Cyanation and Sulfonylation of 5-Substituted Tetrazoles. Imidoyl Azides

*O. Subba Rao and Walter Lwowski**

Department of Chemistry, New Mexico State University, Las Cruces, N.M. 88003 USA

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Reaction of 5-methoxy- and 5-ethoxytetrazole with methanesulfonyl chloride and cyanogen bromide was found to occur in the 1-position of the tetrazole. This is in marked contrast to other acylations of 5-substituted tetrazoles, where high yields of the 2-acyl derivatives are reported for dozens of examples and a variety of acylating agents. The 1-methanesulfonyl- and 1-cyano-5-alkoxytetrazoles ring-open spontaneously to the corresponding imidoyl azides, which are conveniently prepared by this method.

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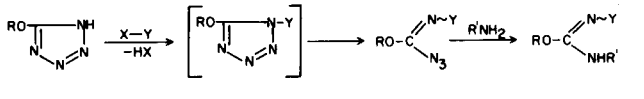
Electrophilic attack on 5-substituted tetrazoles by acyl halides or acyl anhydrides (1,2,3,4,5,6), sulfonyl chlorides (7,8), isocyanates (7), isothiocyanates (7), thioacyl chlorides (7), and carbimidoyl chlorides (9) has been shown to occur in the 2-position. Examples are found in recent reviews (10,11), and these reviews also show the contrasting behavior of alkylating reagents, which often give mixtures of 1- and 2-alkyl-5-substituted tetrazoles. Martin and Weise (11,12) report 2-acetylation for 5-aryloxytetrazoles, and formulate the products from cyanogen bromide as 5-aryloxy-2-cyanotetrazoles. Proof for the 2-acyl structures usually comes from thermally induced ring-opening. This gives nitrogen and nitrilimines, which undergo cycloadditions or cyclize to 1,3,4-oxadiazoles. Huisgen has provided over fifty such examples, and the yields of products derived from the nitrilimines shows that the primary acylation must have occurred exclusively or predominantely in the 2-positions.

We wish to report that the "2-acylation rule" does not hold for the reactions of 5-methoxy- and 5-ethoxytetrazole with methanesulfonyl chloride and with cyanogen bromide. The products of these reactions undergo spontaneous ring opening to the corresponding imidoyl azides, obtained in high yields. Thus, the primary products must be the 1-acyl 5-alkoxytetrazoles:



1 R = C_2H_5
2 R = CH_3

3 R = C_2H_5, Y = SO_2CH_3
4 R = CH_3, Y = SO_2CH_3
5 R = C_2H_5, Y = CN
6 R = CH_3, Y = CN

7 R = C_2H_5, Y = SO_2CH_3, R' = OH
8 R = C_2H_5, Y = CN, R' = H_3CO

Compounds **3-6** show strong azide absorption in their infrared spectra. Their nmr spectra show only one set of signals each, excluding the presence of significant amounts of the tetrazole valence tautomer, and indicating a rapid interconversion of the *E* and *Z* isomers. (The presence of only one *E* or *Z* isomer seems less likely). The predominance of the azide form is expected, in view of the strongly electron-withdrawing nature of the substituents Y, cyano or sulfonyl. The elemental analyses and properties of **3-6** are found in Table I.

Our results are a warning against uncritical use of the "2-acylation rule" for 5-substituted tetrazoles. More importantly, the results provide a convenient synthesis for the imidoyl azides **3-6**, especially since the 5-alkoxytetrazoles are easily prepared from azodicarboxylic esters and a hydrazoic acid solution (13). In view of the ready displacement of the azido group (see Experimental), the synthesis could be extended to make certain iso-ureas.

EXPERIMENTAL

Elemental analyses were performed by Baron Consulting Co., Orange, CT. Nmr spectra were taken on a JEOL PS-100 instrument, ir spectra on a Perkin-Elmer model 621 spectrometer, and uv spectra on a Cary 219 spectrometer.

Acylations of 5-Alkoxytetrazoles. Ethyl 1-Azido-*N*-(methanesulfonyl)-formimidate (**3**).

Methanesulfonyl chloride (40.2 g., 0.351 mole) was added with stirring at −5° to a solution of 40 g. (0.351 mole) of 5-ethoxytetrazole (13) in 350 ml. of anhydrous, peroxide-free, tetrahydrofuran. To this mixture was added below 0°, with stirring, over a period of 90 minutes, a solution of triethylamine (35.4 g., 0.351 mole) in 50 ml. of tetrahydrofuran. After another 30 minutes below 0°, the mixture was allowed to warm to room temperature, with continued stirring. Triethylammonium chloride was filtered and washed with tetrahydrofuran. The combined solutions were concentrated *in vacuo* to about 100 ml. and the azide crystallized upon cooling. (Alternatively, all tetrahydrofuran was removed and the residue allowed to crystallize over night). The azide should be filtered as soon as substantial quantities have crystallized, it was immediately recrystallized by cooling its ethyl acetate solution to −25°. The azide decomposes slowly at room temperature, but is stable at −40°, m.p. 58-59°, yield 53.3 g. (79%).

Methyl 1-Azido-*N*-(methanesulfonyl)formimidate (**4**).

The compound was prepared just as was **3**, from 5-methoxytetrazole (7.81 g., 0.078 mole), methanesulfonyl chloride (8.98 g., 0,078 mole), and

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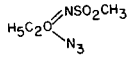
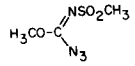
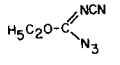
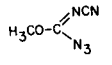
Table I

Imidoylazides (Alkyl 1-Azido-*N*-acylformimidates)

	Compound	m.p.	^{1}H mmr spectrum (δ from TMS)	Uv max (ε) nm	Infrared Spectrum cm^{-1}		Elemental Analysis C	H	N
3		58-59°	1.43 t (3), 3.07 s (3), 4.36 q (2)	230.5 (9,500)	2200 w, 2150 s, 1600 vs, 1305 vs, 1138 s	Calcd.	25.00	4.14	29.17
						Found	25.31	4.44	29.55
4		118.5-120°	3.98 s (3), 3.07 s (3),	230.5 (9.900)	2205 w, 2153 s, 1603 vs, 1310 vs, 1135 s	Calcd.	20.22	3.37	31.46
						Found	20.28	3.13	31.25
5		liq.	1.45 t (3), 4.47 q (2)	240.5 (10,800)	2218 s, 2197 s, 2164 vs, 1615 vs	Calcd.	34.53	3.60	50.36
						Found	34.73	3.35	50.10
6		liq.	4.07 s	240.0 (10,600)	2212 s, 2184 s, 2147 vs, 1610 vs	Calcd.	28.80	2.40	56.00
						Found	28.76	2.68	55.76

triethylamine (7.9 g., 0.078 mole) in 100 ml. of tetrahydrofuran, m.p. 118.5-120°, from ethyl acetate, yield 12.26 g. (87%).

Ethyl 1-Azido-*N*-cyanoformimidate (**5**).

The compound was prepared as was **3**, from 5-ethoxytetrazole (10.4 g., 0.91 mole), cyanogen bromide (9.67 g., 0.091 mole), and triethylamine (9.67 g., 0.091 mole) in 300 ml. of tetrahydrofuran. After removal of the triethylammonium chloride, the combined tetrahydrofuran solutions were evaporated *in vacuo* and the viscous residue was passed three times over short columns of 25 g. of silica gel each, using benzene as the eluent. Most of the azide was found in the first 250 ml. (of a total of 1,000 ml.) of eluate. The solvent was removed *in vacuo*, and the residue dried at room temperature at 0.2 mm Hg. The residue was pure **5**, 11.85 g. (93%). It decomposes slowly at room temperature, rapidly at 95°, and is stable at −40°.

Methyl 1-Azido-*N*-cyanoformimidate (**6**).

The compound was prepared just like **5**, from 5-methoxytetrazole (30.0 g., 0.3 mole), cyanogen bromide (31.77 g., 0.3 mole), and triethylamine (41.76 g., 0.3 mole) in 350 ml. of tetrahydrofuran. After three passes through short silica gel columns (22 g. each), the yield was 34.7 g. (93%).

Reaction of **3** with Hydroxylamine. *O*-Ethyl-*N*-hydroxy-*N'*-methanesulfonylisourea (**7**).

A solution of hydroxylamine in ethanol was prepared at 0° from hydroxylammonium chloride (1.086 g., 0.016 mole), triethylamine (1.62 g., 0.016 mole) and 30 ml. of 95% ethanol. It was added at 0° to a solution of **3** (3.0 g., 0.016 mole) in 15 ml. of ethanol, over a period of 15 minutes. After one more hour, the solution was allowed to warm to room temperature, the volatile components were removed *in vacuo*, and the semi-solid residue was extracted with ether. Evaporation gave a viscous liquid which was dissolved in ethyl acetate. After addition of petroleum ether, 1.93 g. (68% yield) of crystals separated during two days at −25°. The *O*-ethyl-*N*-hydroxy-*N'*-methanesulfonylisourea melted at 63.5-65.5° after recrystallization from ethyl acetate-petroleum ether; ir (chloroform): 3540 cm^{-1}, w, broad, 3332 broad, 1661 w, 1132 m; ms: 182 (M$^+$); nmr: δ 1.37, t (3); 3.03 s (3); 4.30 q (2) and 2 very broad signals between 6.6 and 9.4 (2).

Anal. Calcd. for $C_4H_{10}N_2O_4S$: C, 26.37; H, 5.49; N, 15.38; Found:C, 26.72; H, 5.71; N, 15.66.

Reaction of **5** with Methoxyamine. *O*-Ethyl-*N*-cyano-*N'*-methoxyisourea (**8**).

To a solution of methoxyammonium chloride (1.21 g., 0.0144 mole) in 5 ml. of 95% ethanol was added with stirring below 0° a solution of triethylamine (1.46 g., 0.0144 mole) in 20 ml. of ethanol. To this was added with stirring below 0° a solution of **3** (2.0 g., 0.0144 mole) in 20 ml. of ethanol. After 90 minutes at 0°, the mixture was allowed to warm to room temperature and concentrated *in vacuo*, eventually using a pressure of 0.2 mm Hg. The solid residue was extracted with 250 ml. of ether, evaporation of which left 1.973 g. of a solid. Recrystallization from ethyl acetate-pentane, with cooling to −25°, gave 1.721 g. (83% yield) of *O*-ethyl-*N*-cyano-*N'*-methoxyisourea, m.p. 86.5-88°; ir (chloroform): 3360 w, broad, 3200-3125 broad, 2197 vs, 1633 s, 1597 vs; nmr: δ 1.36, t (3); 3.76, s (3); 4.33, q (2); 10.3, broad (1).

Anal. Calcd. for $C_5H_9N_3O_2$: C, 41.96; H, 6.29; N, 29.37; Found: C, 41.99; H, 6.54; N, 29.07.

Acknowledgement.

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