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1,2,4-Triazoles. VII.[1] Methylation of 1,2,4-Triazoles

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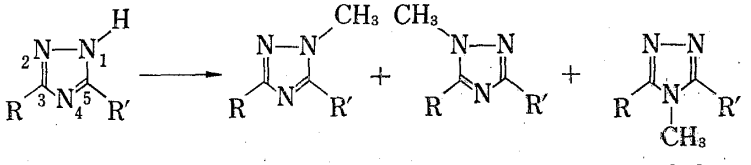
The methylations of twenty-five 1,2,4-triazoles with methyl iodide and diazomethane were studied and substituent effects on the product ratios are discussed. Methylation of 1,2,4-triazole and its symmetrically 3,5-disubstituted derivatives occurred almost exclusively at the 1-position. These results are interpreted in terms of the α-effect of the α-diaza structures of the 1- and 2-positions in the 1,2,4-triazoles. Methylations of 3-substituted 1,2,4-triazoles with methyl iodide and diazomethane occurred preferentially at the N-1 atom, which is sterically less hindered. However, methylation of 3-α-pyridyl-1,2,4-triazole with diazomethane occurred preferentially at the N-2 atom next to the α-pyridyl group due to the particular space effect of the α-pyridyl group. Methylation of 3,5-disubstituted 1,2,4-triazoles occurred predominantly at the vicinal nitrogen atom next to the electron-releasing group, but 3-α-pyridyl derivatives were methylated mainly at the vicinal nitrogen atom next to the α-pyridyl group.

Methylation of 1,2,4-triazoles yields three N-methylated isomers as shown in Chart 1. The ratio of these isomers produced is expected to be affected by the methylating agent, solvent, and especially substituents in positions 3 and 5. Studies on the methylations of 1,2,4-triazoles, such as 3,5-dimethyl,[3] 3,5-diphenyl,[3] 3-methyl,[4] 3-methyl-5-phenyl,[4] 3-β-phthalimidoethyl,[5] 3-amino-5-(2-furyl),[6] 3-nitro,[7] 3-α-pyridyl-5-methylthio,[8] 3-methyl-5-methylthio,[9] and 3-amino[10] derivatives, have been reported, but no general rule for the product ratios on methylation of 1,2,4-triazoles has been established. In this paper the methylations of twenty-five 1,2,4-triazoles with methyl iodide and diazomethane are described and the effects of substituents on the product ratios are discussed.



1-methyl isomer 2-methyl isomer 4-methyl isomer

Chart 1

Results and Discussion

Methylation of 1,2,4-Triazoles and Its Symmetrically 3,5-Disubstituted Derivatives

Methylation of symmetrically 3,5-disubstituted 1,2,4-triazoles gives isomeric 1- and 4-methylated derivatives. To study the differences between the reactivities of the N-1 and N-4

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2) Location: *Shomachi, Tokushima.*
3) M.R. Atkinson and J.B. Polya, *J. Chem. Soc.*, **1954**, 141.
4) M.R. Atkinson and J.B. Polya, *J. Chem. Soc.*, **1954**, 3319.
5) C. Ainsworth and R.G. Jones, *J. Am. Chem. Soc.*, **77**, 621 (1955).
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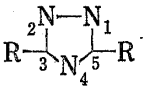
atoms in 1,2,4-triazoles, the methylations of 1,2,4-triazole (**1**) and its four symmetrically 3,5-disubstituted derivatives (**2**—**5**) were first examined. As shown in Table I, all these compounds were found to be methylated with either methyl iodide or diazomethane almost exclusively at the 1-position. The preferential 1-methylation seems to be due to the high nucleophilicities of the vicinal nitrogen atoms. That is, the enhanced reactivities of the N-1 atom in these 1,2,4-triazoles can be explained in terms of the α-effect[11] of these α-diaza structures, which have an unshared electron-pair in the α position to the nucleophilic center. Substitution of methyl, phenyl, and pyridyl groups at both positions 3 and 5 in 1,2,4-triazole decreased 4-methylation. These results are reasonable since the 4-positions are sterically hindered by the groups in both adjacent positions.

TABLE I. Product Ratios on Methylations of 1,2,4-Triazole and Its Symmetrically 3,5-Disubstituted Derivatives



Substrate[a]		Methylating agent	Solvent[b]	Yield (%)	Product ratio (%)	
No.	R				1-Methyl isomer	4-Methyl isomer
1	H	CH_3I	A	100	83	17
		CH_2N_2	B	100	87	13
2	CH_3	CH_3I	A	100	90	10
		CH_2N_2	B	100	93	7
3	C_6H_5	CH_3I	A	74	98	2
		CH_2N_2	B	65	99	1
4	α-Py	CH_3I	A	90	93	7
		CH_2N_2	B	93	96	4
5	γ-Py	CH_3I	A	73	100	0
		CH_2N_2	B	60	100	0

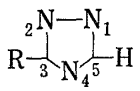
a) Py: pyridyl
b) A: 1N aqueous sodium hydroxide, B: methanol

Methylation of 3-Substituted 1,2,4-Triazoles

To study the influences of substituents in position 3 on the reactivities of the N-1 and N-2 atoms, the methylations of seven 3-substituted 1,2,4-triazoles were examined. As shown in Table II, the methylations of these compounds with methyl iodide in alkaline solution occurred preferentially at the 1-position. No predominant formation of the 2-methylated products was observed with 1,2,4-triazoles which have electron-releasing groups, such as a methyl, methylthio, or isopropyl group at position 3. These data indicate that the product ratios on methylations of 3-substituted 1,2,4-triazoles are influenced by the steric effects of the substituents rather than their electronic effects. This is supported by the fact that the yields of the 2-methylated products decreased with increase in bulk of the substituent in position 3 in order with methyl, methylthio, and isopropyl groups. Substitution of a phenyl group at position 3 also decreased N-2 methylation. This can be explained in the same way. Therefore, substitution of pyridyl groups at position 3 is expected to decrease N-2 methylation to a great extent, because it causes not only steric hindrance but also reduction of the π-electron density on the N-2 atom. Actually, the methylations of 3-β-pyridyl-1,2,4-triazole (**11**) and 3-γ-pyridyl-1,2,4-triazole (**12**) with methyl iodide gave the 2-methylated products in very poor yields. However, unexpectedly methylation of 3-α-pyridyl-1,2,4-triazole (**10**) with methyl iodide gave a considerable amount of the 2-methylated product.

11) J.A. Zoltewicz and L.W. Deady, *J. Am. Chem. Soc.*, **94**, 2765 (1972).

TABLE II. Product Ratios on Methylations of 3-Substituted 1,2,4-Triazoles



Substrate[a] No.	R	Methylating agent	Solvent[b]	Yield (%)	Product ratio (%) 1-Methyl isomer	2-Methyl isomer	4-Methyl isomer
6	CH_3	CH_3I	A	100	45	42	13
		CH_2N_2	B	100	46	45	9
7	SCH_3	CH_3I	A	95	58	30	12
		CH_2N_2	B	90	45	46	9
8	iso-C_3H_7	CH_3I	A	88	65	28	7
		CH_2N_2	B	84	54	41	5
9	C_6H_5	CH_3I	A	76	65	30	5
		CH_2N_2	B	88	62	34	4
10	α-Py	CH_3I	A	100	47	39	14
		CH_2N_2	B	100	16	67	17
11	β-Py	CH_3I	A	88	75	22	3
		CH_2N_2	B	90	71	26	3
12	γ-Py	CH_3I	A	84	77	18	5
		CH_2N_2	B	78	70	27	3

a) Py: pyridyl
b) A: 1N aqueous sodium hydroxide, B: methanol

Methylation of all 3-substituted 1,2,4-triazoles, except 3-methylthio-1,2,4-triazole (**7**) and **10**, with diazomethane gave similar product ratios to those obtained by methylation with methyl iodide. It is notable that methylation of 3-α-pyridyl derivative (**10**) with diazomethane occurred mainly at the 2-position, though the N-2 atom is sterically hindered and its π-electron density is expected to be greatly reduced by the α-pyridyl group which is a powerful electron attractor. This remarkable enhancement of reactivity of the N-2 atom in **10** is considered to be due to the particular space effect of the α-pyridyl group. The difference between the reactivities of the N-2 atom in **10** with methyl iodide and with diazomethane can be explained as follows. The first step of methylation with diazomethane involves the loss of a proton from compound (**10**) forming a methyldiazonium cation. Previously, we reported that the ring protons of 3-α-pyridyl-1,2,4-triazoles are located preferentially at the N-2 atom next to the α-pyridyl group.[12] Consequently, the methyldiazonium cation is thought to be captured preferentially by the N-2 atom in co-operation with the nitrogen atom in the α-pyridyl group. On the other hand, methylation with methyl iodide in alkaline solution proceeds by an S_N2 reaction and involves the triazole anion, so the less sterically hindered N-1 atom is probably methylated slightly preferentially to the N-2 atom. The influence of the α-pyridyl group is also expected to enhance the reactivity of the adjacent N-4 atom, so it is understandable that only methylation of 3-α-pyridyl derivative (**10**) gave an appreciable amount of the 4-methylated product. Similarly, the high reactivities of the N-2 and N-4 atoms in 3-methylthio-1,2,4-triazole (**7**) seem to be due to the effect of the methylthio group which has an unshared electron-pair.

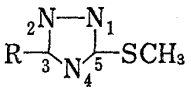
Methylation of 3,5-Disubstituted 1,2,4-Triazoles

The product ratios on methylation of six 3-substituted 5-methylthio-1,2,4-triazoles are shown in Table III. All these compounds (**13**—**18**) have aromatic rings in position 3 and methylthio groups in position 5, so they have the same steric conditions for methylation. Therefore, the differences between the product ratios of these compounds are probably due

12) S. Kubota and M. Uda, *Chem. Pharm. Bull.* (Tokyo), **23**, 955 (1975).

to the electronic effects of their substituents. The data in Table III show that substitution of the electron-attracting groups, *p*-chlorophenyl and *p*-nitrophenyl, in position 3 increases N-1 methylation. The 3-*β*-pyridyl derivative (**17**) and 3-*γ*-pyridyl derivative (**18**) were also methylated predominantly at the N-1 atom. However, methylation of the 3-*α*-pyridyl derivative (**16**) was exceptional in giving mainly the 2-methylated product with an appreciable amount of the 4-methylated product also. These facts support the idea that the *α*-pyridyl group enhances the reactivities of the adjacent N-2 and N-4 atoms.

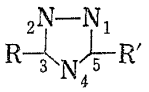
TABLE III. Product Ratios on Methylations of 3-Substituted 5-Methylthio-1,2,4-triazoles



Substrate No.	R	Methylating agent	Solvent[a]	Yield (%)	Product ratio (%) 1-Methyl isomer	2-Methyl isomer	4-Methyl isomer
13	C_6H_5	CH_3I	A	97	56	39	5
		CH_2N_2	B	90	59	37	4
14	*p*-ClC_6H_4	CH_3I	A	100	60	35	5
		CH_2N_2	B	100	64	33	3
15	*p*-$NO_2C_6H_4$	CH_3I	A	100	66	30	4
		CH_2N_2	B	92	68	29	3
16	*α*-Pyridyl	CH_3I	A	97	30	56	14
		CH_2N_2	B	90	15	69	16
17	*β*-Pyridyl	CH_3I	A	90	61	33	6
		CH_2N_2	B	82	65	31	4
18	*γ*-Pyridyl	CH_3I	A	94	66	29	5
		CH_2N_2	B	97	69	28	3

a) A: 1N aqueous sodium hydroxide B: methanol

TABLE IV. Product Ratios on Methylations of Unsymmetrically 3,5-Disubstituted 1,2,4-Triazoles



Substrate[a] No.	R	R′	Methylating agent	Solvent[b]	Yield (%)	Product ratio (%) 1-Methyl isomer	2-Methyl isomer	4-Methyl isomer
19	SCH_3	CH_3	CH_3I	A	100	55	34	11
			CH_2N_2	B	100	42	52	6
20	C_6H_5	CH_3	CH_3I	A	90	64	32	4
			CH_2N_2	B	84	58	39	3
21	*γ*-Py	CH_3	CH_3I	A	92	76	21	3
			CH_2N_2	B	88	62	36	2
22	*α*-Py	CH_3	CH_3I	A	100	47	43	10
			CH_2N_2	B	94	12	75	13
23	*α*-Py	C_6H_5	CH_3I	A	90	20	75	5
			CH_2N_2	B	85	14	83	3
24	*α*-Py	*β*-Py	CH_3I	A	88	20	77	3
			CH_2N_2	B	74	13	85	2
25	*α*-Py	*γ*-Py	CH_3I	A	87	18	80	2
			CH_2N_2	B	82	10	88	2

a) Py: pyridyl
b) A: 1N aqueous sodium hydroxide, B: methanol

The product ratios on methylations of seven 3,5-disubstituted 1,2,4-triazoles are summarized in Table IV. Methylation of 3-methylthio-5-methyl-1,2,4-triazole (**19**) with methyl iodide occurred preferentially at the N-1 atom, which is sterically less hindered, whereas methylation of **19** with diazomethane occurred preferentially at the N-2 atom next to the methylthio group. The methylations of 3-phenyl-5-methyl-1,2,4-triazole (**20**) and 3-γ-pyridyl-5-methyl-1,2,4-triazole (**21**) with methyl iodide and diazomethane occurred predominantly at the N-1 atom, which is sterically less hindered and has a higher π-electron density. The very high yields of the N-2 methylated products on methylations of 3-α-pyridyl derivatives (**23**, **24**, and **25**) are due to the fact that the reactivities of the N-2 atoms are enhanced by the α-pyridyl group, while those of the N-1 atoms are greatly decreased by the phenyl, β-pyridyl, and γ-pyridyl groups, respectively.

Experimental

Method——Studies were made by nuclear magnetic resonance (NMR) spectroscopy. The products obtained by methylations of compounds (**1**, **6**, **7**, **9**, **10**, **12**, **13**—**16**, **18**, and **19**) were identified by comparison of the chemical shifts of their N-methyl signals with those[12,13] of authentic samples. The N-methyl peaks of the mixtures of products obtained by methylations of compounds (**2**—**5**, **20**—**23**, and **25**) were assigned by use of the calculated chemical shifts[13] expected from substituent effects on the chemical shifts of the N-methyl protons. The NMR spectra of the methylated products obtained by methylations of 3-isopropyl-1,2,4-triazole (**8**), 3-β-pyridyl-1,2,4-triazole (**11**), 3-β-pyridyl-5-methylthio-1,2,4-triazole (**17**), and 3-α-pyridyl-5-β-pyridyl-1,2,4-triazole (**24**) show the three N-methyl peaks of the 1-, 2-, and 4-methylated products at 3.84, 3.80, 3.62 ppm; 3.98, 4.03, 3.85 ppm; 3.80, 3.96, 3.63 ppm; 4.10, 4.38, 4.22 ppm, respectively. These assignments are based on the assumption that the effects of isopropyl and β-pyridyl groups on the chemical shifts of the N-methyl groups are almost equal to those[13] of methyl and γ-pyridyl groups, respectively. The yields and ratios of the products were determined by measuring the relative intensities of the N-methyl peaks in the NMR spectra of the methylated products. NMR spectra were recorded with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard.

General Procedure for Methylation with Methyl Iodide——An appropriate 1,2,4-triazole (**1**—**25**, 0.2 mM) was weighed into a small glass tube and **1** N aqueous sodium hydroxide (1.0 ml) was added. To this solution was added methyl iodide (0.22 mM) in EtOH (0.15 ml), and the glass tube was stoppered tightly and shaken at room temperature for 3 days. The reaction mixture was extracted five times with $CHCl_3$ (3 ml), and the $CHCl_3$ extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in $CDCl_3$ for NMR measurements.

On methylation of 3-pyridyl derivatives (**4**, **5**, **10**—**12**, **16**—**18**, and **21**—**25**), very small amounts of quaternary salts were formed but they remained in the alkaline solution when the reaction mixture was extracted with $CHCl_3$.

General Procedure for Methylation with Diazomethane——Ethereal diazomethane (0.6 mM, about 2 ml) was added to a solution of an appropriate 1,2,4-triazole (**1**—**25**, 0.2 mM) in MeOH (5 ml) and the mixture was stood at room temperature for 3 days. Evaporation of the solvent gave an oily residue, which was dissolved in $CDCl_3$ for NMR measurements.

Materials——The compounds used in this study were prepared as follows. All melting points were determined in a Yanagimoto Micro Melting Point apparatus and are uncorrected.

3-α-Pyridyl-1,2,4-triazole (**10**) was synthesized by the reaction of picolinic acid amidrazone with formic acid, and by desulfurization with hydrogen peroxide from 3-α-pyridyl-1,2,4-triazoline-5-thione.[8] 3-β-Pyridyl-5-methylthio-1,2,4-triazole (**17**) was prepared by methylation of 3-β-pyridyl-1,2,4-triazoline-5-thione[14] with an equivalent amount of methyl iodide in alkaline solution. 3-α-Pyridyl-5-β-pyridyl-1,2,4-triazole (**24**) was synthesized by reaction of nicotinic acid hydrazide with excess 2-cyanopyridine.

Other compounds were prepared as described in the literature; **1**,[5] **2**,[15] **3**,[16] **4**—**5**,[13] **6**,[17] **7**,[18] **8**,[19] **9**,[20] **11**—**12**,[14] **13**,[20] **14**,[21] **15**,[12] **16**,[8] **18**,[22] **19**,[18] **20**,[16] **21**—**23**,[13] and **25**.[13]

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19) H.G.O. Becker, L. Krahnert, G. Rasch, W. Riediger, and J. Witthauer, *J. Prakt. Chem.*, **311**, 477 (1969).
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3-α-Pyridyl-1,2,4-triazole (10)——a) Picolinic acid amidrazone (4.0 g) was dissolved in 99% formic acid (6 ml) under cooling and the mixture was kept at room temperature for 30 min. Then it was refluxed for 1 hr, and excess formic acid was removed by evaporation. The residue was neutralized with 10% Na_2CO_3 and extracted five times with $CHCl_3$ (5 ml). The $CHCl_3$ extract was dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from benzene–EtOH (1: 1) to give colorless needles (3.5 g), mp 164—165°. *Anal.* Calcd. for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.75; H, 4.06; N, 38.14.

b) To a solution of 3-α-pyridyl-1,2,4-triazoline-5-thione[8] (0.39 g) in acetic acid (20 ml) 30% hydrogen peroxide was added dropwise and the mixture was refluxed for 8 hr. Then it was evaporated *in vacuo* and the residue was neutralized with 1 N NaOH. The solution was evaporated *in vacuo* and the residue was extracted with EtOH. The extract was evaporated and the residue was chromatographed on silica gel with $CHCl_3$ as eluent. The eluate gave colorless crystals (0.1 g).

3-β-Pyridyl-5-methylthio-1,2,4-triazole (17)——To a solution of 3-β-pyridyl-1,2,4-triazoline-5-thione[14] (0.7 g) in 1 N NaOH (5 ml) was added methyl iodide (0.52 g) in EtOH (0.5 ml), and the mixture was stirred at room temperature for 1 hr. The precipitate formed was collected by filtration and recrystallized from EtOH as colorless needles (0.39 g), mp 177—178°. *Anal. Calcd.* for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14. Found: C, 49.77; H, 4.18; N, 29.34.

3-α-Pyridyl-5-β-pyridyl-1,2,4-triazole (24)——A mixture of nicotinic acid hydrazide (1.2 g) and 2-cyanopyridine (10 g) was heated on an oil bath at 225—230° for 7 hr. Then the mixture was cooled and the precipitate formed was collected by filtration and recrystallized from EtOH as colorless needles (1.3 g), mp 253—254°. *Anal.* Calcd. for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.78; H, 4.02; N, 31.30.

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