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NMR Study of the Tautomeric Behavior of *N*-(α-Aminoalkyl)tetrazoles

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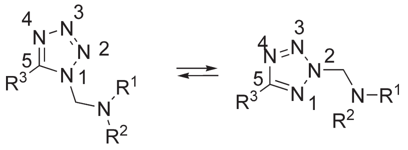

N-(α-Aminoalkyl)tetrazoles exist in solution as equilibrium mixtures of N1 and N2 tautomers. The position of equilibrium depends significantly on the polarity of the solvent and the substituents in the tetrazole ring. Interconversion between individual tautomers is shown to proceed via tight ion-pair intermediates in which intramolecular recombination is faster than the intermolecular crossover since the latter probably requires solvent separation of ion-pair intermediates.

Introduction

Tetrazoles have wide application in chemistry:[1] the ring can serve as a metabolically stable analogue for the carboxyl group[2a−c] and confer useful biological activity. Tetrazoles bind anions tightly in polar solution when compared to the corresponding carboxylic acids. Tetrazole-containing hosts bind anions ≥50000 times stronger than the corresponding acidic hosts. This remarkable difference in binding strength is rationalized by considering the tautomeric equilibria in tetrazoles and the conformational preferences in carboxylic acids. The tetrazole 1H tautomer is energetically more favored than the 2H tautomer by 3 kcal/mol, and it resembles the *anti* conformation of carboxylic acid which is disfavored energetically but is the preferred conformation for binding.[2d]

The tetrazole ring appears in some well-known drugs such as diovan, benicar, avapro, atacand, and hyzaar, which are generally used as cardiovascular or hypertension drugs. In biological systems, free NH- tetrazoles usually exist mainly in the anionic form.[2e]

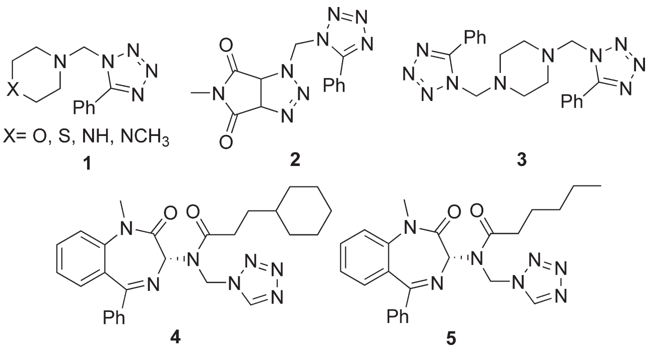

FIGURE 1. Some examples of bioactive compounds containing *N*-(α-aminoalkyl)tetrazole scaffolds.

N-(α-Aminoalkyl)tetrazoles **1**−**3** have recently provided modified protein-formation inhibitors for the prevention and treatment of diseases associated with AGEs (advanced glycation end products) and ALEs (advanced lipoxidation end products) (Figure 1).[3a] Benzodiazepine analogues (**4** and **5**) were found to be effective in treating cardiac arrhythmias[3b,c] and Meniere's disease[3d,e] in mammals by modulating the slowly activating delayed rectifier potassium current (IKs)

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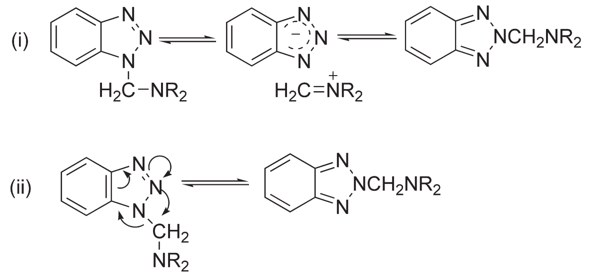
SCHEME 1. **N1 to N2 Substituent Isomerization of (*N*,*N*-Disubstituted aminomethyl)benzotriazoles**



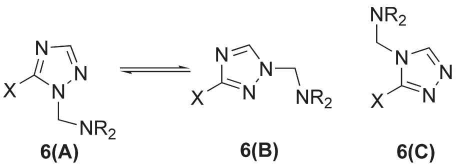
and the rapidly activating and deactivating relayed rectifier potassium current (IKr). All of these compounds are of particular interest as therapeutic agents, and all of them are reported without considering their tautomeric equilibria. Individual tautomers may interact differently with a particular receptor.

Tautomerism of α-aminoalkylbenzotriazoles, -1,2,4-triazoles, -1,2,3-triazoles, and -tetrazoles. *N*-(*N*,*N*-Disubstituted aminomethyl)benzotriazoles exist in solution as equilibrium mixtures of the corresponding 1-(*N*,*N*-disubstituted aminomethyl)- and 2-(*N*,*N*-disubstituted aminomethyl)benzotriazoles[4] with interconversion taking place via a dissociation−recombination mechanism,[5,6] involving an iminium cation and a benzotriazole anion, the formation which is facilitated by easy cleavage of the C−N bond. This type of tautomerism is known as cationotropy since it is the cation which moves from one position to another in a molecule. The equilibrium position of such benzotriazoles depends on the polarity of the solvent and on the substrate structure. Increasing solvent polarity favors the 1-isomer as expected from dipole moment measurements, which showed that 1-substituted benzotriazoles are more polar than their 2-substituted isomers.[7,8] However, the N2 tautomer may predominate when the dialkyaminoalkyl substituent is bulky.[4,6] Crossover experiments showed that this isomerization process is intermolecular and occurs by a dissociation−recombination mechanism (Scheme 1 (i)) rather than an intramolecular concerted mechanism (Scheme 1 (ii)).[5]

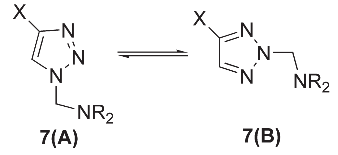
N-(α-Aminoalkyl)-1,2,4-triazoles also exist in solution as mixtures of N1 [**6**(**A**)] and N2 [**6**(**B**)] isomers, and a previous report[9a] demonstrated that a series of such compounds convert easily between the N1- and N2- tautomers, but no evidence for the N4 tautomer **6**(**C**) was found [Scheme 2 (i)]. Recent work on the tautomerism of *N*-(α-aminoalkyl)-1,2,3-triazoles[9b] showed that these compounds exist in nonpolar $CDCl_3$ predominantly as the 2-isomer **7**(**B**), although in polar DMSO (and D_2O, when soluble) some of the 1-isomer **7**(**A**) is present [Scheme 2 (ii)]. The present paper reports the analogous intermediates of 1- and 2-tetrazoles.

SCHEME 2. **(i) N1-, N2-, and N4-Substituted Isomers of *N*-(α-Aminoalkyl)-1,2,4-triazoles and (ii) N1- and N2-Substituted Isomers of *N*-(α-Aminoalkyl)-1,2,3-triazoles.**

(i) N1-, N2-, and N4-Substituted Isomers of *N*-(α-Aminoalkyl)-1,2,4-triazoles



(ii) N1- and N2-Substituted Isomers of *N*-(α-Aminoalkyl)-1,2,3-triazoles



Results and Discussion

1*H*-Tetrazole **8a** and 5-phenyl-1*H*-tetrazole **8e** are commercially available. The other parent tetrazoles were synthesized according to known methods A[10] (**8b**), B[11] (**8d**−**f**), and C[12] (**8c**,**g**−**i**,**k**).

The parent tetrazoles were used to prepare the desired *N*-(α-aminoalkyl)tetrazoles by the procedure of Bechmann and Heisey[13] for compounds **9a**,**e**−**o** (Table 1). This failed for compounds **9b**−**d** (Table 1), which were prepared by another synthetic route.[14]

Preliminary work on the tautomeric composition of *N*-(α-aminoalkyl)tetrazoles reported that 4-(1*H*-tetrazol-1-ylmethyl)morpholine (**9a**) exists predominately as the N2-isomer **9a**(**B**) in $CDBr_3$ with $\Delta G° = -1.03$ kcal/mol and $\Delta G^{\ddagger} = 17.6$ kcal/mol.[9a] The N2-isomer of **9a**(**B**) was also predominant in toluene-d_8, but substantial amounts of the N1-isomer [**9a**(**A**)] appeared in CD_3NO_2. Similarly, for 4-((5-methyl-1*H*-tetrazol-1-yl)methyl)morpholine (**9e**), the N2-isomer **9e**(**B**) was the dominant isomer in $CDBr_3$ with $\Delta G^{\ddagger} = 20.0$ kcal/mol for the interconversion of tautomers.[9a]

N1-Substituted tetrazoles have dipole moments higher than those of N2-substituted tetrazoles[17a−c] (e.g., 1-methyl-5-phenyltetrazole, $\mu = 5.88$ D, and its 2-methyl-isomer, $\mu = 2.52$ D); this higher polarity is consistent with the N1-isomer predominating in polar solvents.[17a]

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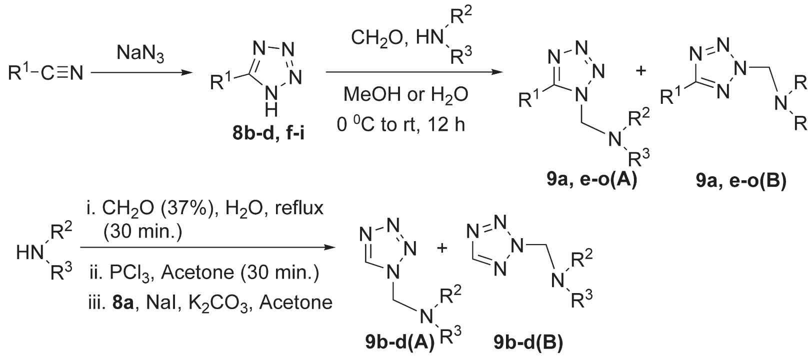
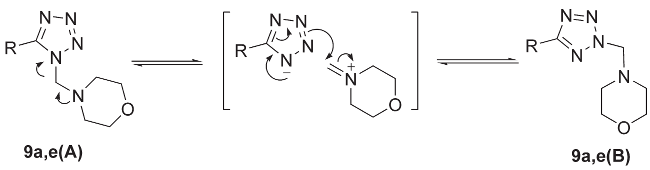
TABLE 1. Synthesis of *N*-(α-Aminoalkyl)tetrazoles 9a−o



compd	*N*-(α-aminoalkyl)tetrazoles			yield (%)	mp °C (lit. mp °C)
	R^1	R^2	R^3		
9a	H	$(CH_2)_2O(CH_2)_2$		75	81.0−82.0 (80.0−82.0)[9]
9b	H	$CO(CH_2)_2CO$		64	146.0−147.0
9c	H	CO-*o*-C_6H_4CO		74	139.0−145.0
9d	H	CO-*o*-$C_6H_4SO_2$		60	177.0−179.0
9e	CH_3	$(CH_2)_2O(CH_2)_2$		60	75.0−77.0 (75.0)[9]
9f	$(CH_3)_2CH$	$(CH_2)_2O(CH_2)_2$		80	oil
9g	$PhCH_2$	$(CH_2)_2O(CH_2)_2$		70	59.0−61.0
9h	$PhCH_2$	$(CH_2)_5$		60	oil
9i	Ph	$(CH_2)_2O(CH_2)_2$		75	57.0−59.0 (60.0−61.0)[15]
9j	Ph	$(CH_2)_5$		74	67.0−69.0 (65.0−66.0)[16]
9k	Ph	CH_3	CH_3	70	50.0−51.0
9l	*p*-$NO_2C_6H_4$	$(CH_2)_2O(CH_2)_2$		86	133.0−135.0
9m	*p*-ClC_6H_4	$(CH_2)_2O(CH_2)_2$		80	111.0−112.0
9n	*p*-$(CH_3)_2NC_6H_4$	$(CH_2)_2O(CH_2)_2$		70	146.0−148.0
9o	*p*-$MeOC_6H_4$	$(CH_2)_2O(CH_2)_2$		55	146.0−147.0

SCHEME 3. N1 to N2 Substituent Isomerization of 9a (R = H) and 9e (R = Me)



Nonempirical quantum mechanical calculations (MP2/6-31G* and MP2/6-31G*//HF/6-31G*) concluded that N2-substituted tetrazoles are more stable than the N1-isomers in the gas phase and in nonpolar solvents and also suggested that the equilibrium would be displaced toward the N1-tautomer by increasing solvent polarity.[18]

Tautomeric Equilibria of 1- and 2-Substituted Tetrazoles. We now show that both **9a** and **9e** exist mainly as the N2-isomeric form [**9a,e**(**B**) in Scheme 3] in nonpolar solvents but as the N1-isomers **9a,e**(**A**) in polar solvents (Table 2). At ambient temperatures, the ^{1}H NMR spectra of **9a,e** showed broad signals throughout the range, indicating that the N1 and N2-isomers were exchanging rapidly as reported previously (Scheme 3).[9a]

The chemical shifts for both **9b** and **9c** were fully assigned by 2D NMR experiments carried out in DMSO-*d*$_6$ (Tables 3−5). In both cases, the N2-isomer was predominant, and both compounds have the following characteristic patterns: in the A isomer, the $-N(CH_2)N-$ protons are more shielded and the $-NCH{=}N$ protons are more deshielded relative to the B isomer. Also, as previously reported,[19] the tetrazole carbon is more deshielded in the B isomer than in the A isomer.

The ^{15}N chemical shifts were assigned on the basis of the following correlations seen in the ^{1}H−^{15}N CIGAR-gHMBC experiment: In **9b**(**A**), the methylene protons H-1′(6.02 ppm) showed two-bond correlation with N1(239.4 ppm) and pyrrolidine nitrogen N1″ (180.4 ppm) and three-bond correlation with N2 (370.0 ppm). H-5 (9.42 ppm) showed two-bond correlation to both N1 (239.4 ppm) and N4 (395.0 ppm). In **9b**(**B**), the methylene protons H-1′ (6.20 ppm) showed two-bond correlations to N2 (307.9 ppm) and pyrrolidine nitrogen N1″ (180.0 ppm) and three-bond correlations to both N1 (383.5 ppm) and N3 (284.1 ppm). Moreover, N1 and N2 showed correlations to H-5 (9.01 ppm) by large coupling to N1 and small coupling to N2 (Table 5).

N-((1*H*-Tetrazol-1-yl)methyl)-1,2-benzisothiazole-3(2*H*)-one 1,1-dioxide (**9d**) exists in benzene-*d*$_6$ mainly as a 2-substituted tetrazole, but in all other solvents the 1-isomer predominates (Table 2). The ^{1}H, ^{13}C, and four ^{15}N chemical shifts were assigned in both isomers using 2D NMR techniques (Tables 3−5).

The assignments for **9d**(**A**) were based on the correlation seen in gHMBC between the methylene protons and C-5 of the tetrazole ring; such a correlation was not seen in the case of **9d**(**B**). The ^{1}H and ^{13}C chemical shifts of NCH=N

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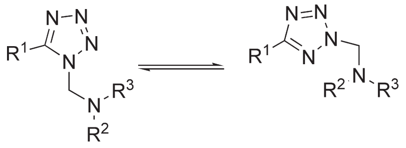
TABLE 2. Percentage of N1 Isomer Observed in Different Solvents

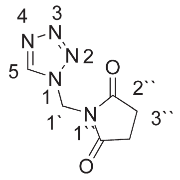


9a-o(A) **9a-o(B)**

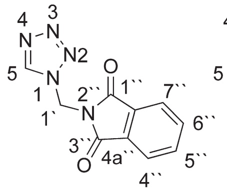
compd	D_2O (62.8)[a]	$(CD_3)_2SO$ (45.1)[a]	CD_3CN (45.6)[a]	CD_3OD (55.4)[a]	$(CD_3)_2CO$ (42.2)[a]	$CDCl_3$ (39.1)[a]	C_6D_6 (34.3)[a]
9a	85	> 99	67	81	59	17	17
9b	40	40	40	40	40	NS[b]	20
9c	NS[b]	15	15	reacts[c]	15	15	15
9d	58	80	79	62	83	57	24
9e	63	71	64	reacts[c]	55	18	20
9f	NS[b]	29	26	86	20	5	<1
9g	92	44	33	20	30	11	10
9h	NM[d]	<1	<1	NM[d]	NM[d]	<1	NM[d]
9i	<1	<1	<1	<1	<1	<1	<1
9j	NM[d]	<1	<1	NM[d]	NM[d]	<1	NM[d]
9k	NM[d]	<1	<1	NM[d]	NM[d]	<1	NM[d]
9l	<1	<1	<1	56/44	reacts[c]	<1	<1
9m	NS[b]	<1	<1	reacts[c]	<1	<1	<1
9n	NS[b]	<1	<1	<1	<1	<1	<1
9o	NS[b]	<1	<1	reacts[c]	reacts[c]	<1	<1

[a] Dimroth−Reichardt polarity index $E_T(30)$. [b] Insoluble. [c] Reacts with the solvent. [d] Not measured.

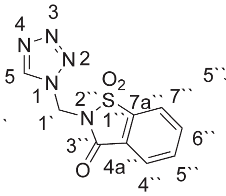
TABLE 3. Numbering and ^1H Chemical Shift Assignments in 9b,c,d,f (DMSO-d_6)



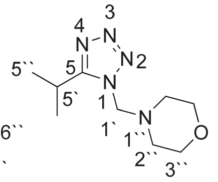
9b



9c



9d



9f

compd		H-5	H-1′	H-2″	H-3″	other
9b	**9b(A)**	9.42	6.02		2.69	
	9b(B)	9.01	6.20		2.74	
9c	**9c(A)**	9.54	6.27			H-4″ (7.91), H-5″ (7.95), H-6″ (7.95), H-7″ (7.91)
	9c(B)	9.02	6.46			H-4″ (7.97), H-5″ (7.88), H-6″ (7.88), H-7″ (7.99)
9d	**9d(A)**	9.59	6.57			H-4″ (8.36), H-5″ (8.10), H-6″ (8.03), H-7″ (8.18)
	9d(B)	9.02	6.72			H-4″ (8.36), H-5″ (8.10), H-6″ (8.03), H-7″ (8.18)
9f	**9f(A)**		5.51	2.53	3.57	H-5′ (3.23), H-5″ (1.33)

TABLE 4. ^{13}C Chemical Shift Assignments in 9b,c,d,f (DMSO-d_6)

compd		C-5	C-1′	C-2″	C-3″	other
9b	**9b(A)**	146.4	48.9	178.4	30.0	
	9b(B)	155.3	53.4	178.0	29.9	
9c	**9c(A)**	145.1	48.9		167.1	C-1″ (167.1), C-4a″ (131.7), C-4″ (135.9), C-5″ (124.5),C-6″ (124.5),C-7″ (135.9), C-7a″ (131.7)
	9c(B)	154.2	53.3		166.8	C-1″ (166.8), C-4a″ (131.9), C-4″ (124.3), C-5″ (135.7),C-6″ (135.7),C-7″ (124.3), C-7a″ (131.9)
9d	**9d(A)**	145.4	49.2		158.6	C-4a″ (137.7), C-4″ (122.7), C-5″ (137.3),C-6″ (136.3),C-7″ (126.5)
	9d(B)	154.2	53.7		158.6	C-4a″ (137.7), C-4″ (122.7), C-5″ (137.3),C-6″ (136.3),C-7″ (126.5)
9f	**9f(A)**	161.0	73.9	50.0	66.6	C-5′ (26.0), C-5″ (50.0)

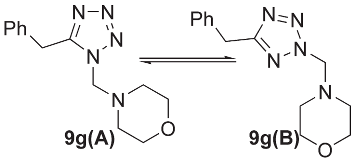
TABLE 5. ^{15}N Chemical Shift Assignments in 9b,c,d,f (DMSO-d_6)

compd		N1	N2	N3	N4	other
9b	**9b(A)**	239.3	370.0	NM[a]	395.0	N1″ (180.4)
	9b(B)	383.5	307.9	284.1	NM[a]	N1″ (180.0)
9c	**9c(A)**	240.7	369.2	NM[a]	395.7	N2″ (162.4)
	9c(B)	382.5	307.1	287.8	NM[a]	N2″ (161.7)
9d	**9d(A)**	239.0	370.2	NM[a]	396.4	N2″ (160.9)
	9d(B)	384.4	308.2	285.1	NM[a]	N2″ (160.9)

[a] Not measured.

(H-5 and C-5) and NCH_2N- (H-1′ and C-1′) follow the usual trend. We recorded the ^{15}N chemical shifts of all four nitrogens in both isomers. In **9d(A)**, the methylene protons H-1′ (6.57 ppm) showed two-bond correlation to N1 (239.0 ppm) and to saccharine nitrogen N2″ (160.9 ppm) and three-bond correlation to N2 (370.2 ppm). The tetrazole proton H-5 (9.59 ppm) showed two-bond correlations to N1 (239.0 ppm) and to N4 (396.4 ppm) and a three-bond correlation to N2 (370.2 ppm). In the case of **9d(B)**, N1 (384.4 ppm) was

TABLE 6. Coalescence Temperatures (T_c), Equilibrium Constants (K), Chemical Shift Differences ($\Delta\nu$), Free Energy Barriers ($\Delta G^{\ddagger}$), and Natural Logarithm of Exchange Rate Constant (k_r) from the ^1H and ^{13}C NMR Spectra of 9g (Acetonitrile-d_3 as Solvent)



	T_c (K)	K^c	$\Delta\nu$ (Hz)	$\Delta G^{\ddagger}_{A\to B}(T_c)$ (kcal mol^{-1})	ln k_r A→B	$\Delta G^{\ddagger}_{B\to A}(T_c)$ (kcal mol^{-1})	ln k_r B→A
$-N(CH_2)N-$[a]	338	0.54	195.0	17.5	3.5	15.8	6.0
$PhCH_2-$[a]	325	0.55	40.7	17.2	2.9	15.8	5.1
$PhCH_2-$[b]	343	0.55[d]	271	17.4	4.1	15.8	6.4
$-N(CH_2)_2-$[a]	318	0.58	30.3	17.1	2.4	16	4.2
$-N(CH_2)_2-$[b]	323	0.58[d]	45	17.2	2.7	16.2	4.3
$-O(CH_2)_2-$[a]	318	0.55	38.7	17.3	2.1	15.8	4.5
$-O(CH_2)_2-$[b]	308	0.55[d]	13.8	17.4	1.0	16	3.3

[a] T_c calculated from ^1H NMR. [b] T_c calculated from ^{13}C NMR. [c] Calculated at 273 K, $K = P_A/P_B$ where P_A and P_B are the population of 1- and 2-isomers (A and B). [d] Assumed to be the same as in ^1H NMR.

identified through a two-bond correlation to H-5 (9.09 ppm) and three-bond correlations to the methylene protons H-1′ (6.72 ppm). The methylene protons correlate to N2 (308.2 ppm), N3 (285.1 ppm), and to saccharine nitrogen N2″ (160.9 ppm) (Table 5).

4-((5-Isopropyl-1*H*-tetrazol-1-yl)methyl)morpholine (**9f**) exists exclusively as the N2-isomer **9f**(**B**) in C_6D_6 and $CDCl_3$ (nonpolar solvents) as is clear from the ^{13}C chemical shift of tetrazole C-5 (171.5 ppm) (Table 4). On increasing the polarity of the solvent, the N1 isomer **9f**(**A**) appears in the ^1H NMR spectra. The highest ratio of N1-isomer (1 to 2) was obtained in DMSO-d_6, which is the most polar in the series of solvents used (Table 2). We were able to assign completely the ^1H and ^{13}C chemical shifts for **9f**(**A**) (cf. Tables 3–5) but were unable to assign chemical shifts for **9f**(**B**) due to broad peaks of low intensity in DMSO-d_6.

4-((5-Benzyl-1*H*-tetrazol-1-yl)methyl)morpholine (**9g**) exists in C_6D_6 and in $CDCl_3$ as a mixture of N2/N1 isomers with a ratio of 9:1. The proportion of the N1 isomer increases with increasing solvent polarity so the N1 isomer is dominant in D_2O with a ratio of 9:1 (Table 2).

1-((5-Benzyl-2*H*-tetrazol-2-yl)methyl)piperidine (**9h**) exists in $CDCl_3$, CD_3CN, DMSO-d_6, and toluene-d_8 at −60 °C as the N2-isomer with no evidence for N1-isomer in any of these solvents (Table 2).

For *N*-(α-aminoalkyl)tetrazoles **9i**–**o** only the N2-isomers **9i**–**o**(**B**) were observed in solution (cf. Table 2), probably because of the steric bulk of the C-5 substituent. The ^{13}C chemical shifts of C-5 in **9i**–**o** range from 152.8 to 179.0, which is in agreement with literature values for the N2-isomer reported by Begtrup et al.[19] It was also shown by Binda et al.[15] that the aminomethylation of 5-substituted tetrazoles bearing aromatic substituents at C-5 occur regioselectively at the N2 of the tetrazole ring. Finally, an X-ray crystal structure for **9i** (Figure 2) showed clearly that this compound exists exclusively in the solid state as the N2-isomer thus avoiding steric interaction between the substituents at N1 and C-5.

Thermodynamic and Kinetic Parameters. Free energies of activation for the isomerization of **9a** and **9e** were measured previously.[9a] A variable-temperature ^1H NMR study of compounds **9c** and **9d** failed to detect coalescence even at 150 °C in DMSO-d_6, probably due to the electron-withdrawing groups on nitrogen destabilizing the iminium ion and therefore slowing down the isomerization process.

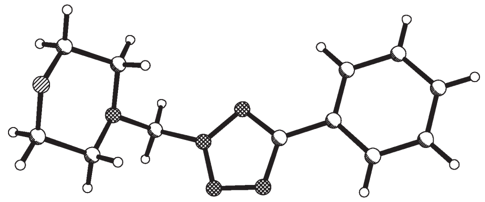


FIGURE 2. X-ray structure of **9i**.

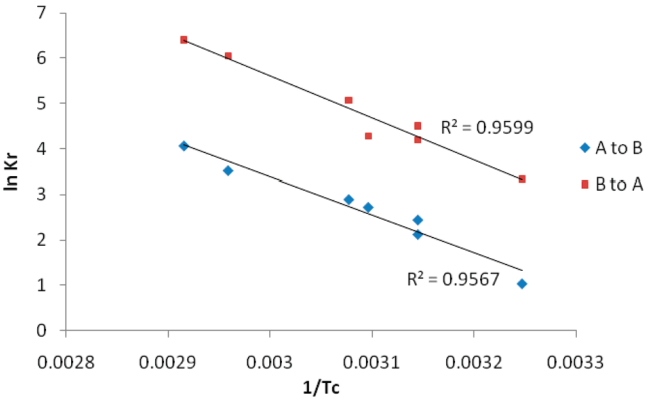


FIGURE 3. Plot of ln k_r vs $1/T_c$ in case of interconversion of A → B and B → A.

Variable-temperature ^1H and ^{13}C NMR were carried out for **9g** in CD_3CN; seven different sites within the molecule showed coalescence at six different temperatures (see Figure S1, Supporting Information, for VT ^1H NMR).

Free energy barriers ($\Delta G^{\ddagger}$), calculated using the method of Shanan-Atidi and Bar-Eli[20] for the case of unequal populations ($P_A \neq P_B$) (Table 6), showed that the 2-substituted isomer **9g**(**B**) is less stable than the 1-substituted isomer **9g**(**A**) in CD_3CN by on average 0.56 kcalmol^{-1}.

For interconversion of A → B, a plot of ln k_r vs $1/T_c$ gave a straight line (Figure 3) from which values of E_a (16.5 kcal mol^{-1}), $\Delta H^{\ddagger}$ (15.9 kcal mol^{-1}), and $\Delta S^{\ddagger}$ (−4.5 eu) were derived.

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(20) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961–963.

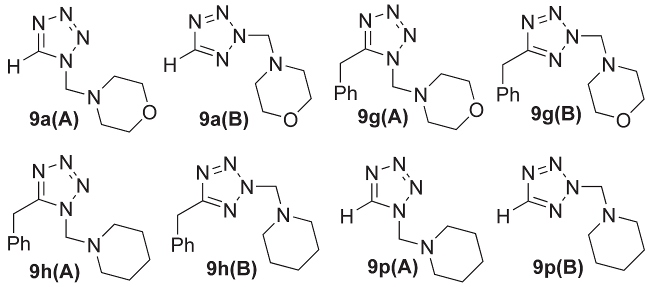

FIGURE 4. Different isomers expected from crossover experiment between **9a** and **9h**.

For interconversion of B → A, a similar plot (Figure 3) gave values of E_a (18.5 kcalmol^{-1}), $\Delta H^{\ddagger}$ (17.9 kcal mol^{-1}), and $\Delta S^{\ddagger}$ (−6.0 eu).

The low entropies of activation in both directions suggest that the isomerization process occurs via a unimolecular dissociation-recombination mechanism involving a tight ion pair (Scheme 3). This is entirely consistent with a polar solvent (e.g., CD_3CN) facilitating the isomerization. By contrast, in the less polar solvent $CDCl_3$ solution no coalescence was observed up to 55 °C.

Crossover Experiment. An equimolar mixture of **9a** with **9h** in toluene-*d8* was prepared at 20 °C and its ^1H NMR recorded at −10 °C, displayed twelve signals in the region 4.9−3.7 ppm, corresponding to the eight possible isomers resulting from the cross-reaction (Figure 4).

The four signals for the methylene protons in the benzyl moiety in **9 g(A)**, **9 g(B)**, **9 h(A)**, and **9 h(B)**, were identified by their cross-peaks in the gHMBC spectrum with three sp^2 carbons, namely C_{ipso} and C_{ortho} on the phenyl ring and C-5 on the tetrazole moiety. Two of these methylene protons, at 3.77 **9 g(A)** and 3.82 **9 h(A)** ppm, coupled with C-5 signal at 153.7 ppm, while the other two at 4.05 **9 g(B)** and 4.08 **9 h(B)** ppm coupled with C-5 signals at 165.4 and 165.1 ppm, indicating that the first pair are 1-substituted tetrazole and the second pair the 2-substituted isomers.

The signals for the H-5 proton in tetrazoles **9a** and **9p** were assigned in a similar manner as 7.50 [**9a(A)**] and 7.49 [**9p(A)**] on carbons at 142.4 assigned to 1-substituted compounds and 7.99 [**9a(B)**] and 8.04 [**9p(B)**] on the carbons at 152.3 and 152.5 corresponding to 2-substituted compounds.

The triplets at 3.30, 3.29, 3.26, and 3.18 have the distinct chemical shifts of the methylene hydrogens α to the oxygen in morpholine. They display cross-peaks in the NOESY spectrum with triplets at 2.18, 2.12, 1.78, and 1.82, which are the methylene protons α to nitrogen. These protons display NOE peaks with protons at 4.66 [**9 g(B)**], 4.70 [**9a(B)**], 4.14 [**9a(A)**], and 3.98 [**9 g(A)**], which are the methylene protons attached to the morpholine moiety. The other four signals at 4.84 [**9p(B)**], 4.80 [**9 h(B)**], 4.29 [**9p(A)**], and 4.15 [**9 h(A)**] are for the methylene protons attached to the piperidine group and show NOEs with the two protons at 2.33 and 2.28.

A NOE between the benzyl protons at 3.77 ppm and the morpholine protons at 3.98 ppm identified these signals as from the **9 g(A)** compound, as confirmed by their equal integrals. The other signals of the methylene groups bearing piperidine or morpholine moieties were assigned by matching their integrals to the integrals of H-5 or to the integrals of the benzyl protons. The assignment of the significant proton signals and the molar percentage of compounds in the mixture are given in Table 7. It is worth mentioning here that the molar percentage of the 2-isomers is higher than the 1-isomer because the 2-isomer predominates in nonpolar solvents. The size of the exchange peaks in the NOESY spectrum demonstrates that piperidine isomerizes faster than morpholine and that exchange between positions 1 and 2 is faster than the intermolecular crossover process (Figure 5).

TABLE 7. **Signal Assignments and Molar Percentage Ratios of Compounds 9a, 9g, 9h, and 9p in Crossover Experiment**

compd	9a(A)	9a(B)	9 g(A)	9 g(B)	9 h(A)	9 h(B)	9p(A)	9p(B)
δH (ppm)[a]	4.14	4.70	3.98	4.66	4.15	4.80	4.29	4.84
molar %	5.2	24.8	2.6	26.1	1.7	17.4	4.5	17.6
δH (ppm)[b]	7.50	7.99	3.77	4.05	3.82	4.08	7.49	8.04

[a] Protons in the methylene group carrying a piperidine or a morpholine moiety. [b] Benzyl protons or H5.

The crossover experiment was initially carried out in polar solvent (acetonitrile-d_3), and it gave almost the same crossover products with different molar ratios, but the $-NCH_2N-$ protons of the eight isomers were not well separated in this solvent.

Conclusions

In conclusion, we have shown that the equilibrium between the N1 and N2 tautomers of *N*-(α-aminoalkyl)tetrazoles favors the N2 tautomer in nonpolar solvents but that the equilibrium shifts to favor the N1 tautomer with increasing solvent polarity. Bulky substituents in the 5-position of the tetrazole ring favor the N2 tautomer; this is analogous to *C*-substituted 1,2,4-triazoles.[9a] Because of symmetry, the equilibrium constant in the case of unsubstituted 1,2,4-triazoles is equal to 1, but since there is no such symmetry in the unsubstituted tetrazoles, their tautomeric ratios depend mainly on the polarity of the solvent.

The N2 isomer of *N*-(α-aminoalkyl)-1,2,3-triazoles is usually favored in all solvents, but the N1 isomer predominates when electron-withdrawing groups are attached to the exocyclic amino group.[9b] *N*-(α-Aminoalkyl)tetrazoles behave similarly with the N1 isomer predominating in polar solvents, but with substituents at C-5 the N2 was the major isomer in nonpolar solvents.

The N1 isomer for *N*,*N*-(disubstitutedaminomethyl)-benzotriazoles dominates in the solid phase. However, in solution and in the vapor phase a mixture of N1 and N2 isomers is observed with the N1 isomer dominant due to the greater aromaticity of N1 substituted benzotriazoles.[5]

The detailed mechanism of interconversion between the N1 and N2 isomers is shown to involve tight ion pairs, which can (i) relax to give isomerism without crossover or (ii) become solvent-separated and thus lead to crossover between different components in a mixture of two tetrazoles in which both the tetrazole ring and the amino substituents differ.

Experimental Section

General Procedures. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected.

The ^1H and ^{13}C NMR spectra for starting materials were recorded on a Varian Gemini instrument, operating at 300 MHz for ^1H and 75 MHz for ^{13}C. The NMR spectra for final products were recorded on a Varian Inova instrument, operating

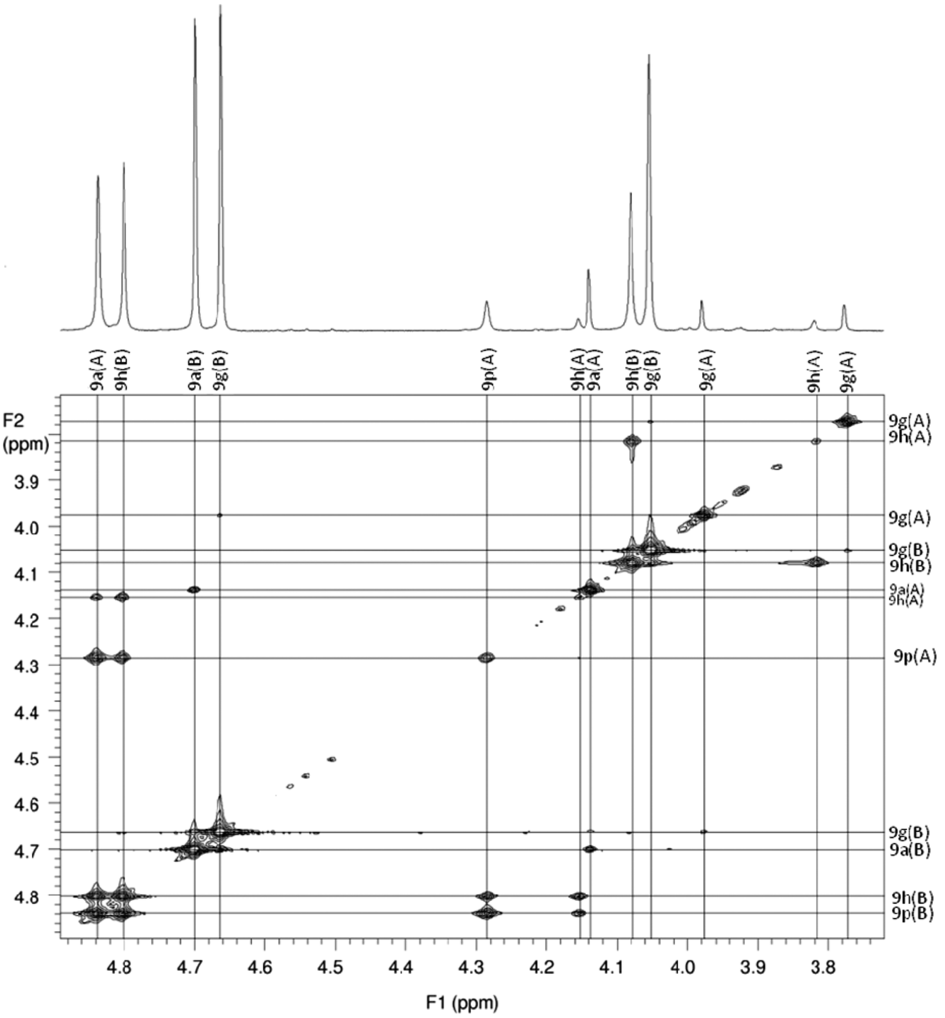

FIGURE 5. NOESY spectrum of crossover experiment between **9a** and **9h** in toluene-d_8 at −10 °C.

at 500 MHz for ^{1}H, 125 MHz for ^{13}C and 50 MHz for ^{15}N, equipped with a three-channel, 5 mm, indirect detection probe, with *z*-axis gradients. The ^{1}H NMR spectra were recorded in deuterium oxide, dimethyl sulfoxide-d_6, acetonitrile-d_3, methanol-d, acetone-d_6, chloroform-d, and benzene-d_6 with TMS for ^{1}H (500 MHz) and ^{13}C (125 MHz) as an internal reference. The chemical shifts for ^{15}N were referenced to Ξ = 10.1328898, corresponding to 0 for neat ammonia. On the Ξ scale the frequency of protons in tetramethylsilane is 100.0000000 MHz. For conversion to the neat nitromethane scale, subtract 381.7 ppm.

^{1}H spectra were acquired in one transient, with a 90° pulse, no relaxation delay, and an acquisition time of 5 s over a spectral window from +16 to −2 ppm. The FID was zero-filled to 131072 points prior to Fourier transform.

Typically, ^{1}H−^{13}C gHMBC spectra were acquired in 4096 points in f2, on a spectral window from 1.5 to 11 ppm, and 1 s relaxation delay. 512 increments were acquired in 1 transient over a spectral window from 170 to 10 ppm, and then the corresponding FIDs were zero-filled twice prior to the second Fourier transform.

^{1}H−^{15}N CIGAR-gHMBC spectra were acquired with a pulse sequence optimized for ^{15}N, as described in ref 21. A total of 2048 points were acquired in f2, over a spectral window typically from 1.5 to 11 ppm, with 1 s relaxation delay. A total of 1024 increments were acquired in f1, on a spectral window from 0 to 400 ppm, and the corresponding FID was zero-filled twice prior to Fourier transform. The accordion delay was optimized for a value of ^{1}H−^{15}N coupling constants between 3 and 10 Hz. The number of transients per increment was between 4 and 64, depending on the concentration of the sample.

General Procedures for Synthesis of Compounds 8b−d,f−i. Method A:[10] **Preparation of 5-Methyltetrazole (8b).** Sodium azide (4.88 g, 75 mmol) was added to a solution of acetonitrile (1.03 g, 25 mmol) in dry tetrahydrofuran (5 mL). A solution of aluminum chloride (3.5 g, 26 mmol) in dry tetrahydrofuran (20 mL) was added to the previous suspension. The reaction mixture was heated under reflux for 40 h and then allowed to cool to room temperature. Hydrochloric acid (5 mL, 10%) was added, and the mixture was allowed to stir for 8 h. The solvent was removed under reduced pressure, and the residue was extracted with 25 mL of hot acetone to give oil that crystallized under vacuum. The solid formed was recrystallized from chloroform to give compound **8b** in 10% yield (0.25 g): mp 145.0−147.0 °C (lit.[2] mp 143.0 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 2.57 (s, 3H). ^{13}C NMR (75 MHz, Acetone-*d6*) δ 153.5, 8.83.

Method B:[11] **Preparation of Compounds 8d and 8f.** A mixture of benzyl nitrile (0.12 g, 1 mmol) or 4-nitrobenzonitrile (0.148 g, 1 mmol), sodium azide (0.195 g, 3 mmol), ammonium chloride (0.214 g, 4 mmol), and dimethylformamide (5 mL) was heated under reflux for 12 h. After the reaction was allowed to cool to room temperature, water (20 mL) was added with continuous stirring. The mixture was then acidified with HCl (6 N) to pH 2.

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(21) Kline, M.; Cheatham, S. *Magn. Reson. Chem.* **2003**, *41*, 307–314.

The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resultant solid was recrystallized to give compounds **8d** and **8f**, respectively.

5-Benzyl-1*H*-tetrazole (8d). The product was crystallized from DCM/hexanes to give gray needles (81%): mp 118.0−120.0 °C (lit.[22] mp 120.0−121.0 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7 0.23 (m, 5H), 4.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 134.4, 129.2, 128.9, 127.8, 30.0. Anal. Calcd for $C_8H_8N_4$ (160.18): C, 59.99; H, 5.03; N, 34.98. Found: C, 60.13; H, 5.11; N, 35.10.

5-(4-Nitrophenyl)-1*H*-tetrazole (8f). The product was crystallized from EtOH to give brown microcrystals (94%): mp 218.0−220.0 °C (lit.[23] mp 219.0−220.0 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 8.8 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.5, 148.7, 130.7, 128.2, 124.6. Anal. Calcd for $C_7H_5N_5O_2$ (191.15): C, 43.98; H, 2.64; N, 36.64. Found: C, 44.35; H, 2.17; N, 36.25.

Method C:[12] Preparation of Compounds 8c,g,h,i. A mixture of the corresponding nitrile (10 mmol), sodium azide (0.72 g, 11 mmol), zinc bromide (2.25 g, 10 mmol), and water (20 mL) was heated under reflux for 24 h. The reaction mixture was allowed to cool and acidified with HCl (6 N) to pH 1. The product was extracted with ethyl acetate (3 × 50 mL). Ethyl acetate was then evaporated, and 100 mL of 0.25 N NaOH was added. The mixture was stirred for 30 min until the solid dissolved, and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid was washed with 10 mL of 1 N NaOH. The filtrate was acidified again with HCl (6 N) and stirred vigorously until the tetrazole precipitated. In some cases, the tetrazole did not precipitate from water and was extracted from water with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and then distilled under reduced pressure to give the desired product.

5-Isopropyl-1*H*-tetrazole (8c). The product was crystallized from DCM/hexanes to give white sharp needles (32%): mp 98.0−100.0 °C (lit.[24] mp 113.0−114.0 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 12.42 (br s, 1H), 3.60−3.46 (septet, J = 7.0 Hz, 1H), 1.50 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 24.8, 21.3. Anal. Calcd for $C_4H_8N_4$ (112.14): C, 42.84; H, 7.19; N, 49.96. Found: C, 43.07; H, 7.32; N, 49.88.

5-(4-Chlorophenyl)-1*H*-tetrazole (8g). The product was obtained in analytically pure form as white crystals (75%): mp 246.0−255.0 °C (lit.[25] mp 252.0−253.0 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 6.0 Hz, 2H), 7.56 (d, J = 6.0 Hz, 2H), 5.50−6.50 (br s, 1H); ^{13}C NMR (75 MHz, DMSO -*d6*) δ 154.9, 135.9, 129.2, 128.4, 123.2. Anal. Calcd for $C_8H_8N_4$ (176.18): C, 46.55; H, 2.79; N, 31.02. Found: C, 46.94; H, 2.80; N, 30.88.

***N*,*N*-Dimethyl-4-(1*H*-tetrazol-5-yl)aniline (8h).** The product was obtained as yellow microcrystals (63%), mp 78.0−80.0 °C (lit.[26] mp 81.0−83.0 °C); ^1H NMR (300 MHz, Acetone-d_6) δ 7.94 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.05 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 153.2, 129.1, 128.7, 112.9, 40.2.

5-(4-Methoxyphenyl)-1*H*-tetrazole (8i). The product was obtained in analytically pure form as white needles (68%): mp 234.0−239.0 °C (lit.[27] mp 233.0−235.0 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 7.99 (d, J = 8.65 Hz, 2H), 7.17 (d, J = 8.65 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 128.4, 128.0, 116.3, 114.6, 55.2. Anal. Calcd for $C_8H_8N_4$ (176.18): C, 54.54; H, 4.58; N, 31.80. Found: C, 54.56; H, 4.42; N, 31.73.

General Procedure for Synthesis of Compounds 9a,e−o[13]. Tetrazoles **8a−i** were dissolved in methanol (5 mL) unless otherwise specified, and the solutions were cooled in an ice bath. Morpholine (1.1 mmol, 0.086 mL) was added, and the mixture was allowed to stir for 15 min. Formalin 37% (1.2 mmol, 0.096 mL) was added dropwise and the mixture stirred for 1 h. The ice bath was then removed, and the reaction was stirred for additional 12 h. The solvent was evaporated, and the residue was recrystallized to give **9a,e−o**.

4-(1*H*-Tetrazol-1-ylmethyl)morpholine (9a). The product was obtained as colorless prisms after recrystallization from DCM/hexanes (75%): mp 81.0−82.0 °C (lit.[9a] mp 80.0−82.0 °C). Two tautomers: ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 0.3H from A), 8.53 (s, 0.7H from B), 5.50 (s, 1.6 H from B), 5.29 (s, 0.4 H from A), 3.69 (t, J = 4.7 Hz, 4H), 2.63 (t, J = 4.7 Hz, 3.3H from B), 2.58 (t, J = 4.5 Hz, 0.7 H from A). Two tautomers: ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8 (B), 142.8 (A), 74.1 (B), 70.0 (A), 66.8 (B), 66.6 (A), 49.9. Anal. Calcd for $C_6H_{11}N_5O$ (169.19): C, 42.59; H, 6.55; N, 41.39. Found: C, 42.92; H, 6.67; N, 41.41.

4-((5-Methyl-1*H*-tetrazol-1-yl)methyl)morpholine (9e). The product was obtained as colorless prisms after recrystallization from chloroform/hexanes (60%): mp 75.0−77.0 °C (lit.[9a] mp 75.0 °C). Two tautomers: ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (s, 1.6H from B), 5.05 (s, 0.4H from A), 3.67 (t, J = 4.4 Hz, 4H), 2.62 (t, J = 4.6 Hz, 4H), 2.62 (t, J = 4.6 Hz, 4H), 2.53 (s, 3H). Two tautomers: ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 73.8, 68.6, 66.8, 66.6, 50.4, 50.0, 31.0, 11.0, 9.26. Anal. Calcd for $C_6H_{11}N_5O$ (169.19): C, 45.89; H, 7.15; N, 38.23. Found: C, 46.33; H, 6.78; N, 37.75.

4-((5-Isopropyl-1*H*-tetrazol-1-yl)methyl)morpholine (9f). The reaction was carried out in water, and the product was obtained as a colorless oil (80%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 2H), 3.64 (t, J = 4.7 Hz, 4H), 3.22 (septet, J = 7.0 Hz, 1H), 2.59 (t, J = 4.7 Hz, 4H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 77.6, 73.6, 66.7, 49.9, 26.1, 21.5. Anal. Calcd for $C_9H_{17}N_5O$ (211.27): C, 51.17; H, 8.11; N, 33.15. Found: C, 50.99; H, 8.32; N, 32.96.

4-((5-Benzyl-1*H*-tetrazol-1-yl)methyl)morpholine (9g). The product was obtained as colorless needles after recrystallization from DCM/hexanes (70%): mp 59.0−61.0 °C. Two tautomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.15 (m, 5H), 5.36 (s, 1.8H from B), 4.77 (s, 0.2H from A), 4.33 (s, 0.2H from A), 4.22 (s, 1.8H from B), 3.64 (t, J = 4.7 Hz, 3.5H from B), 3.57 (t, J = 4.5 Hz, 0.5H from A), 2.59 (t, J = 4.7 Hz, 3.5H from B), 2.43 (t, J = 4.5 Hz, 0.5H from A). ^{13}C NMR (75 MHz, $CDCl_3$) Two tautomers: δ 165.6 (B), 136.8 (A), 129.3 (A), 128.9 (B), 128.8 (B), 128.7 (A), 127.9 (A), 127.0 (B), 73.9 (B), 68.8 (A), 66.8 (B), 66.6 (A), 50.5 (A), 50.0 (B), 32.0 (B), 29.9 (A). Anal. Calcd for $C_{13}H_{17}N_5O$ (259.13): C, 60.12; H, 6.61; N, 27.01. Found: C, 60.59; H, 6.74; N, 27.12.

1-((5-Benzyl-2*H*-tetrazol-2-yl)methyl)piperidine (9h). The reaction was carried out in water and the product was obtained as a sticky yellow oil (60%). ^1H NMR (500 MHz, acetonitrile-d_3) δ 7.34−7.24 (m, 5H), 5.27 (br s, 2H), 4.26 (s, 2H), 2.51 (t, J = 5.1 Hz, 4H), 1.54−1.49 (m, 4H), 1.34−1.29 (m, 2H); ^{13}C NMR (125 MHz, acetonitrile-d_3) δ 129.8, 129.7, 128.0, 51.8, 26.6, 24.4. Anal. Calcd for $C_{14}H_{19}N_5$ (257.34): C, 65.34; H, 7.44; N, 27.21. Found: C, 65.13; H, 7.46; N, 27.50.

4-((5-Phenyl-2*H*-tetrazol-2-yl)methyl)morpholine (9i). The reaction was carried out in water, and the product was obtained as colorless sheets (75%): mp 57.0−59.0 °C (lit.[15] mp 60.0−61.0 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 7.51−7.48 (m, 3H), 5.50 (s, 2H), 3.71 (t, J = 4.7 Hz, 4H), 2.71 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 130.5, 129.0, 127.5, 127.1, 74.2, 66.8, 50.0. Anal. Calcd for $C_{12}H_{15}N_5O$ (245.29): C, 58.76; H, 6.16; N, 28.55. Found: C, 58.91; H, 6.24; N, 28.63.

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1-((5-Phenyl-2*H*-tetrazol-2-yl)methyl)piperidine (9j). The product was obtained as white prisms after recrystallization from DCM/hexanes (74%): mp 67.0−69.0 °C (lit.[16] mp 65.0−66.0 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18−8.16 (m, 2H), 7.51−7.46 (m, 3H), 5.50 (s, 2H), 2.65 (t, *J* = 5.4 Hz, 4H), 1.62−1.57 (m, 4H), 1.36−1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 130.3, 129.0, 127.7, 127.0, 126.9, 75.2, 51.0, 25.9, 23.5. Anal. Calcd for $C_{13}H_{17}N_5$ (243.31): C, 64.17; H, 7.04; N, 28.78. Found: C, 64.08; H, 7.15; N, 28.70.

***N,N*-Dimethyl-1-(5-phenyl-2*H*-tetrazol-2-yl)methanamine (9k).** The product was obtained as white prisms (70%): mp 50.0−51.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10−8.06 (m, 2H), 7.59−7.53 (m, 3H), 5.58 (s, 2H), 2.35 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 130.4, 129.2, 127.0, 126.4, 75.1, 41.3. Anal. Calcd for $C_{10}H_{13}N_5$ (203.25): C, 59.09; H, 6.45; N, 34.46. Found: C, 58.94; H, 6.34; N, 34.60.

4-((5-(4-Nitrophenyl)-2*H*-tetrazol-2-yl)methyl)morpholine (9l). The product was crystallized from DCM/hexanes to give yellow microcrystals (86%): mp 133.0−135.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 4H), 5.55 (s, 2H), 3.72 (t, *J* = 4.7 Hz, 4H), 2.72 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 149.1, 133.5, 127.9, 124.4, 74.7, 66.8, 50.0. Anal. Calcd for $C_{12}H_{14}N_6O_3$ (290.28): C, 49.65; H, 4.86; N, 28.95. Found: C, 49.87; H, 4.48; N, 28.91.

4-((5-(4-Chlorophenyl)-2*H*-tetrazol-2-yl)methyl)morpholine (9m). The product was crystallized from toluene to give white prisms (80%): mp 111.0−112.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.51 (s, 2H), 3.72 (t, *J* = 4.6 Hz, 4H), 2.71 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 164.2, 136.4, 129.2, 128.2, 125.9, 74.2, 66.6, 49.8. Anal. Calcd for $C_{12}H_{14}N_5OCl$ (279.73): C, 51.53; H, 5.04; N, 25.04. Found C, 51.93; H, 5.07; N, 24.64.

***N,N*-Dimethyl-4-(2-(morpholinomethyl)-2*H*-tetrazol-5-yl)-aniline (9n).** The product was crystallized from toluene to give white prisms (70%): mp 146.0−148.0 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.96 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.54 (s, 2H), 3.63 (t, *J* = 4.5 Hz, 4H), 2.67 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (125 MHz, acetone-d_6) δ 153.1, 128.7, 113.0, 74.7, 67.4, 51.0, 40.4, 30.6, 30.3. Anal. Calcd for $C_{14}H_{20}N_6O$ (288.36): C, 58.31; H, 6.99; N, 29.14. Found C, 57.97; H, 6.70; N, 28.97.

4-((5-(4-Methoxyphenyl)-2*H*-tetrazol-2-yl)methyl)morpholine (9o). The reaction was carried out in ethanol, and the product was crystallized from toluene to give white crystals (55%): mp 146.0−147.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 5.48 (s, 2H), 3.88 (s, 3H), 3.72 (t, *J* = 4.6 Hz, 4H), 2.72 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 161.5, 128.6, 120.2, 114.5, 74.1, 66.9, 55.6, 50.1, 46.7. Anal. Calcd for $C_{13}H_{17}N_5O_2$ (275.31): C, 56.72; H, 6.22; N, 25.44. Found: C, 56.34; H, 6.19; N, 25.04.

General Procedure for Synthesis of Compounds 9b−d. Equimolar amounts (1 mmol) of *N*-chloromethyl derivatives of the corresponding amide, potassium carbonate, sodium iodide, and 1*H*-tetrazole **8a** were added to dry acetone (5 mL) and stirred for 12 h. The mixture was diluted with methylene chloride (50 mL) and filtered. The filtrate was extracted with 10 mL of 0.5% NaOH solution. The organic phase was collected, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give the desired product.

1-((1*H*-Tetrazol-1-yl)methyl)pyrrolidine-2,5-dione (9b). The reaction was carried out in acetonitrile, and the product was crystallized from toluene/ethanol (5:1) to give white crystals (64%): mp 146.0−147.0 °C. Two tautomers: ^{1}H NMR (500 MHz, acetone-d_6) δ 9.12 (s, 0.4H from A), 8.74 (s, 0.6H from B), 6.26 (s, 1.2H from B), 6.13 (s, 0.8H from A), 2.84 (s, 2.4H from B), 2.80 (s, 1.6H from A). Two tautomers: ^{13}C NMR (125 MHz, acetone-d_6) δ 177.0 (B), 176.5 (A), 154.0 (B), 145.1 (A), 53.6 (B), 49.1(A), 28.9 (B), 28.9 (A). Anal. Calcd for $C_6H_7N_5O_2$ (181.5): C, 39.78; H, 3.89; N, 38.66. Found: C, 39.52; H, 4.23; N, 37.90.

2-((2*H*-Tetrazol-2-yl)methyl)isoindoline-1,3-dione (9c). The reaction was carried out in acetonitrile, and the product was crystallized from toluene to give white crystals (60%): mp 139.0−145.0 °C. Two tautomers: ^{1}H NMR (500 MHz, acetone-d_6) δ 9.29(s, 0.2H from A), 8.76 (s, 0.8H from B), 7.99−7.92 (m, 6H), 6.54 (s, 2H from B), 6.41 (s, 0.5H from A). Two tautomers: ^{13}C NMR (125 MHz, acetone-d_6) δ 167.4 (A), 167.0 (B), 154.2 (B), 145.0 (A), 136.0 (B), 135.8 (A), 132.7 (A), 123.6 (B), 124.7 (B), 124.6 (A), 53.5 (B), 49.0 (A). Anal. Calcd for $C_{10}H_7N_5O_2$ (229.2): C, 52.40; H, 3.08; N, 30.56. Found: C, 52.65; H, 3.30; N, 30.02.

N-((1*H*-Tetrazol-1-yl)methyl)-1,2-benzisothiazole-3(2*H*)-one 1,1-Dioxide (9d). The product was obtained as yellow crystals that turned white upon washing with methylene chloride (60%): mp 177.0−179.0 °C. Two tautomers: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 0.5H from B), 9.09 (s, 0.1H from A), 8.39−8.37 (m, 1H), 8.22−8.18 (m, 1H), 8.12−8.09 (m, 1H), 8.07−8.03 (m, 1H), 6.71 (s, 0.5H from A), 6.56 (s, 2H from B). Two tautomers: ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.0, 153.9, 144.7, 136.6, 135.6, 125.7, 125.6, 121.9, 48.4. Anal. Calcd for $C_9H_7N_5O_3S\cdot{}^1/_2H_2O$ (283.27): C, 39.41; H, 2.94; N, 25.54. Found: C, 39.37; H, 2.80; N, 24.60.

Supporting Information Available: ^{1}H and ^{13}C spectra for all reported compounds, 2D NMR spectra for **9b**,**c**,**d**,**f** and full details of the X-ray crystal structure of **9i**. This material is available free of charge via the Internet at http://pubs.acs.org.