N-Substitution Reactions of 1-Substituted Tetrazoline-5-thiones

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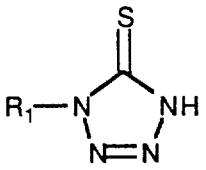
N- *vs.* *S*-Substitution reactions of 1-substituted tetrazoline-5-thiones with various allyl or benzyl halides were studied in order to find effective conditions for *N*-substitution reactions. When allyl or benzyl halides were reacted with 1-substituted tetrazoline-5-thiones in the presence of TMSI or BF_3·OEt_2 (or other Lewis acids), *N*-substitution at 4-position in addition to *S*-substitution occurred. Reactions were performed either with or without a solvent such as dioxane or propionitrile in the presence of potassium iodide.

Introduction

It is known that alkylation reactions of 1-substituted tetrazoline-5-thione (5-thio-1,4-dihydro-5*H*-tetrazoles) (**1**) (R = alkyl or aryl) usually occur on sulfur.[1] However, there have been reported examples of reactions at the ring nitrogens, usually at *N*-4, such as hydroxymethylation[2] as well as addition of α,β-unsaturated carbonyl compounds to 1-phenyl or 1-benzyltetrazoline-5-thione in the presence of triethylamine.[3] In the latter case, only *S*-alkylated product was observed in the absence of base. Acylation of 1-substituted tetrazoline-5-thiones usually occurs on sulfur.[4] In fact, literature survey reveals that *N*-alkylation of thioamide suffers from the unavailability of generally applicable method.[5] Thus, the lack of a general method to achieve *N*-alkylation as well as the potential usefulness of substituted tetrazoles in biological and medicinal applications[6] led us to investigate the substitution reactions of 1-substituted tetrazoline-5-thiones with various electrophiles.

Results and Discussion

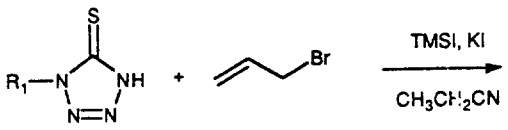
Synthesis of the required 1-substituted tetrazoline-5-thiones, **1a-d** was easily achieved by the reaction of sodium azide with the corresponding isothiocyanates.[7]



1a R_1 = CH_3
b R_1 = benzyl
c R_1 = Ph
d R_1 = allyl

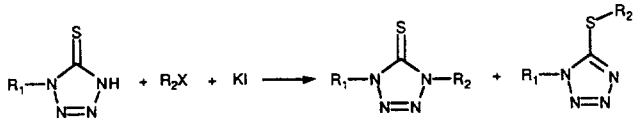
Initial trials aimed at achieving *N*-alkylation were not encouraging. For example, base treatment of **1** followed by treatment with electrophiles such as allyl, benzyl, or alkyl halides gave rise to *S*-substituted products. It occurred to us that use of acids, instead of bases might provide a better chance to yield *N*-substituted products. Indeed, we were pleased to find that with addition of acids, particularly, Lewis acids, the reactions provided *N*-substituted product (**2**) in addition to *S*-substituted one (**3**) (Table 1). Eventually we found that trimethylsilyl iodide (TMSI) was the best reagent for effecting this *N*-substitution. The importance of TMSI or BF_3OEt_2 (and other acids) in the reaction was easily recognized from the fact that virtually exclusive attack on sulfur was observed in almost all cases in the absence of these reagents. Reactions were carried out either with a solvent (e.g., propionitrile or dioxane)[8] in the presence of potassium iodide or without a solvent (no KI was added) at reflux in the presence of excess halide as shown in the following equation.

Table 1. *N*- and *S*-Substituted Product Ratios upon Addition of Reagents



Reagents	*N*-Substitution/*S*-Substitution[a]			
	1a	**1b**	**1c**	**1d**
TMSI	60/30	44/45	10/27	14/42
BF_3·OEt_2	37/24	28/39	20/30	—
$AlCl_3$	27/41	20/36	—	—
$SnCl_4$	12/60	—	—	—
$TiCl_4$	21/38	—	—	—
TMSOTf	31/59	—	—	—
Et_2AlCl	26/51	—	—	—
HI	9/69	—	—	—
HBr	7/83	—	—	—
$AgBF_4$	31/48	—	—	—

[a]Ratios of % isolated yields.



1 **2** **3**

a: R_1=CH_3, **b:** R_1=benzyl, **c:** R_1=Ph, **d:** R_1=allyl

No better ratios of *N*- *vs.* *R*-substitution in terms of isolated yield were observe as the amounts of the TMSI or BF_3OEt_2 were increased over one equivalent (with respect to 1). Therefore, 0.1 equivalents of TMSI were used unless otherwise specified. It has already been reported that α,β-unsaturated carbonyl compounds undergo *N*-alkylation in the present of a base (e.g., Et_3N).[3] In contrast to this result, our reactions with TMSI or BF_3·OEt_2 always gave *N*-substitued products with variable ratios in yields between *N*- and *S*-alkylated products.

Although *N*-alkylation of 1-substituted tetrazo-

Table 2. *N*- *vs.* *S*-substitution Reaction of 1-Substituted Tetrazoline-5-thione

Entry	Electrophiles	*N*-Substitution/*S*-Substitution (% yield)[a]		
		1a	**1b**	**1c**
1	$CH_2=CHCH_2Br$	A[b].83/13	59/27	34/58
		B[c]. 60/30	44/45	7.66
		C[d]. 78/15	95/trace	tract /81
2	(*E*)-$CH_3CH=CHCH_2Br$	A . 91/trace	89/trace	
		B . 42/28	43/46	
		C . 78/15	95/trace	
3	$CH_3CHClCH=CH_2$	A . 77/8	34/57	
		B . 46/48	26/34	
		C . 79/trace		
4	$CH_2=C(CH_3)CH_2Cl$	A . 12/71	7/56	16/81
		B . 19/80	7/56	10/46
		C . 3/83		
5	$PhCH_2Br$	A . 10/71	12/82	
		B . 29/70		
6	Ph_2CHBr	A . 70/12		
		B . 51/28		
7	$CH_2=CHCOCH_3$	A . 25/66	10/38	
		B . 5/83(30/70)[e]		
8	EtI	B . trace/59	trace/93	

[a]Ratios of % isolated yields, [b]Method A: TMSI was used with dioxane as a solvent, [c]Method B: TMSI was used with propionitrile as solvent, [d]Method C: TMSI was used without solvent (see text for details), [e]BF_3·OEt was used.

line-5-thiones has been known to occur at the *N*-4 position, attack at *N*-2 is also conceivable and in fact, isolation of *N*-2 displaced product has been reported.[9] In order to resolve this regiochemical question, we have conducted *N*-alkylation on **1b** and **1d** with benzyl and allyl bromide (in the presence of KI), repectively. Isolated *N*-substituted products **[2b(R_2=benzyl)** or **2d(R_2=allyl)]** show that both products have symmetrical structures by the analysis of ^{13}C and ^1H-NMR spectra which confirms that substitutions occur at *N*-4.

The scope of this *N*-substitution reaction was explored (Table 2) using three methods, that is, addition of TMSI *with* a solvent [(dioxane: Method A), (propionitrile: Method B)] or *without* a solvent (Method C)(Table 2). Spectral as well as combustion analysis data of the representative compounds prepared are given in Table 3. Allyl and benzyl halides were found to be good electrophiles for *N*-substitution. However, only *S*-alkylation was observed for simple alkyl halides. In general, **1a** provided more *N*-substitution products than **1b** or **1c**. Identical *N*- and *S*-substitution products were obtained from 1-bromo-2-butene (entry 2) and 3-chloro-1-butene (entry 3), namely **3a[R_2=(*E*)-$CH_2CH=CHCH_3$]** and **2a[R_2=-$CH(CH_3)CH=CH_2$]**. With benzyl bromide *S*-benzyl products were primarily formed (entry 5). However, diphenylmethyl bromide generated a higher yield of *N*-substituted product (entry 6). An α,β-unsaturated carbonyl compound (entry 7) was examined to compare with the base-promoted case.[3] *S*-Substitution was the major reaction pathway with TMSI. BF_3·OEt yielded more *N*-substitution products in this case. With simple alkyl halide such as ethyl iodide, *S*-alkylation was exclusively observed even in our conditions (entry 8).

The possibility of interconversion between *N*- and *S*-substitution products could be important for understanding the reaction methanims. *S*-allyl product was isolated, and resubjected to the reaction conditions. When BF_3·OEt_2 was used, no conversion into the corresponding *N*-allyl product was observed. With TMSI in propionitrile as a solvent *S*-allyl to *N*-allyl conversion does not take place, either. However, conversion of the *S*-allyl products to the *N*-allyl ones was observed in the absence of propionitrile. Also, with TMSI in dioxane, *S*-allyl to *N*-allyl conversion also takes place. The origin of this solvent effect remains unclear. Conversion from *S*-alkylated products to *N*-substituted ones was only successful with the allyl halides (no conversion with benzyl or alkyl halides). *N*- *vs.* *S*-Substitution ratios from the reaction of 1-methyl-5-allylthiotetrazole**[3a(R_2=allyl)]** with allyl bromide in the presence of TMSI, KI, and dioxane wer 27:66[{**2a(R_2=allyl)**}:[**3a(R_2=allyl)**}] (at reflux after one day, in isolated yields) and 72:13 (at reflux after seven days with an additionl 5 equiv. of allyl bromide). Conversion from *N*- to *S*-substituted products was not observed employing the same conditions as described for the *S*- to *N*- conversion.

A change in the mechanism from S_N2-like to S_N1-like by the addition of BF_3·OEt_2 or TMSI could be used to explain the behavior of the substitution reaction reported here.[10] In other words, addition of acids to the reaction leads to more cationic character (*i.e., via* S_N1-like mechanism). Nitrogen is more electronegative than sulfur, which means it is a "harder" base. Therefore, nitrogen is favored to react with a "harder" cationic intermediate. This rationalization is very attractive when employed to explain the formation of the major products in Table 2 (particularly, entries 2, 3, and 8).[11]

Table 3. Representative 1,4- and 1,5-Disubstituted Tetrazolines Prepared

Product[Lit]	mp (°C)	Molecular Formula	anal. data	% C	% H	% N	IR (cm^{-1})	^1H NMR and ^{13}C NMR ($CDCl_3$, TMS) ( )	MS (*m/z*) (rel intensity)
1-methyl-4-allyltetrazoline-5-thione[12] **[2a(R_2=allyl)]**	oil	$C_5H_8N_4S$	HRMS calcd			156.0470	2920,2860, 1450,1410, 1360	^1H NMR: 6.40–5.10(m, 3H, allyl), 4.90(br d, 2H, NCH_2, J=6 Hz), 3.90(s, 3H, CH_3) ^{13}C NMR: 34.12, 49.38, 119.54, 128.70, 163.31(C=S)	156(M^+), 95(100)
			found			156.0468			
1-Methyl-5- allylthiotetrazole[12] **[3a(R_2=allyl)]**	oil	$C_5H_8N_4S$					1637,1426, 1278	^1H NMR: 6.30–5.77 and 5.50–5.00 (m, 1H+2H, allyl), 3.95 (s, 5H, SCH_2+CH_3)	156(M^+) 95(100)
1,4-Dibenzyltetrazoline-5-thione[3] **[2b(R_2=benzyl])**	103–105	$C_{15}H_{14}N_4S$	63.81	5.00	19.84		1452,1431, 1355,1298, 1230,1203	^1H NMR:7.64–7.10(m, 10H, H_{arom}), 5.38(s, 4H, CH_2Ph) ^{13}C NMR: 52.1, 126.4, 124.9, 129.5, 134.2, 165.0(C=S)	282(M^+), 91(100)
			63.90	4.98	19.70				
1-Benzyl-5-benzylthiotetrazole **[3b(R_2=benzyl)]**	oil	$C_{15}H_{14}N_4S$	63.81	5.00	19.84		1495,1452, 1428,1389	^1H NMR: 7.50–7.10(m, 10H, H_{arom}), 5.63(s, 2H, NCH_2Ph), 4.33(s, 2H, SCH_2Ph)	282(M^+), 91(100)
			63.70	4.96	19.84				
1,4-Diallyltetrazoline-5-thione	67–70	$C_7H_{10}N_4S$	46.13	5.53	30.75		1646,1497, 1400,1306, 1253	^1H NMR: 6.28–5.00 (m, 6H, allyl), 4.90(d, 4H, NCH_2 J=6 Hz) ^{13}C NMR: 50.8, 121.3, 129.8, 164.1(C=S)	182(M^+). 77(100)
			46.20	5.47	30.51				
1-Allyl-5-allylthiotetrazole **[3d(R_2=ally)]**	oil	$C_7H_{10}N_4S$	46.13	5.53	30.75		1641,1450, 1426,1196	^1H NMR: 6.40–4.77 (m, 8H), 4.07(d, 2H, J=7 Hz)	182(M^+). 121(100)
			45.90	5.49	30.30				
1-Phenyl-4-allyltetrazoline-5-thione **[2c(R_2=allyl)]**	oil	$C_{10}H_{10}N_4S$	55.04	4.58	25.68		1644,1593, 1418.1367,	^1H NMR: 8.17–7.43(m, 5H, phenyl), 6.50–5.17(m, 3H, allyl), 4.97(d, 2H, NCH_2, J=6 Hz)	218(M^+), 157(100)
			54.97	4.58	25.51				
1-Phenyl-5-allylthiotetrazole **[3c(R_2=allyl)]**	oil	$C_{10}H_{10}N_4S$					1637,1595, 1499,1399	^1H NMR: 7.63(s, 5H), 6.50–5.10(m, 3H), 4.05(d, 2H, SCH_2, J=6 Hz) ^{13}C NMR: 19.2, 35.0, 57.1, 118.6, 135.6, 164.2 (C=S)	218(M^+) 77(100)
1-Phenyl-5-(2-buten-3-yl)tetrazoline 5-thione **[(2c(R_2=-CH(CH3)CH=CH)]**	oil	$C_{11}H_{12}N_4S$	56.80	5.20	24.09		1644,1595, 1497,1359	^1H NMR: 8.21–7.30 (m, 5H, H_{arom}), 6.50–5.12(m, 4H, allyl+NCH), 2.70(d, 3H, CH_3, J=6Hz)	232(M^+) 77(100)
			57.00	5.21	23.7				

With TMSI it is also conceivable that exchange of H^+ with TMS^+ leaves the nucleophile (in this case, the nitrogen of tetrazoline-5-thiones) freer and therefore more likely to undergo attack.

In summary, we have described an efficient way to effect *N*-substitution of 1-substituted tetrazoline-5-thiones which could potentially be useful for the preparation of tetrazole-related heterocyclic compounds.

Experimental

Proton nuclear magnetic resonance (^1H-NMR) spectra were obtained with one of the following: a Jeol PMX60SI, a Varian FT-80A, or a Bruker AM 200 spectrometer. Carbon-13 nuclear magnetic resonance spectra (^{13}C-NMR) are determined with a Varian FT-80A or a Bruker AM 200 spectrometer. Infrared (IR) spectra are obtained with a Perkin-Elmer 1310 spectrometer. Mass spectra are recorded on a HP 5840 A mass spectrometer and Varian-MAT 731 spectrometer. Elemental Analysis were performed at Korea Institute of Science and Technology (KIST) Analytical Laboratory.

Typical Procedure: 1-Methyl-4-allyltetrazoline-5-thione (2a, R_2=allyl).

Method A. To a solution of allyl bromide (1.5g, 12.9 mmol) in dioxane (15 m*l*) is added potassium iodide (2.07g, 12.9 mmol), 1-methyltetrazoline-5-thione (**1d**) (300 mg, 2.58 mmol), and trimethylsilyl iodide (51.6 mg, 0.25 mmol). The reaction mixture is heated at reflux for 13 h after which it is cooled to room temperature and concentrated. The residue is diluted with ethyl acetate (50 m*l*), washed with saturated sodium chloride solution (20 m*l*), dried ($MgSO_4$), and evaporated. Purification of the residue on silica gel with 20% ethyl acetate in hexane as eluent furnished 1-methyl-4-allylte-

trazoline-5-thione (**2a, R_2=allyl**)[12] (334 mg, 83%, based on 1-methyltetrazoline-5-thione) and of 1-methyl-5-allylthiotetrazole (**3a, R_2=allyl**)[12] (54 mg, 13%) as oils.

Method B. To a solution of allyl bromide (1.56g, 12.9 mmol) in dry propionitrile (15 ml) is added potassium iodide (2.07g, 12.9 mmol), 1-methyltetrazoline-5-thione (**1c**) (300 mg, 2.58 mmol), and trimethylsilyl iodide (51.6 mg, 0.25 mmol). The reaction mixture is heated at reflux for 13 h after which it is cooled to room temperature and concentrated. The same workup procedure followed by purification as described in the preceding procedure furnished 1-methyl-4-allyltetrazoline-5-thione (242 mg, 60%) and of 1-methyl-5-allylthiotetrazole (121 mg, 30%) as oils.

Method C. To a mixture of 1-methyltetrazoline-5-thione (300 mg, 2.58 mmol) in allyl bromide (1.56g, 12.91 mmol) is added trimethylsilyl iodide (51.6 mg, 0.25 mmol). The mixture was heated at 85-90 °C for 4 h after which it is cooled to room temperature. The same workup procedure followed by purification as described in the procedure A afforded 1-methyl-4-allyltetrazoline-5-thione (314 mg, 78%) and 1-methyl-5-allylthiotetrazole (62 mg, 15%) as oils.

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10. On the other hand, the mechanistic pathway *via* [3,3] rearrangement of *S*-allyl product to *N*-allyl product is conceivable. Concerted [3,3] rearrangement as a major reaction pathway, however, seems to be unlikely, since the reactio of **3a**[R_2=(*E*)-CH_2CH=$CHCH_3$] with 1-bromo-2-butene (5 equiv) furnished **2a**[R_2=$CH(CH_3)CH$=CH_2] and **2a**[R_2=(*E*)-CH_2CH=$CHCH_3$] (69% in total, not separated, ca. 1:1 ratio) and **3a**[R_2=(*E*)-CH_2CH=$CHCH_3$] (6%) in dioxane after nine days at reflux (in the presence of KI and TMSI).
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The Measurement of Transfer Enthalpy in Mixed Solvent (Part I). Enthalpies of Solution of Aniline, Pyridine and Benzylamine in the Isodielectric Binary Mixtures of Methanol with Acetonitrile, Nitrobenzene and Nitromethane

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Enthalpies of solution of aniline, pyridine and benzylamine in iso-dielectric mixtures of methanol with acetonitrile (AN), nitrobenzene (NB) and nitromethane (NM) have been measured calorimetrically. The solute-solvent interaction was analyzed using a model developed by Waghorne *et al.* and found that the relatively weak base, aniline, tended to behave anomalously, especially in the NB and NM binary systems by forming bidentate hydrogen bonds between the two $-NH_2$ hydrogens and the two $-NO_2$ oxygens. Pyridine and benzylamine were found to be preferentially solvated by methanol in all the binary mixtures.

Introduction

Thermodynamics of solvation of organic non-electrolytes has attracted considerable interest in the elucidation of organic reaction mechanism. Information on the variation of the transition state(TS) structure with solvent changes can be obtained from the enthalpies of solution of reactants in a series of solvent together with the enthalpies of activation.[1-4]

Recently[5] we have been interested in the solvent effects on the mechanisme of S_N2 type reactions, especially involving with isodielectric binary solvent systems of methanol-acetonitrile(MeOH-AN), methanol-nitrobenzene (MeOH-NB) and methanol-nitromethane (MeOH-NM) binary systems. In a previous work,[6] we reported on the relative partial