All-Union Scientific Center for Oncology, Academy of Medical Sciences of the USSR, Moscow 115478. All-Union Research Institute for Antibiotics, Minmedmikrobioprom USSR, Moscow 113105.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 920-924, July, 1988. Original article submitted January 26, 1987.

 0009-3122/88/2407-0756$12.50

TABLE 1. N-Alkyl-4-chloro-5-cyano-1,2,3-triazole (VII-XI)

Compound	UV spectrum (in ethanol)		PMR spectrum in $CDCl_3$, δ, ppm	Mass spectrum, M^+, m/z	Found, %			Empirical formula	Calculated, %		
	λ_{max}, nm	lg ε			C	H	Cl		C	H	Cl
VII	208 235	3,76 3,83	4,25 (s, CH_3)	142	33,8	2,9	25,1	$C_4H_3ClN_4$	33,7	2,1	24,9
VIII+ IX	215,5	3,87	4,26 and 4,11 (both s, CH_3)	142	34,0	2,4	25,0	$C_4H_3ClN_4$	33,7	2,1	24,9
X	208 235	3,70 3,80	4,52 (d, d CH_2), 1,61 (t, CH_3)	156	39,1	3,6	—	$C_5H_5ClN_4$	38,5	3,2	—
XI	209 236	3,72 3,85	4,56 (t, CH_2),*/3,87 (t, CH_2)	172	35,4	3,3	20,1	$C_5H_5ClN_4O$	34,8	2,9	20,6

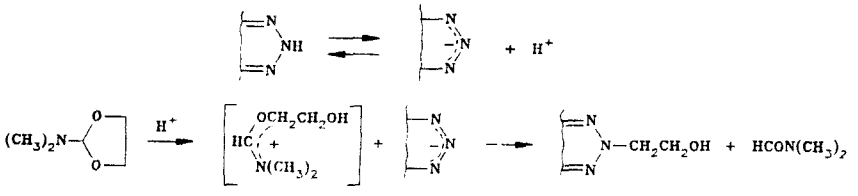
*Spectrum obtained in DMSO-D_6.

TABLE 2. ^{13}C Spectral Data for the Triazole (I) and Its N-Alkyl Derivatives (VII-X) (in DMSO-D_6)

Compound	Chemical shift, δ, ppm (SSCC, $J_{C,H}$, Hz)			
	$C_{(4)}$ (J^3_{C,CH_3})	$C_{(5)}$ (J^3_{C,CH_3})	CN	CH_3 ($J^1_{C,H}$; $J^2_{C,H(CH_2)}$)
I	140,76	119,74	111,38	—
VII	140,96	120,03	110,82	44,79 (J^1=144,6)
VIII	140,98	112,06 (J^3=3,3)	108,29	38,98 (J^1=144,6)
IX	134,42 (J^3=3,3)	119,35	111,50	36,58 (J^1=144,6)
X	140,89	119,91	110,84	14,70* (J^1=129,2; J^2=3,6)

*δ_{CH_2} 53.20 ppm (J^1 = 145.2; J^2 = 4.4 Hz).

dioxolane ring of the acetal as a result of protonation with partial dissociation of the heterocycle, followed by electrophilic attack on the heterocycle anion.



This method may be used for a simple one-step synthesis of acyclic hydroxyalkyl analogs of biologically important nucleosides.

In the IR spectra of (VII-XI), absorption is seen at 2245...2256 cm^{-1} for the CN group. The UV spectra of the 2-substituted 4-chloro-5-cyano-1,2,3-triazole (VII), (X), and (XI) are very similar. The absorption maximum for these compounds lies at 235...236 nm, whereas the UV spectrum of the mixture of isomers (VIII) and (IX) differs markedly from these. In the ^1H NMR spectrum of (VII-XI) (Table 2), signals are present for the protons of the alkyl substituents. The mass spectra of (VII-XI) show the molecular ion peaks.

The site of entry of the alkyl group into the heterocycle in (VII-X) was established by comparison of the chemical shifts and multiplicity of the signals in the ^{13}C NMR spectra of these compounds with the spectral properties of the heterocycle (I).

The spectrum of the starting material (I) consists of three singlet signals for the carbon atoms of the triazole ring and the CN group. The signal at 111.38 ppm is assigned the carbon atom of the cyano group, as described in [4]. Assignment of the signals at 140.76 and 119.74 ppm to $C_{(4)}$ and $C_{(5)}$ of the heterocycle respectively was made on the basis of the chemical shifts of the carbon atoms in the unsubstituted triazole with δ 130.1 ppm [5], and the increments of the substituents (chlorine atom and cyano group) in substituted benzenes [6, p. 170]. Comparison of the spectral data for (I), (VII), and (X) shows that the chemical shifts of the signals for the carbon atoms in the triazole ring and the cyano group in the spectra of the alkyl-compounds (VII) and (X) are only very slightly different from those of the starting heterocycle (I) (Fig. 1). In the spectra of (I), (VII), and (X), obtained without suppression of proton-carbon coupling, the signals for $C_{(4)}$ and $C_{(5)}$ are seen as singlets.

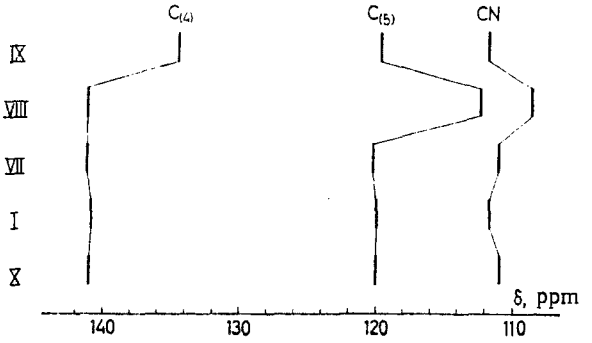


Fig. 1. Changes in the chemical shifts of signals for atoms $C(_4)$, $C(_5)$, and the C of the CN group in the ^{13}C NMR spectra of (I) and (VII-X).

The absence of any changes in the multiplicity of these signals when alkyl substituents are introduced into (I) indicates the absence of substitution at the outer nitrogen atoms $N(_1)$ and $N(_3)$. Compounds (VII) and (X) are therefore to be regarded as the $N(_2)$ alkyltriazoles.

In the spectra of the mixture of isomers (VIII) and (IX), a double set of signals is seen, the integral intensity ratio of which (3:2) shows the composition of the mixture. Two signals for $C(_4)$ are seen at low field, 140.98 and 134.42 ppm. The signal at higher field must be assigned to $C(_4)$ in (IX), since in the spectrum obtained without suppression of proton-carbon coupling it is split into a quartet by interaction with the methyl protons at $N(_3)$. In addition, the high-field shift of this signal as compared with the chemical shift of $C(_4)$ in (I), by 6.3 ppm, enables the conclusion to be drawn on the basis of previous observations [1] that the methyl substituent in (IX) is present in the α-position to $C(_4)$, i.e., at $N(_3)$. The similarity of the chemical shifts for $C(_4)$ in isomer (VIII) and the shifts of this carbon in (I) and in the $N(_2)$-alkyl derivatives (VII) and (X) shows that the methyl group in (VIII) is located in the β-position relative to $C(_4)$, i.e., at $N(_1)$.

The signals for $C(_5)$ in isomers (VIII) and (IX) are seen at 119.35 and 112.06 ppm, the signal at higher field being split into a quartet with J^3 = 3.3 Hz (Table 2) by coupling with the methyl protons at $N(_1)$, enabling this signal to be assigned to $C(_5)$ in isomer (VIII). In comparison with the original heterocycle (I) and the $N(_2)$-alkylated triazoles (VII) and (X), this signal is shifted to higher field by 7.7-8.0 ppm (the α-shift), which also shows the presence of the alkyl substituent in (VIII) at the nitrogen α- to $C(_5)$, i.e., $N(_1)$. The absence of fine structure in the signal for $C(_5)$ in isomer (IX) and the similarity of its chemical shift to those of this atom in (I), (VII), and (X), together with the quartet structure for the signal for $C(_4)$, establish the position of the methyl group in (IX) at $N(_3)$.

Assignment of the signals for the carbon of the CN group in (VIII) and (IX) was made by comparing the integral intensities. The stronger signal at 108.29 ppm is attributed to the CN carbon in (VIII). The presence of a methyl group at $N(_1)$ in (VIII) is also confirmed by the marked shift to higher field of this signal as a result of the steric influence of the $N(_1)$-methyl substituent.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Bruker WH-90 spectrometer (West Germany), operating frequencies 90 MHz (^1H) and 22.62 MHz (^{13}C), at 30°C. The chemical shifts were measured relative to the internal standards TMS (^1H, δ_{TMS} = 0.00 ppm) and dioxane (^{13}C, δ_{DO} = 67.4 ppm). The precision of measurement of the chemical shifts and coupling constants in the ^{13}C NMR spectra, determined by numerical resolution, were 0.02 ppm and 0.5 Hz. UV spectra were obtained on a Unicam SP-800 spectrophotometer, IR spectra on a Perkin-Elmer 283 in KBr disks, and mass spectra on a Varian MAT-311A mass spectrometer. HPLC was carried out on a Hewlett-Packard 1084B chromatograph (USA) with a 250 × 4.0 mm column, Lichrosorb RP-18, 10 μm, eluted with aqueous methanol in gradient mode from 10 to 50% methanol over 15 min, elution rate 1 ml/min. Analytical TLC was carried out on Silufol UV-254 (for systems see Table 3), and preparative chromatography on 20 × 20 cm plates of unbound silica gel LSL 5/40 (Czech SSR), layer thickness 1.5 mm, using the same solvent systems as in TLC.

The triazole (I) used in this work was kindly presented by the authors of [7]. Acetals (IV) and (V) were prepared as in [8].

TABLE 3. Conditions and Results of the N-Alkylation of 4-Chloro-5-cyano-1,2,3-triazole (I) with Orthoformic Acid Derivatives

Reactant	Reaction time, h	Reaction product	R_f (chloroform)	Yield, %
II	3	VII	0.57	55
		VIII+IX	0.31*	29
III	5	X	0.65	68
IV	3	VII	0.57	57
		VIII+IX	0.31*	30
V	3	X	0.65	74
VI	5	XI	0.30†	74

*Retention time of the mixture of isomers (VIII) and (IX) in HPLC R_t = 9.47 min.
†In chloroform–methanol, 95:5.

Dimethylformamide Ethylene Acetal (VI). To 25.0 g (0.17 mole) of the acetal (V) was added dropwise at 20°C over one hour with stirring 15.5 g (0.25 mole) of freshly-distilled ethylene glycol. The mixture was stirred for 2 h at 20°C, then fractionated in vacuo, the fraction bp 36-44°C (17 mm) being collected. The yield of (VI) was 16.0 g (80%), n_D^{20} 1.4260. ^{1}H NMR spectrum ($CDCl_3$): 5.38 (1H, s, CH), 4.00 and 3.89 (both 2H, m, $2CH_2$), 2.34 ppm (6H, s, $2CH_3$). According to [9], n_D^{20} 1.4290, bp 142-144°C. According to the ^{1}H NMR spectrum, (VI) contained up to 5% of DMF.

General Method of Alkylation of 4-Chloro-5-cyano-1,2,3-triazole (I) with Orthoformic Acid Derivatives. A mixture of 0.5 g (4 mmole) of (I) and 2-3 ml of the orthoester (II) or (III), or the acetal (IV-VI) was heated, the progress of the reaction being followed by TLC in the appropriate solvent system. The resulting solution was evaporated, the residue twice evaporated with 5 ml portions of toluene, and the residue subjected to chromatography on silica gel to give the N-alkyl derivative (VII-XI) as yellow oils. The reaction conditions, properties and yields of the products are given in Tables 1 and 3.

LITERATURE CITED

1. Yu. N. Bulychev, M. N. Preobrazhenskaya, A. I. Chernyshev, and S. E. Esipov, Khim. Geterotsikl. Soedin., No. 7, 914 (1988).
2. Yu. N. Bulychev, I. A. Korbukh, M. N. Preobrazhenskaya, A. I. Chernyshev, and S. E. Esipov, Khim. Geterotsikl. Soedin., No. 2, 259 (1984).
3. S. Hanessian, A. Bargiotti, and M. LaRue, Tetrahedron Lett., No. 8, 737 (1978).
4. I. D. Shingarova, A. T. Lebedev, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 7, 937 (1987).
5. F. J. Weigert and J. D. Roberts, J. Am. Chem. Soc., 90, 3543 (1968).
6. B. I. Ionin, V. A. Ershov, and A. I. Kol'tsov, NMR Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1983).
7. M. P. Nemeryuk, A. A. Sedov, I. Krzhepelka, Ya. Benesh, and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 10, 1398 (1983).
8. H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffman, and P. Grieshaber, Chem. Ber., 101, 41 (1968).
9. R. F. Abdulla and R. S. Brinkmeyer, Tetrahedron, 35, 1675 (1979).