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1,2,4-Triazoles. VI.[1] Methylation of 3-Phenyl-1,2,4-triazolin-5-one, 3-Phenyl-1,2,4-triazoline-5-thione, and Their Monomethylated Derivatives

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The product distributions resulting from methylation of 3-phenyl-1,2,4-triazolin-5-one (**1a**) and 3-phenyl-1,2,4-triazoline-5-thione (**1b**) and their monomethylated derivatives (**2a,b**—**5a,b**) with methyl iodide and diazomethane in various solvents were studied by nuclear magnetic resonance spectroscopy. The methylations of 1-methyl-3-phenyl-1,2,4-triazolin-5-one (**3a**), 5-hydroxy-2-methyl-3-phenyl-1,2,4-triazole (**4a**), and 4-methyl-3-phenyl-1,2,4-triazolin-5-one (**5a**), with methyl iodide in alkaline solution occurred preferentially at the N-atoms and afforded mainly 1,4-dimethyl-3-phenyl-1,2,4-triazolin-5-one (**9a**), mesoionic anhydro-2,4-dimethyl-5-hydroxy-3-phenyl-1,2,4-triazolium hydroxide (**11a**), and **9a**, respectively. The product ratios on methylations of **3a**, **4a**, and **5a** with diazomethane were affected variously by the type of solvent, the nucleophilicities of the four reaction sites, and the steric factor. Dimethyl sulfoxide (DMSO) increased O-methylation in all cases and especially with **4a**, which exists in the OH form, methylation occurred almost exclusively at the oxygen atom in DMSO. The methylations of **1b** and its N-methylated derivatives (**3b**—**5b**) with either methyl iodide or diazomethane gave S-methylated products predominantly in all the solvents used.

Previously, we studied the methylation of 3-α-pyridyl-1,2,4-triazoline-5-thione[3] and monomethylated 3-phenyl-1,2,4-triazoline-5-thiones,[4] but did not make systematic studies on the distributions of products obtained by methylation of these 1,2,4-triazolines. The methylation of 4-phenyl-1,2,4-triazoline-5-thione has been reported.[5] Moreover, solvent effects on the product distributions resulting from methylation of 3-methyl-1,2,4-triazoline-5-thione and its monomethylated derivatives have been studied.[6] However, no detailed studies on methylation of 1,2,4-triazolin-5-ones have been reported.

This paper describes the effects of methylating agents, solvents, the steric factor, and the nucleophilicities of the reaction sites on the product distributions on methylation of 3-phenyl-1,2,4-triazolin-5-one (**1a**) and 3-phenyl-1,2,4-triazoline-5-thione (**1b**) and their monomethylated derivatives (**2a,b**—**5a,b**). The structures of **1a,b**—**5a,b** and the theoretically obtainable dimethylated products (**6a,b**—**11a,b**) are shown in Chart 1.

The yields and ratios of the products were determined by measuring the relative intensities of the N-methyl peaks in the nuclear magnetic resonance (NMR) spectra of the methylated products. The products were identified by comparison of the chemical shifts of the N- and O(or S)-methyl peaks of the products with those of the authentic compounds, obtained by other synthetic procedures. The NMR data of these reference compounds are listed in Tables I and II.

The procedures used for preparation of compounds **1a**, **4a**—**10a**, **4b**, **6b**, **7b**, and **10b** were reported in our previous paper.[4] The other compounds (**1b**,[7] **2a**,[8] **2b**,[7]

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2) Location: *Shomachi, Tokushima.*
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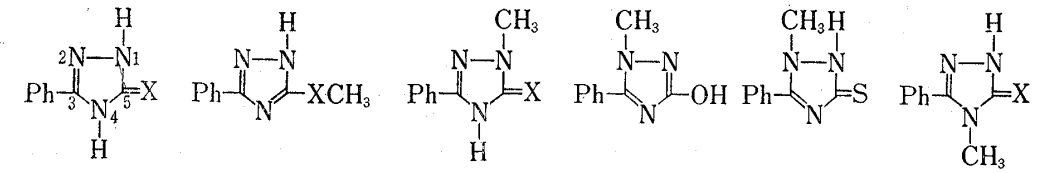
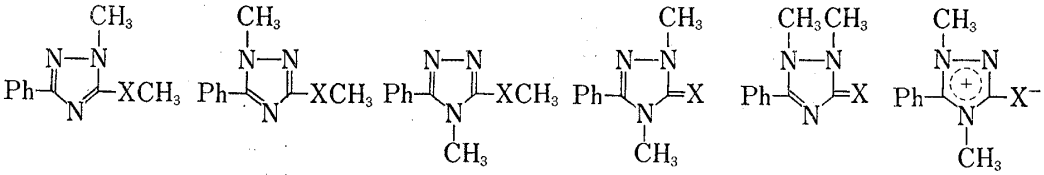


1a, b **2a, b** **3a, b** **4a** **4b** **5a, b**



6a, b **7a, b** **8a, b** **9a, b** **10a, b** **11a, b**

a : X=O, **b** : X=S
Ph=phenyl

Chart 1

TABLE I. NMR Data on Methyl Derivatives of 3-Phenyl-1,2,4-triazolin-5-one

Compd. No.	Solvent	Position of methyl group			
		1	2	4	5
2a	$CDCl_3$				4.08[a]
	DMSO-d_6				3.95
3a	$CDCl_3$	3.57			
	DMSO-d_6	3.36			
4a	$CDCl_3$		3.87[b]		
	DMSO-d_6		3.74		
5a	$CDCl_3$			3.40[b]	
	DMSO-d_6			3.24	
6a	$CDCl_3$	3.62[b]			4.12[b]
	DMSO-d_6	3.61			4.09
7a	$CDCl_3$		3.85[b]		4.00[b]
	DMSO-d_6		3.81		3.87
8a	$CDCl_3$			3.46[b]	4.20[b]
	DMSO-d_6			3.42	4.06
9a	$CDCl_3$	3.54[b]		3.38[b]	
	DMSO-d_6	3.39		3.26	
10a	$CDCl_3$	3.48[b]	3.58[b]		
	DMSO-d_6	3.48	3.59		
11a	$CDCl_3$		3.62	3.27	
	DMSO-d_6		3.51	3.09	

a) These chemical shifts have been reported in our previous papers (S. Kubota and M. Uda, *Chem. Pharm. Bull.* (Tokyo), **23**, 955 (1975)).
b) See ref. 4.

3a,[9] **3b**,[10] **5b**,[9] **8b**,[11] **9b**,[11] and **11a,b**[12]) used in the present study were prepared as described in the literature.

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Table II. NMR Data on Methyl Derivatives of 3-Phenyl-1,2,4-triazoline-5-thione

Compd. No.	Solvent	Position of methyl group			
		1	2	4	5
2b	$CDCl_3$				2.68[a]
	DMSO-d_6				2.62
3b	$CDCl_3$	3.83			
	DMSO-d_6	3.70			
4b	$CDCl_3$		3.84[b]		
	DMSO-d_6		3.77		
5b	$CDCl_3$			3.64	
	DMSO-d_6			3.53	
6b	$CDCl_3$	3.77[b]			2.72[b]
	DMSO-d_6	3.77			2.70
7b	$CDCl_3$		3.90[b]		2.60[b]
	DMSO-d_6		3.90		2.54
8b	$CDCl_3$			3.57[c]	2.77[a]
	DMSO-d_6			3.58	2.66
9b	$CDCl_3$	3.86		3.64	
	DMSO-d_6	3.75		3.55	
10b	$CDCl_3$	3.81	3.91		
	DMSO-d_6	3.82	3.82		
11b	$CDCl_3$		3.75	3.56	
	DMSO-d_6		3.62	3.38	

a), *b*), *c*): These chemical shifts have been reported in our previous papers (Table I.*a*),*b*), and Ref. No. 1.

Results and Discussion

Methylation of Monomethylated 3-Phenyl-1,2,4-triazolin-5-ones (2a—5a)

Data on the product distributions resulting from methylation of 5-methoxy-3-phenyl-1,2,4-triazole (**2a**), 1-methyl-3-phenyl-1,2,4-triazolin-5-one (**3a**), 5-hydroxy-2-methyl-3-phenyl-1,2,4-triazole (**4a**) and 4-methyl-3-phenyl-1,2,4-triazolin-5-one (**5a**) are summarized in Table III. Methylation of **2a** with methyl iodide and diazomethane occurred at positions 1 and 2 preferentially to position 4. Methylation of N-1 atom was slightly greater than that of N-2 atom on treatment with diazomethane in various solvents.

Methylation of **3a** with methyl iodide occurred almost exclusively at the N-4 atom, and gave 98% of 1,4-dimethyl-3-phenyl-1,2,4-triazolin-5-one (**9a**) with a trace of 1-methyl-5-methoxy-3-phenyl-1,2,4-triazole (**6a**). Methylation of **5a** under the same conditions gave 83% of **9a** and 17% of mesoionic anhydro-2,4-dimethyl-5-hydroxy-3-phenyl-1,2,4-triazolium hydroxide (**11a**), whereas methylation of **4a** gave 65% of **11a**. The predominant formation of **11a** from **4a** can be explained by differences in the reactivities of the three competitive nucleophilic sites. Since methylation with methyl iodide in alkaline solution is considered to proceed by an S_N2 reaction, the major factors affecting the product ratios are the nucleophilicities of the reaction sites and the steric factor. Therefore, the more polarizable nitrogen atom should be more reactive than the oxygen atom. Actually, N-methylation was predominant on treatment of **3a**, **4a**, and **5a** with methyl iodide. 1,2-Dimethyl-3-phenyl-1,2,4-triazolin-5-one (**10a**) was not formed predominantly from **4a**, because **10a** has two methyl groups in adjacent positions 1 and 2, causing steric hindrance.

On the other hand, the ratios of O-methylation to N-methylation of **3a**—**5a** were higher on treatment with diazomethane than on treatment with methyl iodide. It has been known that two routes, S_N1 and S_N2, are possible as reaction mechanism of methylation with diazometh-

Table III. Product Distributions on Methylation of Monomethylated 3-Phenyl-1,2,4-triazolin-5-ones (**2a**—**5a**)

Substrate No.	Methylating agent	Solvent[a]	Yield (%)	Product distribution (%)					
				6a	**7a**	**8a**	**9a**	**10a**	**11a**
2a	CH_3I	A	100	45	51	4			
	CH_2N_2	D	100	53	42	5			
	CH_2N_2	M	95	54	38	8			
	CH_2N_2	B	60	60	37	3			
	CH_2N_2	E	50	63	35	2			
3a	CH_3I	A	52	2			98		
	CH_2N_2	D	100	44			56		
	CH_2N_2	M	60	26			74		
	CH_2N_2	B	100	37			63		
	CH_2N_2	E	90	35			65		
4a	CH_3I	A	100		12			23	65
	CH_2N_2	D	100		94			2	4
	CH_2N_2	M	100		60			14	26
	CH_2N_2	B	100		67			21	12
	CH_2N_2	E	100		63			11	26
5a	CH_3I	A	100				83		17
	CH_2N_2	D	75			20	73		7
	CH_2N_2	M	90			10	82		8
	CH_2N_2	B	68			12	81		7
	CH_2N_2	E	53			13	80		7

a) A: 1N aqueous sodium hydroxide, D: dimethyl sulfoxide, M: methanol, B: benzene, E: diethyl ether

ane.[13,14] In S_N1 reaction, the atom with the greater electron density in the mesomeric anion of 1,2,4-triazolin-5-ones is considered to be the more reactive; that is, the oxygen atom is more reactive than the nitrogen atom. In S_N2 reaction, the nucleophilicities of the atoms in the mesomeric anion are the most important factors in determining the product ratio; that is, the more polarizable nitrogen atom is more reactive than the oxygen atom.

Therefore, polar solvents such as dimethyl sulfoxide (DMSO) and methanol should increase O-methylation, and in practice the yield of O-methylated products was higher on methylation in DMSO than in the other solvents used. In methanol, however, O-methylation did not occur so much as was expected from the polar character of this solvent. This seemed to be due to the protic character of methanol which tends to solvate to an oxygen atom of high electron density and so weaken its nucleophilicity. In nonpolar solvents, such as ether and benzene, the O-methylated product was produced in fairly high yield, though less than in DMSO.

The ratio of N-methylation to O-methylation was larger with **5a** than with **3a** in all solvents. This seems to be because the reactivity of the N-1 atom in **5a** is enhanced by the α-effect[15] of the adjacent N-2 atom. Methylation of **4a** with diazomethane occurred mainly at the oxygen atom in most solvents and almost exclusively at this position in DMSO. This predominant formation of the O-methylated product from **4a** may be related to the facts[4] that **4a** exists in the OH form, while **3a** and **5a** exist in the 4-NH form and 1-NH form, respectively.

Methylation of 3-Phenyl-1,2,4-triazolin-5-one (1a)

Compound **1a** has two acidic protons, so its methylation was carried out with both equivalent and excess amounts of methylating agents. Product distribution data for methylation

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Table IV. Product Distributions on Methylation of 3-Phenyl-1,2,4-triazolin-5-one (**1a**)

Methylating agent[a]		Solvent[b]	Yield (%)	Product distribution (%)							
				2a	**3a**	**5a**	**6a**	**7a**	**8a**	**9a**	**11a**
CH_3I	Eq.	A	42		92	8					
CH_3I	Ex.	A	95				2	2		92	4
CH_2N_2	Eq.	D	27	37		63					
CH_2N_2	Ex.	D	96			10	25	17	10	38	
CH_2N_2	Eq.	M	20	44	5	51					
CH_2N_2	Ex.	M	100	25		33	14	10	3	15	
CH_2N_2	Eq.[c]	B	0								
CH_2N_2	Ex.	B	95	24		20	22	15	4	15	

a) Eq.: methylation with an equivalent amount of methylating agent, Ex.: methylation with excess methylating agent
b) A: 1N aqueous sodium hydroxide, D: dimethyl sulfoxide, M: methanol, B: benzene
c) No methylated products were detected under these conditions.

Table V. Product Distributions on Methylation of 3-Phenyl-1,2,4-triazoline-5-thione (**1b**) and Its Monomethylated Derivatives (**2b**—**5b**)

Substrate No.	Methylating agent[a]		Solvent[b]	Yield (%)	Product distribution (%)				
					2b	**6b**	**7b**	**8b**	**9b**
1b	CHI_3	Eq.	A	100	100				
	CH_3I	Ex.	A	100		55	40	5	
	CH_2N_2	Eq.	D	56	100				
	CH_2N_2	Ex.	D	83		53	42	5	
	CH_2N_2	Eq.	M	40	100				
	CH_2N_2	Ex.	M	50		58	34	8	
	CH_2N_2	Eq.	B	65	100				
	CH_2N_2	Ex.	B	95		62	30	8	
	CH_2N_2	Eq.	E	87	100				
	CH_2N_2	Ex.	E	100		64	30	6	
2b	CH_3I		A	100		57	38	5	
	CH_2N_2		D	82		52	45	3	
	CH_2N_2		M	85		60	36	4	
	CH_2N_2		B	95		67	31	2	
	CH_2N_2		E	90		65	33	2	
3b	CH_3I		A	100	100				
	CH_2N_2		D	100		93			7
	CH_2N_2		M	90		95			5
	CH_2N_2		B	100		89			11
	CH_2N_2		E	100		94			6
4b	CH_3I		A	100			100		
	CH_2N_2		D	85			100		
	CH_2N_2		M	95			100		
	CH_2N_2		B	100			100		
	CH_2N_2		E	100			100		
5b	CH_3I		A	100				100	
	CH_2N_2		D	80				67	33
	CH_2N_2		M	100				80	20
	CH_2N_2		B	100				70	30
	CH_2N_2		E	100				68	32

a) Eq.: methylation with an equivalent amount of methylating agent, Ex.: methylation with excess methylating agent
b) A: 1N aqueous sodium hydroxide, D: dimethyl sulfoxide, M: methanol, B: benzene, E: diethyl ether

of **1a** are summarized in Table IV. Methylation of **1a** with an equivalent amount of methyl iodide in alkaline solution gave the N-1 methylated product (**3a**) almost exclusively, because S_N2 reaction does not favor O-methylation, and because the N-4 and N-2 atoms are less reactive than the N-1 atom, as already discussed. Treatment of **1a** with excess methyl iodide gave 92% of **9a**, 4% of **11a**, and traces of **6a** and **7a**. These results agree well with the product ratios expected from the observed product distributions of 92% of **3a** and 8% of **5a** with an equivalent amount of methyl iodide.

The reactivity of **1a** was very low on methylation with an equivalent amount of diazomethane, especially in benzene, in which no methylated product was detected. In DMSO and methanol, the O-methylated product (**2a**) and N-4 methylated product (**5a**) were formed mainly, although a considerable amount of unreacted substrate (**1a**) remained after the reaction. Using excess diazomethane, appreciable amounts of the dimethylated compounds, **6a**, **7a**, and **9a**, were obtained probably *via* **2a** and **5a**.

Methylation of 3-Phenyl-1,2,4-triazoline-5-thione (1b) and Its Monomethylated Derivatives (2b—5b)

The product distributions observed on methylation of compounds **1b—5b** are summarized in Table V. The product distributions on methylation of **1b** show a very simple pattern. Methylation with an equivalent amount of methyl iodide or diazomethane occurred exclusively at the sulfur atom. Thus, the product ratios for methylation of **1b** with excess methylating agents were very similar to those obtained on methylation of the S-methylated derivative (**2b**) under the corresponding conditions.

Methylations of 5-methylthio-3-phenyl-1,2,4-triazole (**2b**) with methyl iodide and diazomethane occurred at the N-1 and N-2 atoms preferentially to the N-4 atom with a predominance of N-1 methylation. Exclusive S-methylation was observed in the reaction of **3b—5b** with methyl iodide in alkaline solution. These results agree well with those obtained on methylation of 3-methyl-1,2,4-triazoline-5-thiones.[6] The selective S-methylation of these compounds must be due to the great nucleophilicity of the S-atom, since methylation proceeds by S_N2 reaction under these conditions.

Methylation of compounds **3b—5b** with diazomethane also favors S-methylation and treatment of **4b** with diazomethane in particular gave only the S-methylated product (**7b**). The slightly greater formation of **9b** from **5b** than from **3b** is because the N-1 atom in **5b** is more reactive than the N-4 atom. No remarkable solvent effect on the product ratio was observed.

Experimental

NMR spectra were recorded with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. The solvents used were $CDCl_3$ and DMSO-d_6 and all chemical shifts are given in δ(ppm) values.

General Procedure for Methylation of Monomethylated 1,2,4-Triazoles (2a,b—5a,b) with Methyl Iodide——Samples of monomethylated 1,2,4-triazoles (**2a,b—5a,b**, 0.2 mM) were weighed in small glass tubes and the 1 N aqueous NaOH (1.0 ml) was added. A mixture of CH_3I (42.6 mg, 0.3 mM) in EtOH (0.15 ml) was added to this solution. Then the glass tube was stoppered and shaken at room temperature for 3 days. The reaction mixture was extracted five times with $CHCl_3$ (2 ml), and the $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in $CDCl_3$ for NMR measurements.

General Procedure for Methylation of 3-Phenyl-1,2,4-triazolin-5-one (1a) and 3-Phenyl-1,2,4-triazoline-5-thione (1b) with Methyl Iodide——A solution of **1a** or **1b** (0.2 mM) in 1 N aqueous NaOH (1.0 ml) was mixed with an equivalent amount of CH_3I (28.2 mg, 0.2 mM) in EtOH (0.15 ml). The mixture in a small stoppered glass tube was shaken at room temperature for 3 days and then extracted five times with $CHCl_3$ (2 ml). The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in $CDCl_3$ or DMSO-d_6 for NMR measurements.

For methylation with excess CH_3I, 71.0 mg (0.5 mM) of CH_3I was used with 0.2 mM of substrate.

General Procedure for Methylation of Monomethylated 1,2,4-Triazoles (2a,b—5a,b) with Diazomethane——Monomethylated 1,2,4-triazoles (**2a,b—5a,b**, 0.2 mM) were dissolved in the solvent (10 ml) as listed in Tables III and V, and excess ethereal CH_2N_2 (0.6 mM, about 2 ml) was added dropwise. The mixture was stood at room temperature for 3 days, and then evaporated *in vacuo*. The residue, consisting of a mixture of methylated products, was dissolved in $CDCl_3$ for NMR measurements.

General Procedure for Methylation of 1a and 1b with Diazomethane——A suspension of **1a** or **1b** (0.2 mM) in the solvent (10 ml) as listed in Tables IV and V was mixed with an equivalent amount of CH_2N_2 (0.2 mM) in ether (about 2 ml) or excess CH_2N_2 (1.0 mM) as ethereal CH_2N_2 (about 2 ml). The mixture was stirred at room temperature for 3 days. The solvent was removed by evaporation *in vacuo*, and the residue was dissolved in $CDCl_3$ or DMSO-d_6 for NMR measurements.

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