Equilibria of the 5-Substituted-1,2-acylated Tetrazoles and Imidoyl Azides†

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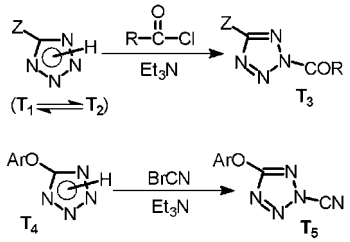
Equilibrium of acylated-5-alkyloxy (aryloxy) tetrazoles and acylated-imidoyl azides was measured by ^{1}H NMR and/or IR spectroscopy. In nonpolar solvents the relatively weakly electron-withdrawing acyl group (CO_2CH_3) favored acylation at the 2-position of the 5-substituted tetrazoles. Moderately electron-withdrawing groups ($CO_2CH_2CCl_3$, CO_2CCl_3) move the equilibrium to the side of 1-acyl-5-substituted tetrazole. Strong electron-withdrawing groups (CN, SO_2CH_3, SO_2CF_3) favored the formation of the azide. The rate of isomerization of tetrazoles and the azide increases at higher concentrations and polarity of the solvent. In solid phase or in the nonpolar solvent (diethyl ether), only one of the three isomers is present, its structure depending on the nature of the substituents at the 1 or 2 positions of tetrazoles.

Introduction

Increasing attention has been paid over the past two decades to the chemistry of tetrazoles and tetrazole derivatives. The major area of interest has been the application of tetrazoles in pharmacological compounds with antihypertensive, antiallergenic, antibiotic, and other pharmaceutical activities. Another research area of interest is the isomerization of tetrazoles.[1−16]

Scheme 1



Tetrazoles, substituted at the 5-position, are known to exist as equilibrium mixtures of their 1*H*- and 2*H*-tautomers.[1] In a review, Buttler[2] discussed the rapid equilibrium of 1*H*- and 2*H*-5-substituted tetrazoles. In the present work, ^{15}N NMR spectra of 5-methoxytetrazole indicate only two signals (rapid equilibrium) at −19.0 ppm and at −126.0 ppm (relative to liquid ammonia) corresponding to N=N and N−H, respectively.

It has been reported that the acylation of 5-substituted tetrazole always gives the 2-acyl derivative **T$_3$**.[17,18] Accordingly, the reaction of cyanogen bromide with aryloxytetrazoles **T$_4$** was reported to produce 5-aryloxy-2-cyanotetrazole **T$_5$**, Scheme 1.[19]

Subba Rao and Lwowski reported that reactions of 5-methoxy- or 5-ethoxytetrazoles with cyanogen bromide or methane sulfonyl chloride gave imidoyl azides, aparently by ring opening of 1-acylated-5-substituted terazoles, followed by spontaneous ring opening to the corresponding imidoyl azides, Scheme 2.[20,21] Obviously, the "2-acylation rule" (acylation taking place exclusively at 2-position) does not hold in this case. The nearly quan-

† Based in part on the thesis of H. A. Dabbagh, New Mexico State University, 1985.

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(1) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 4, p 621.

(2) Butler, R. N. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boutton, A. J., Eds.; Academic Press: New York, 1977; Vol. 21.

(3) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; J. Wiley and Sons: New York, 1984; p 559.

(4) Singh, H.; Chawla, A. S.; Kapoor, U. K.; Paul, D.; Malhotra, R. K. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier: North-Holland, 1980; Vol. 17, p 151.

(5) Cubero, E.; Orozco, M.; Luque, F. *J. Org. Chem.* **1998**, *63*, 2354.

(6) Cubero, G.; Orozco, M.; Luque, F. *J. Am. Chem. Soc.* **1998**, *120*, 4723.

(7) Dabbagh, H. A.; Ghaelee, S. *J. Org. Chem.* **1996**, *61*, 3439.

(8) Kamiya, N. J.; Shiro, Y.; Iwatee, T.; Iizuka, T.; Iwasaki, H. *J. Am. Chem. Soc.* **1991**, *113*, 1826.

(9) Katritzky, A. R.; Jozwiak, A. R.; Jozwiak, A. R.; Jozwiak, A.; Lue, P.; Yannakopoulou, K.; Palenik, G. J.; Zhang, Z. Y. *Tetrahedron* **1990**, *46*, 633.

(10) Katritzky, A. R.; Yannakopoulou, K.; Anders, E.; Stevens, J.; Szafran, M. *J. Org. Chem.* **1990**, *55*, 5683.

(11) (a) Hall, J. H.; Parcell, W. L. *Inorg. Chem.* **1990**, *29*, 3806. (b) Temple, C., Jr.; Montgomory, J. A. *J. Org. Chem.* **1965**, *30*, 826. (c). Temple, C., Jr.; Mckee, R. L.; Montgomory, J. A. *J. Org. Chem.* **1965**, *30*, 829. (d) Bruke, L. A.; Elguero, J.; Leroy, G.; Sana, M. *J. Am. Chem. Soc.* **1976**, *98*, 1685. (e) Denisov, A. Y.; Krivopalov, V. P.; Mamatyuk, V. I.; Mamaev, V. P. *Magn. Reson. Chem.* **1988**, *26*, 42. (f) Markgraf, J. H.; Bachmann, W. T.; Hollis, D. P. *J. Org. Chem.* **1965**, *30*, 3472. (g) Tisler, M. *Synthesis* **1973**, 123. (h) Sasaki, T.; Kanematsu, M.; Murata, M. *Tetrahedron* **1971**, *27*, 5121. (i) Temple, C.; Montgemory, J. A. *J. Org. Chem.* **1965**, *30*, 826. (j) Temple, C.; Montgemory, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2946. (k) Temple, C.; McKee, J. A.; Montgemory, J. A. *J. Org. Chem.* **1965**, *30*, 829.

(12) Dabbagh, H. A.; Lwowski, W. *J. Org. Chem.* **1989**, *54*, 3952.

(13) Zabrocki, J.; Smith, G. D.; Dunbar, J. B.; Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875.

(14) Yu, K. L.; Johnson, R. L. *J. Org. Chem.* **1987**, *52*, 2051.

(15) Elguero, J.; Claramunt, R. M.; Summers, A. J. *Adv. Heterocycl. Chem.* **1978**, *22*, 183.

(16) Konnecke, A.; Lippmann, E.; Klein, P. *Tetrahedron Lett.* **1976**, 533.

(17) Herbst, R. M. *J. Org. Chem.* **1961**, *26*, 2372.

(18) Ginberg, F. *J. Org. Chem.* **1967**, *32*, 3686.

(19) Martin, D.; Weise, A. *Chem. Ber.* **1966**, *99*, 317.

(20) Subba Rao.; Lwowski, W. *J. Heterocycl. Chem.* **1980**, *17*, 187.

(21) Subba Rao.; Lwowski, W. *Tertrahedron Lett.* **1980**, *21*, 727.

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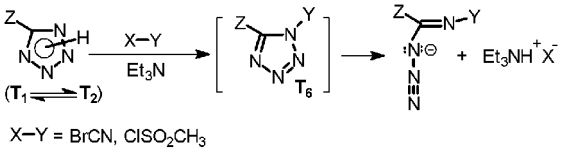
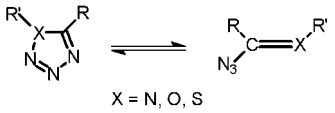
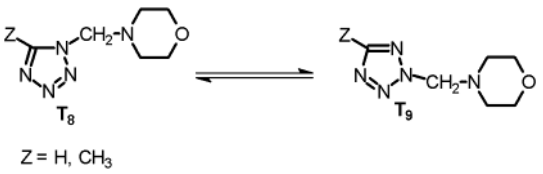
Scheme 2



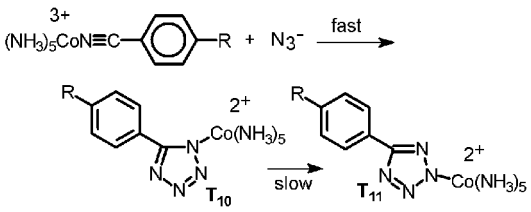
Scheme 3



Scheme 4



Scheme 5



titative yields of imidoyl azide $\mathbf{A_7}$ show that either the 1-acyl compound $\mathbf{T_6}$ was the major primary product or any 2-acyltetrazole formed was converted to the 1-isomer and then removed from the system by ring opening.

Theoretical study of azido−tetrazole isomerzation, the effect of solvent and substitution, and the mechanism of isomerzation have been investigated by self-consistent reaction field (SCRF) and Monte Carlo-Free Energy Perturbation (MC-FEP) techniques in three different solvents (carbon tetrachloride, chloroform, and water).[5,6] The results show that the azido form of thiazole[3,2-*d*]-tetrazole is clearly disfavored as the solvent polarity increases. The effect of substitution is also consistent with the experimental available data, with electron-withdrawing groups shown to favor the azido isomer while the opposite effect is observed for electron-donating substituents, Scheme 3.

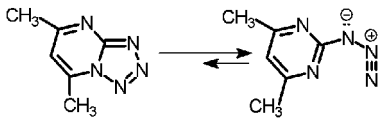
Katritzky et al.[9,10] recently reported that tetrazoles $\mathbf{T_8} \rightleftharpoons \mathbf{T_9}$ undergo fast N-1 to N-2 substituent isomerization, Scheme 4.

Purcell and Hall investigated the novel linkage isomerization of 5-substituted tetrazole complexes and explored the effect of the electronic and steric factors on the mechanism of the interconversion of the isomerizing ligand. They concluded that the relief of steric hindrance as a major driving force for the isomerzation is consistent with the experimental observations, Scheme 5.[11a]

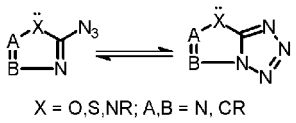
The azidoazomethine−tetrazole equilibrium for pyrimidine derivatives has been examined by means of infrared and proton magnetic resonance spectroscopy.[11b,c] The authors concluded that an electron-releasing group on the pyrimidine ring would destabilized the tetrazole, Scheme 6.

The potential energy hypersurface for the isomerization of aziodoazomethine−tetrazole isomerization has

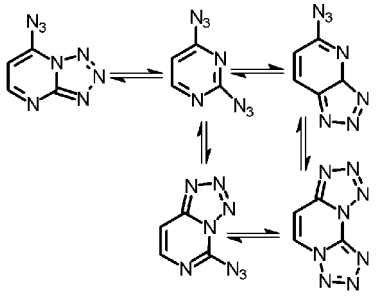
Scheme 6



Scheme 7



Scheme 8



been studied by ab initio calculations using the STO-3G basis set.[11d] The authors predicted that the transition state resembled strongly the azide rather than the tetrazole and that cyclization should be accelerated in polar solvents. Their theoretical results are in reasonable agreement with available experimental ones, Scheme 7.

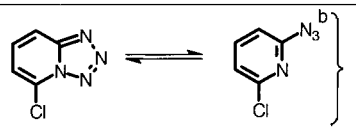
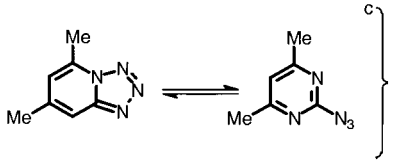
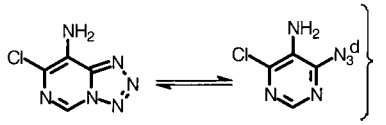
Denisov and co-workers used $^{13}C-^{1}H$ coupling constants for the investigation of azide−tetrazole tautomerism of 2,4- and 4,6-diazidopyrimidines in chloroform-*d* and DMSO-d_6.[11e] They demonstrated that the position of equilibrium depends on the polarity of the solvent, Scheme 8. Markgraf and Bachmann used proton NMR to study the tautomeric equilibrium of a 5-substituted tetrazole.[11f]

Some aspects of azido−tetrazolo isomerization were reviewed by Tišler.[11g] The effects of substitution, solvent, and temperature on tetazole−azide isomerization on several substituted pyridines and diazines are presented in Table 1.[11h−k]

To this date, there is no evidence indicating that 1*H*-tetrazole gives 1-alkyl or 1-acyltetrazole upon alkylation or acylation or that 2*H*-tetrazole gives only 2-alkyl or 2-acyltetrazole, rather either tetrazole might give, at some rate, either alkyl (acyl) tetrazole. In principle, the alkyl (acyl) tetrazoles could interconvert $k_7 \rightleftharpoons k_8$, Scheme 9.

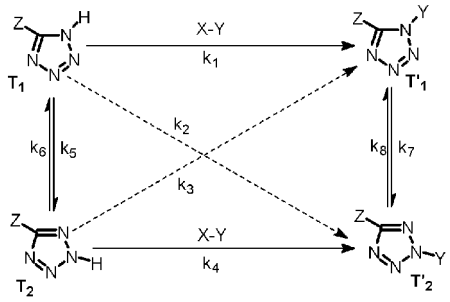
The question raised here was whether 5-substituted tetrazole acylated at one position is in equilibrium with the substituted tetrazole acylated at two positions? Is 1-acylated-5-substituted tetrazole in equilibrium with its opening form, the imidoyl azide? What is the effect of solvent polarity, concentration, and electronic effect of substituent on the rate of achieving equilibrium? A major problem could arise if these tautomers which have different physical and chemical properties equilibrate during the course of the reaction. Three species rather than one might participate in the reaction! To gain more insight into the isomerization of the tetrazoles (and to find the factors that control the rate of their interconversions), several tetrazoles (depicted in Scheme 10) are synthesized and their isomerization is investigated in

Table 1. Effect of Solvent Polarity and Temperature on the Equilibrium of Azidotetrazoles

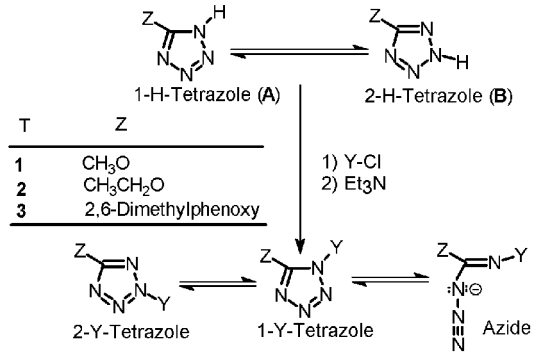
Compound in Equilibrium	T(°C)	K_T[a]	Solvent
 [b]	25	2.51	DMSO-d_6
	80	6.37	DMSO-d_6
 [c]	37-38	0.14	Pyridine-d_5
	37-38	0.36	$CDCl_3$
	37-38	0.08	Acetone-d_6
	37-38	0.12	CD_3OD
 [d]	38	~0	DMSO-d_6
	38	∞	TFA[e]

[a] Ratio azido/tetrazole. [b] See ref h. [c] See ref i and j. [d] See ref k [e] TFA = Trifluoroacetic acid.

Scheme 9



Scheme 10



Z = CH_3O			
Y = CO_2CH_3	**4**	**5**	**6**
Y = $CO_2CH_2CCl_3$	**7**	**8**	**9**
Y = SO_2CF_3	**10**	**11**	**12**
Z = CH_3CH_2O			
Y = CO_2CH_3	**13**	**14**	**15**
Z = 2,6-Dimethylphenoxy			
Y = CO_2CH_3	**16**	**17**	**18**
Y = $CO_2CH_2CCl_3$	**19**	**20**	**21**
Y = CO_2CCl_3	**22**	**23**	**24**

detail (in three solvents: tetrahydrofuran, chloroform, and diethyl ether) at room temperature.

Results

Reactions of 5-Methoxytetrazoles ($1T_A \rightleftharpoons 1T_B$) with (a) Methyl Chloroformate. Tetrazoles ($1T_A \rightleftharpoons 1T_B$), methyl chloroformate, anhydrous peroxide free tetrahydrofurn (THF), and triethylamine in an ice bath produced a liquid mixture of 1- and 2-methoxycarbonyl-5-methoxytetrazoles **4** ⇌ **5**. The proton NMR analysis of the reaction mixture, 5 min after the addition of the base was completed, showed approximately 80% of tetazole **5** in the mixture. The ratio of **5/4**, several hours after the addition of the base was completed, was equal to 0.70, corresponding to 59% **4** in the solution. This clear liquid mixture of **4** ⇌ **5** in diethyl ether at 0 °C or by cooling alone at −25 °C gave pure white crystals of **4** in 83% total yield. When pure **4** was dissolved in chloroform, the same ratio (**5/4** ≅ 0.70) of the equilibrium mixture of **4** ⇌ **5** was produced at room temperature, Figure 1a, Tables 2−5, Scheme 10.

(b) 2,2,2-Trichloroethyl Chloroformate (TCC). Tetrazoles **1**, **TCC**, chloroformate, anhydrous peroxide free THF, and triethylamine produced in an ice bath a liquid mixture of 1- and 2-(2,2,2-trichloroethoxycarbonyl)-5-(methoxy)tetrazoles and methoxy-*N*-2,2,2-trichloroethoxycarbonylcarbimidoyl azide (**7** ⇌ **8** ⇌ **9**). The ^{1}H NMR analysis of the reaction mixture, 5 min after the addition of the base was completed, showed approximately 17% of azide **9** in the mixture. This liquid mixture of **7** ⇌ **8** ⇌ **9** did not yield a single compound in either diethyl ether at 0 °C or by cooling alone at −25 °C. The IR (KBr) spectrum of the mixture showed strong carbonyl and azide bands, Scheme 10, Tables 2−5.

(c) Trifluoromethanesulfonyl Chloride (TFMSC). Tetrazoles **1**, **TFMSC**, anhydrous peroxide free tetrahydrofurn, and triethylamine in an ice bath produced a viscous liquid. This liquid when passed over a silica gel column and crystallized in ethyl ether gave 50% of pure white crystals of methoxy-*N*-trifluoromethanesulfonylcarbimidoyl azide (**12**). ^{1}H NMR analysis of the reaction mixture did not indicate any possible equilibration of **10** ⇌ **11** ⇌ **12**; however, the TLC and ^{13}C NMR of **12** in chloroform showed only compound **12**. The IR (KBr) spectrum of **12** showed an azide band, Scheme 10, Tables 2−5.

Reactions of 5-Ethoxytetrazoles ($2T_A \rightleftharpoons 2T_B$) with Methyl Chloroformate. Reactions of tetrazoles **2** with methyl chloroformate in anhydrous peroxide free THF in an ice bath produced a liquid mixture of 1- and 2-methoxycarbonyl-5-ethoxytetrazoles (**13** ⇌ **14**). ^{1}H NMR

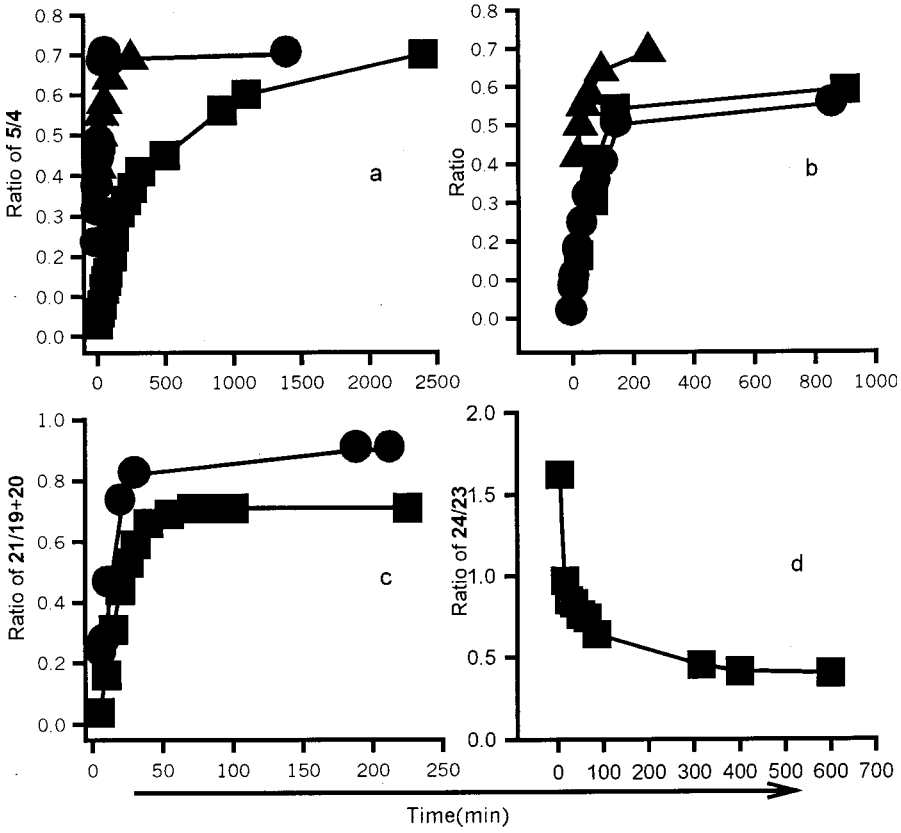


Figure 1. (a) Time dependence of equilibria of 2-methoxycarbonyl-5-methoxy tetrazole (**4**) in a dilute (▲), 0.28 M (●), and 1.27 M (■) chloroform solutions of **24** at room temperature. (b) Comparison of time dependence of equilibria of tetrazoles **5**/**4** (▲), tetrazoles **14/13** (■), and tetrazoles **17/16** (●) in chloroform solutions of **24** at room temperature. (c) Time dependence of equilibria of azide **21** as measured by ^{1}H NMR (●) or by IR (■) in chloroformsolutions of **24** at room temperature. (d) Time dependence of the equilibria of 1-tetrazole **23** and azide **24** in chloroform at room temperature.

Table 2. Effect of Substitution or Solvent on the Equilibrium of Acylated 5-Substituted Tetrazoles at Room Temperature[a]

substituents		relative %[b]		
Z	Y (acyl)	2-tetrazole	1-tetrazole	azide
CH_3O	CO_2CH_3	62 (**4**)	38 (**5**)	0 (**6**)
CH_3O[c]	CO_2CH_3	100 (**4**)	0 (**5**)	0 (**6**)
CH_3O	$CO_2CH_2CCl_3$	46 (**7**)	37 (**8**)	17 (**9**)
CH_3O[c]	SO_2CF_3	0 (**10**)	0 (**11**)	100 (**12**)
CH_3CH_2O	CO_2CH_3	62.5 (**13**)	37.5 (**14**)	(**15**)
CH_3CH_2O[c]	CO_2CH_3	100 (**13**)	0 (**14**)	0 (**15**)
ArO[d]	CO_2CH_3	63 (**16**)	37 (**17**)	0 (**18**)
ArO[d]	$CO_2CH_2CCl_3$	2 (**19**)	30 (**20**)	47 (**21**)
ArO[c,d]	$CO_2CH_2CCl_3$	0 (**19**)	100 (**20**)	0 (**21**)
ArO[d]	CO_2CCl_3	1.5 (**22**)	70 (**23**)	28.5 (**24**)
ArO[c,d]	CO_2CCl_3	0 (**22**)	0 (**23**)	100 (**24**)

[a] The solvent is $CDCl_3$ unless otherwise stated. [b] Calculated by ^{1}H NMR, compound number is given in parnetheses. [c] The solvent is diethyl ether. [d] Ar = 2,6-dimethylphenyl.

analysis of the reaction mixture, 5 min after the addition of the base was completed, showed approximately 65% of 1-substituted tetrazole **14** in the mixture. The ratio of **14**/**13** (measured several hours after the addition of the base was completed by ^{1}H NMR) was equal to 0.60, corresponding to 37.5% **14** in the solution. This clear liquid mixture of **13** ⇌ **14** gave pure white crystals of **13** in high yield either in diethyl ether solvent at 0 °C or by cooling alone at −25 °C . Pure **13**, when dissolved in chloroform, produced the same equilibrium mixture of (**14**/**13** ≅ 0.60**)** at room temperature, Scheme 10, Tables 2−5, Figure 1b.

Reactions of 5-(2,6-Dimethylphenoxy)tetrazoles ($3T_A$ ⇌ $3T_B$) with (a) Methyl Chloroformate. Reactions of tetrazoles **3** with methyl chloroformate, anhydrous peroxide free THF, and triethylamine in an ice bath produced a liquid mixture of 1- and 2-methoxycarbonyl-5-(2,6-dimethylphenoxy)tetrazoles (**16** ⇌ **17**). ^{1}H NMR analysis of the reaction mixture 5 min after the addition of the base was completed showed approximately 37% of tetrazole **16** in the mixture. The ratio of **17**/**16** (measured several hours after the addition of the base was completed by ^{1}H NMR) was equal to 0.60, corresponding to 63% **16** and 37% **17** in the solution. This clear liquid mixture of **16** ⇌ **17** in diethyl ether at 0 °C or by cooling alone at −25 °C gave pure white crystals of **16** in 94% total yield. Pure **16**, when dissolved in chloroform, produced the same equilibrium mixture of (**17**/**16** ≅ 0.60**)** at room temperature, Scheme 10, Tables 2−5, Figure 1b.

(b) 2,2,2-Trichloroethyl Chloroformate (TCC). Tetrazoles **3**, **TCC**, anhydrous peroxide free THF, and triethylamine in an ice bath produced a liquid mixture of 1- and 2-(2,2,2-trichloroethoxycarbonyl)-5-(2,6-dimethylphenoxy)tetrazoles and 2,6-dimethylphenoxy-*N*-2,2,2-trichloroethoxycarbonylimidoyl azide (**19** ⇌ **20** ⇌ **21**). ^{1}H NMR analysis of the reaction mixture 5 min after the addition of the base was completed showed approximately 47% of azide **21** in the mixture. This clear liquid mixture of **19** ⇌ **20** ⇌ **21** in ethyl ether at 0 °C or by cooling alone at −25 °C gave pure white crystals of **20** in 78% total yield. Pure **20**, when dissolved in chloroform, produced the same equilibrium mixture of (**19** ⇌ **20** ⇌ **21**) at room

Table 3. Preparation and Characterization of 1- and 2-Z-Tetrazoles and Imidoyl Azides[a]

			calcd			found				
compd no.	yield,%	mp, °C	C	H	N	C	H	N	M.F.	solvent[b]
4	83	56−57	30.39	3.82	35.43	30.66	3.60	35.56	$C_4H_6N_4O_3$	*c*
12	50	51−52	15.52	1.30	24.13	15.81	1.23	24.16	$C_3H_3N_4O_3F_3S$	*c*
13	74	49−50	34.89	4.68	32.55	NA	NA	NA	$C_5H_8N_4O_3$	*d*
16	94	98−99	53.23	4.68	22.57	53.36	5.07	22.84	$C_{11}H_{12}N_4O_3$	*d*
20	78	99−100	39.42	3.03	15.32	39.83	3.27	15.63	$C_{12}H_{11}N_4O_3Cl_3$	*d*
24	56	105−107[e]	37.58	2.58	15.94	NA	NA	NA	$C_{11}H_9N_4O_3Cl_3$	*d*

[a] Compound **13** and **24** were unstable; they decomposed during purification. [b]Crystallization solvent. [c] Ethyl ether−*n*-hexane. [d] Ethyl ether−chloroform. [e] Decomposition temperature.

Table 4. ^{1}H NMR, IR, and Mass Spectrometry of 1- and 2-Alkoxycarbonyl-Z-tetrazoles and Imidoyl Azides

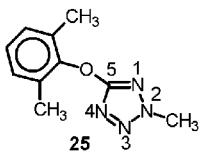
	^{1}H NMR (δ ppm)[a]			IR		
compd no.	Z	ring	Y	KBr	$CHCl_3$	mass (*m*/*z*)
4	4.31 (s)		4.14 (s)	1800		158
5	4.23 (s)		4.18 (s)	1800	1800	158
7	4.22 (s)		5.10 (s)	1790		
8	4.0 (s)		4.79 (s)	1810		
9	4.30 (s)		5.20 (s)	1750, 2155		
12	4.08 (s)			2160, 2200		
13	1.25 (t),4.70 (q)		4.10 (s)	1800		
14	1.20 (t),4.50 (q)		4.20 (s)	1800		
16	2.19 (s)	7.04−7.08	4.15 (s)	1810		
17	2.19 (s)	7.04−7.08	4.19 (s)	1810		
19	2.18 (s)	7.07−7.10	4.17 (s)		1750	364, 366, 368
20	2.20 (s)	7.07−7.10	4.15 (s)	1800	1750	364, 366, 368
21	2.20 (s)	7.13	4.75 (s)		1805,2150	364, 366, 368
23	2.18 (s)	7.08		1765		$M^{-133} = 218$
24	2.23 (s)	7.08		2160		$M^{-133} = 218$

[a] The solvent was $CDCl_3$ unless otherwise stated.

Table 5. ^{13}C NMR and ^{15}N NMR of 1- and 2-Alkoxycarbonyl-Z-tetrazoles and Imidoyl Azides[a]

	^{13}C NMR (δ ppm)[a,b]			^{15}C NMR (δ ppm)[c]			
compd no.	Z	ring	Y	N1	N2	N3	N4
1				−126	−19	−19	−126
4	62.0	163.	57.0 (CH_3), 163.60 (CO)	−102	−122	+9.0	−63
5	60.0	173.50	57.70 (CH_3), 173.50 (CO)	−160	+10	−19	−94
12	59.6 (CH_3)	160.09	118.8 (CF_3) (q, J = 319 Hz)				
13	14.3 (CH_3), 71.2 (CH_2O)	161.4	55.9 (CH_3O), 146.1 (CO)				
14	14.3(CH_3), 68.5 (CH_2O)	171.5	56.6 (CH_3O), 145.9 (CO)				
16				−103	−119	+8	−61.5
17				−162	+8.6	−19	−92.6
19	16.0 (CH_3)	127, 129, 129.4, 144.3 150.9	76.4 (CCl_3), 93 (CH_2O) 156.8 (CO)				
20	16.1 (CH_3)	126.7, 129.3, 129.9 144.2, 150.6,	77.0 (CCl_3), 94.6 (CH_2O) 160.2 (CO)				
21	16.2 (CH_3)	127.4, 129.3 130.1, 148.9	77.6 (CCl_3), 92.9 (CH_2O) 150.4 (CO)				
23	15.9 (CH_3)	126.53, 129.1, 129.2 129.9,147.9	77.3 (CCl_3), 170.4 (CO)				
24	16.2 (CH_3)	127.5,129.2, 129.3 130.0, 148.9	76.9 (CCl_3), 150.7 (CO)				
25				−112	−116	+3	−83
26				−183	+3	−16	−93

[a] The solvent is $CDCl_3$ unless otherwise stated. [b] ^{1}H NMR decoupled. [c] The solvent is CH_3NO_2, $Cr(acac)_3$.



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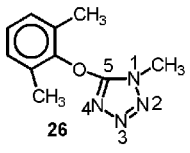

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temperature. An IR of this solution showed two carbonyl bands and one azide band. An IR (KBr) spectrum of **20** showed only a strong carbonyl band but no azide band, Figure 1c, Scheme 10, Tables 2−5.

(c) Trichloromethyl Chloroformate (TCM). Tetrazoles **3**, **TCM**, anhydrous peroxide free tetrahydrofurn, and triethylamine in an ice bath produced a liquid mixture of 1-trichloromethoxycarbonyl-5-(2,6-dimethylphenoxy)tetrazoles and 2,6-dimethylphenoxy-*N*-trichloromethoxycarbonylimidoyl azide (**23** ⇌ **24**). ^{1}H NMR analysis of the reaction mixture 5 min after the addition of the base was completed (in anhydrous peroxide free tetrahydrofuran) showed approximately 34% of azide **24** in the mixture (**24**/**23** ≅ 0.51). This clear liquid mixture

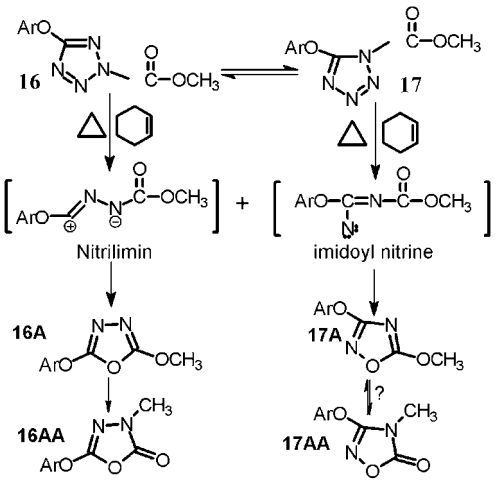
23 ⇌ **24** in ethyl ether at 0 °C or by cooling alone at −25 °C gave pure white crystals of **24** in 56% total yield. Pure **24**, when dissolved in chloroform, produced the same equilibrium mixture (**24**/**23** ≅ 0.40) at room temperature, Figure 1d. The *amount of time required* to achieve equilibrium in anhydrous peroxide free tetrahydrofuran and chloroform is ≅5 and ≅50 min, respectively. An IR (KBr) spectrum of **24** showed strong carbonyl and azide bands, Scheme 10, Tables 2−5.

Discussion

The relative percentages of each tautomer for the systems in this study are given in Table 2. It is shown that in all systems under investigation 1- and 2-acyltetrazoles and, in certain cases, the imidoyl azides may be safely assumed to be in equilibrium. The position of equilibria and the rate of equilibration depend on the electron-withdrawing nature of Y. The more electron-withdrawing Y is, the stronger the shift of the equilibrium will be toward the azide. The reverse of this electronic effect would shift the equilibrium toward the 2-acyltetrazole.

The ^{1}H NMR spectra of the reaction mixture of 1- and 2-methoxycarbonyl-5-methoxy tetrazoles just after the addition of the base was completed (in anhydrous peroxide free THF) indicated that 1-tetrazole **5** is formed and then isomerizes to the more stable 2-tetrazole **4** at room temperature at a rate depending on solvent and concentration, Figure 1a. For an approximately 10% solution of **4** in $CDCl_3$, equilibrium was established within 1 h, while it took over 48 h to achieve equilibrium in a saturated $CDCl_3$ solution. Crystallization of the equilibrium mixture of tetrazoles **4** ⇌ **5** (a clear liquid) in a proper solvent (diethyl ether) allowed us to isolate the (most stable) 2-tetrazole **4**. Equilibrium is reestablished when the pure form of crystal **4** is dissolved in more polar solvents (THF or $CDCl_3$), Table 2, Figure 1. The infrared spectra of the equilibrium mixture of **4** in $CDCl_3$ did not show any azide band; however, the intensity of the carbonyl band corresponding to 1-tetrazole **5** decreased with an increase in the intensity of the carbonyl band of 2-teratzole **4**. The ^{15}N NMR spectrum of the mixture **4** ⇌ **5** showed eight signals, each assigned by comparing its chemical shift with that of ^{15}N NMR signals of 5-methoxytetrazoles (**1T$_A$** ⇌ **1T$_B$**) and other known tetrazoles (**25**, **26**). The sp^3 nitrogens produce the most upfield signals. The N-3 signals (sp^2) always appeared downfield (near the CH_3NO_2 signals). The signals produced by N-4 are found somewhat upfield from that of N-3. The position of the N-1 and N-2 signals depends on which one is the sp^3 nitrogen (which gives the most upfield peaks), Table 5. The ^{13}C NMR spectrum of pure **4** in $CDCl_3$ (in the first several minutes) showed only four signals (similar in their chemical shifts to other 2-acylated tetrazoles, Table 5). After equilibrium was achieved (860 min), four new sets of signals appeared with a ratio of **5**/**4** ≅ 0.70. The mass spectra fragmentation pattern of the equilibrium mixture of **4** ⇌ **5** showed fragments corresponding to both tetrazoles [*m*/*e* = 158 (4%), 130 (2%), 100 (2%), 99 (3%), 87 (3%), 71 (3%), 59 (100%), 44 (13%), 43 (24%), 31 (8)]. The mass spectra fragmentation pattern of solid **4** showed fragments corresponding only to 2-tetrazoles **4** [*m*/*e* = 158 (4%), 130 (2%), 99 (3%), 87 (3%), 59 (100%), 44 (13%), 43 (24%)]. The ^{1}H NMR spectra, mass spectra fragmentation pattern, ^{15}N NMR spectrum, and ^{13}C NMR spectrum of the reaction mixture of 1-and 2-methoxycarbonyl-5-ethoxytetrazoles **13** ⇌ **14** and 1- and 2-methoxycarbonyl-5-(2,6-dimethylphenoxy)-tetrazoles (**16** ⇌ **17**) showed equilibrium patterns similar to that of tetrazoles **4** ⇌ **5**, Scheme 10, Figure 1, Tables 2−5.

Scheme 11



The thermal decomposition of the equilibrium mixture of **16** ⇌ **17** in the presence of cyclohexene produced nitrogen and a mixture consisting of 39% of 2-(2,6-dimethylphenoxy)-4-methyl-1,3,4-oxadiazole-5-one **16AA** and 61% of an approximately 50:50 mixture of 3-(2,6-dimethylphenoxy)-5-methoxy-1,2,4-oxadiazole **17A** and 3-(2,6-dimethylphenoxy)-4-methyl-1,2,4-oxadiazole-5-one **17AA** (all attempts to separate **17A** from **17AA** failed**)**, see Scheme 11. This suggests that (a) intramolecular cyclization is favored over intermolecular cycloaddition with cyclohexene and (b) equilibration is rapid at a high temperature (acetonitrile reflux) and favors the formation of 2-tetrazole **16.** The ratio of the oxadiazoles (**17A** + **17AA**/**16AA** ≅ 0.640) is similar to the ratio of the parent tetrazoles (**17**/**16** ≅ 0.60).

Equilibria of Tetrazoles with Imidoyl Azides. The next step was to investigate the isomerization of tetrazoles with the imidoyl azides. This was accomplished by increasing the electron-withdrawing availability of the acyl group.

Reaction of tetrazoles **3T$_A$** ⇌ **3T$_B$** with 2,2,2-trichloroethyl chloroformate in anhydrous peroxide free THF produced an equilibrium mixture of 1- and 2-(2,2,2-trichloroethoxycarbonyl)-5-(2,6-dimethylphenoxy)tetrazoles and 2,6-dimethylphenoxy-*N*-2,2,2-trichloroethoxycarbonylcarbimidoyl azide (**19** ⇌ **20** ⇌ **21**). In this case, 1-tetrazole is first formed and then equilibrated to a mixture of tetrazoles and azide. The equilibrium shifted to the side of the most stable isomer (in this case the 1-tetrazole **20**) when the mixture of tetrazoles and azide **19** ⇌ **20** ⇌ **21** was dissolved in diethyl ether. In other words, 1-tetrazole (the least soluble in ether solution) is favored in the crystalline form. Equilibrium is reestablished after 50 min when the pure form of **20** is dissolved in more polar solvents (chloroform or THF). The rate of disappearance of tetrazole **20** to an equilibrium mixture was followed by both infrared and ^{1}H NMR spectroscopy in $CDCl_3$. Within experimental error, both methods showed similar results, Table 2, Figure 1c, Scheme 10.

Reaction of tetrazoles **3T$_A$** ⇌ **3T$_B$** with trichloromethyl chloroformate produced an equilibrium mixture of 1- and

2-(trichloromethoxycarbonyl)-5-(2,6-dimethylphenoxy)tetrazoles and 2,6-dimethylphenoxy-*N*-trichloromethoxycarbonylcarbimidoyl azide (**22** ⇌ **23** ⇌ **24**). Again, 1-substituted tetrazole is formed first and then equilibrates to a mixture of tetrazoles and azide. Surprisingly, in this case the equilibrium favored the 1-tetrazole **23** (in contrast to compounds **19** ⇌ **20** ⇌ **21** which at equilibrium favored the azide **21** in chloroform). At this time, there is no explanation for this behavior. The equilibrium favored the side of the most stable isomer (the azide **24**) when the mixture of tetrazoles and azide (**22** ⇌ **23** ⇌ **24**) was dissolved in diethyl ether. In this case, azide is favored in the crystalline form. Equilibrium is reestablished (**24/23** ≅ 0.40) when the pure form of azide **24** is dissolved in chloroform, Table 2, Figure 1d, Scheme 10.

Reaction of tetrazoles $\mathbf{1T_A}$ ⇌ $\mathbf{1T_B}$ with trifluoromethanesulfonyl chloride produced pure white crystals of methoxy-*N*-trifluoromethanesulfonylcarbimidoyl azide (**12**). The ^{1}H NMR or IR analysis of the reaction mixture in several solvents did not indicate any isomers of **10** ⇌ **11** ⇌ **12**, Tables 2−5, Scheme 10.

Conclusion

Acylated-5-alkyloxy (aryloxy) tetrazoles and acylated-imidoyl azides do coexist as an equilibrium mixture. The rate of equilibration depends on the electronic nature of the substituents, the concentration, and the polarity of the solvent. In nonpolar solvents, the less electron-withdrawing acyl group favored acylation at the 2-position of the 5-substituted tetrazole. Moderately electrons-withdrawing groups favor an equilibrium on the side of 1-acyl-5-substituted tetrazoles. Strongly electron-withdrawing groups favor the formation of the azide. The rate of isomerization of tetrazoles and the azide increases at higher concentrations and polarities of the solvent. The rate of equilibrium is less sensitive to the substituents at the 5-position of the tetrazoles. In solid phase or the in less-polar solvent (diethyl ether), one of the three isomers is formed depending on the nature of the substituents at the 1- or 2-positions of tetrazoles.

Experimental Section

General. Elemental analysis was performed by Micanal Organic Microanalysis, Tucson, AZ. Solvents and all the chemicals used were reagent grade and were purchased from J.T. Baker Chemical Co., Mallinkcrodt Inc., Burdick and Jackson Labratories Inc., or Aldrich Chemical Co. All the chemicals were purified properly and stored in the dark under dry conditions prior to use.

The following experimental procedures were carried out at room temperature: (a) ^{1}H NMR spectra (in $CDCl_3$) of each reaction were studied 5 min after the addition of the base (in an ice bath) was completed in anhydrous peroxide free THF and after the completion of the reaction at room temperature; (b) excess solvent (anhydrous peroxide free THF) or reactants were removed under reduced pressure (excess solid reactants were washed out with a suitable solvent); (c) the proton NMR, IR spectrum, and TLC of the residues were analyzed; the liquid residues were either distilled (under reduced pressure) or passed through silica gel or aluminum oxide and eluted with an appropriate solvent; (e) the solid residues (viscous liquids) were either crystallized from a suitable solvent or passed through silica gel or an aluminum oxide column; (f) the proton NMR, IR spectrum, and TLC of each fraction was studied in detail. The proton NMR, ^{13}C NMR, ^{15}N NMR, mass analysis, IR, melting points, and elemental analyses are listed in Tables 3−5.

Equilibrium Studies. The following experimental procedures were performed in order to investigate the equilibrium (isomerization−tautomerzation) of 5-substituted acylated tetrazoles and imidoyl azides. (a) ^{1}H NMR analysis: The ^{1}H NMR spectra of the reaction mixture, just after the addition of the base was completed, indicate which tetrazole is first acylated at the one position. Time dependence of equilibria (the rate to achieve equilibrium) of the most stable isomer and the reversibility and the position of the equilibrium were measured by ^{1}H NMR; the chemical shift for each isomer is listed in Table 4.(b) Crystallization: When the equilibrium mixture of tetrazoles−imidoyl azides was dissolved in a proper solvent (diethyl ether), the least soluble or most prevalent isomer (tetrazole or azide) was crystallized in pure form. Generally the equilibrium is reestablished when pure crystals of the most stable isomer are dissolved in a proper solvent (polar solvents, $CDCl_3$, THF, DMSO, CH_3CN, etc.). (c) IR analysis: The infrared spectra of the equilibrium mixture showed two carbonyl bands in the region of 1700−1800 cm^{-1} for tetrazoles and an azide band near 2200 cm^{-1}. (d) ^{15}N NMR analysis: The ^{15}N NMR spectrum of each tetrazole showed four signals, each assigned by comparing its chemical shift with ^{15}N NMR signals of 5-methoxytetrazoles ($\mathbf{1T_A}$ and $\mathbf{1T_B}$) or with 1- or 2-methyl-5-aryloxytetrazole **26** or **25**, Table 5. (e) ^{13}C NMR analysis: The ^{13}C NMR chemical shift spectrum of each substituted tetrazole is compared with that of unsubstituted tetrazole and/or a known tetrazole, Table 5. (f) Mass spectra analysis: The mass spectra fragmentation pattern shows different fragments corresponding to each tetrazole, Table 4. (g) Thermal decomposition: The thermal decomposition of the equilibrium mixture of tetrazoles is expected to produce nitrogen and nitrene and/or nitrilimines. These reactive intermediates might be either trapped intermolecularly by cyclohexene or cyclized to isomeric oxadiazoles, Scheme 11.

Tetrazoles. 5-Methoxytetrazole, 5-ethoxytetrazole, and 5-(2,6-dimethylphenoxy)tetrazole were prepared as described earlier.[7,12,20,21]

Typical Thermal Reactions. A solution (3.1 g, 0.0124 mol) of **16** and cyclohexene (10.2 g, 0.124 mol) in 50 mL of CH_3CN was heated to reflux for 6 days. At the end of thermolysis (confirmed by TLC analysis), excess cyclohexene and CH_3CN were removed under reduced pressure to give a viscous brown residue. Distillation of the residue by Kugelrohr at 106 ± 2 °C (1.5 mm) gave 0.53 g (39% yield) of a clear liquid, 2-(2,6-dimethylphenoxy)-4-methyl-1,3,4-oxadiazol-5-one (**16AA**). ^{1}H NMR (δ ppm, $CDCl_3$) 2.20 (s, 6H), 3.50 (s, 3H0, 7.10 (s, 3H). ^{13}C NMR (δ ppm, $CDCl_3$, 1H-decl.) 16.18, 40.10, 126.28, 124.05, 130.23, 150.88, 168.80, 171.20. IR (neat), 1800 cm^{-1} (s). Mass spectrum (70 eV) *m/e* M$^+$ 220. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.34; H, 5.26; N, 12.32. The remaining residue from Kugelrohr distillation was passed through a short column of aluminum oxide using chloroform as the eluting solvent to give a white solid (mp 94−99 °C) mixture in a 1:1 ratio of 3-(2,6-dimethylphenoxy)-4-*N*-methyl-1,2,4-oxazole (**17AA**) and 3-(2,6-dimethylphenoxy)-5-methoxy-1,2,4-oxadiazole (**17A**). ^{1}H NMR (δ ppm, $CDCl_3$) 1.19 (s, 6H), 2.21 (s, 6H), 3.34 (s, 3H), 4.00 (s, 3H) 7.12 (s, 6H). ^{13}C NMR (δ ppm, $CDCl_3$, 1H-decl.) 15.94, 16.06, 27.38, 32.03, 124.5, 126.95, 127.30, 129.33, 129.35, 129.6, 148.28, 150.7, 157.47, 159.55, 160.26. IR (KBr) 1805 (s), 1790 (s). Mass spectrum (70 eV) *m/e* M$^+$ 220. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.84; H, 5.47; N, 12.68.

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