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Three-component reaction of ketals, isonitriles, and trimethylsilyl azide

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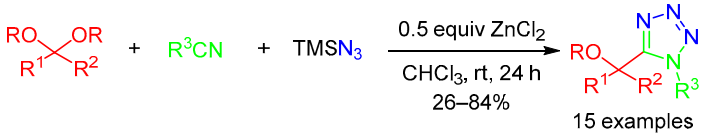


It was demonstrated that a $ZnCl_2$-catalyzed three-component reaction of ketals, isonitriles, and trimethylsilyl azide led to 1,5-disubstituted tetrazoles in moderate to high yields.

Keywords: isonitrile, ketal, tetrazole, trimethylsilyl azide, Passerini reaction.

Tetrazole derivatives represent an important class of heterocyclic compounds that are highly relevant to the search for new biologically active compounds.[1–4] Libraries of such compounds, including tetrazoles, for the use in biological activity screening programs are often created through multicomponent reactions.[5–7] One such reaction is the well-studied interaction of iminium salts with isonitriles and HN_3 or azides – the Ugi-azide reaction, leading to 1,5-disubstituted tetrazoles.[7,8] Iminium salts can be generated *in situ* from carbonyl compounds and amines (the four-component variant) or can be isolated prior to the use in reaction (the three-component variant). A direct reaction of carbonyl compounds with isonitriles and HN_3 (or azides) is also known – it is a variant of the Passerini reaction.[7,9] The process proceeds through the formation of protonated forms of carbonyl compounds, the oxocarbenium ions (or their equivalents). In the case of aldehydes, the reaction produced good yields of 1,5-disubstituted tetrazoles, while the fraction of products arising from the two-component interaction of azide with isonitrile increased for the less reactive ketones, leading to tetrazoles that were monosubstituted at position 1.[9] Good product yields in the three-component reaction with ketones were successfully obtained by using aluminum azide.[9] An effective procedure was proposed very recently for performing the Passerini reaction with trimethylsilyl azide under ultrasonication conditions.[10] Acetals and ketals were also reactive toward isonitriles and produced various products.[11,12] But the three-component reaction of acetals with isonitriles and azide was described with a very limited number of examples featuring cyclic acetals of such specific class as 2-methoxyisochromanes.[13] Analogous transformations of ketals have not been studied.

While continuing our efforts toward the synthesis of tetrazoles through multicomponent reactions involving isonitriles,[14–17] we decided to examine the interaction of ketals with isonitriles and trimethylsilyl azide. The selected model compounds were cyclohexanone dimethyl ketal (**1a**) and benzyl isonitrile (**2a**) (Scheme 1). The main focus during the screening of reaction conditions was toward the use of Lewis acids in aprotic solvent, in order to minimize the two-component interaction of ketal with isonitrile and to prevent side reactions involving nucleophiles that are different than azide. It was found that in the presence of 50 mol % of such readily available and cheap catalyst as $ZnCl_2$ the expected three-component reaction produced a good yield of tetrazole **3a** (Table 1). The other Lewis acids that were tried in this reaction were not effective. The structure of compound **3a** was proved by using its spectral data set and results of elemental analysis (Experimental).

The proposed mechanism of this transformation can be described in the following way (Scheme 1). The initial coordination of Lewis acid at the oxygen atom of the ketal moiety is followed by the formation of the oxocarbenium ion **4**, which reacts with isonitrile and is converted to the nitrilium ion **5**, with subsequent cyclization with azide forming a tetrazole ring.

It is interesting to note that cyclohexanone itself under the indicated conditions formed the 1,5-disubstituted tetrazole **6** in merely 23% yield, while the main product

Scheme 1

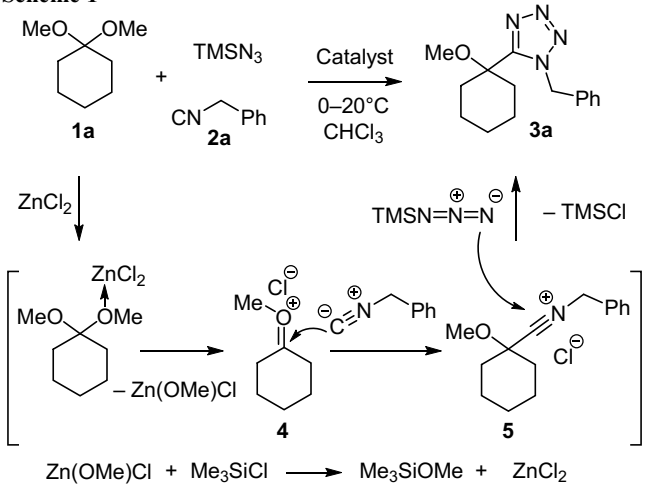


Table 1. Optimization of synthesis conditions for tetrazole **3a**

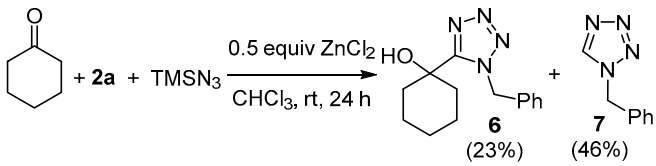
Catalyst (equiv)	Yield, %	Catalyst (equiv)	Yield, %
TfOH (0.2)	0	$AlCl_3$ (0.5)	15
$ZnCl_2$ (0.2)	26	$BF_3{\cdot}Et_2O$ (0.5)	0
$ZnCl_2$ (0.5)	76	$SnCl_4$ (0.5)	14
$ZnCl_2$ (1.0)	61	$SnCl_4$ (0.2)	8

was 1-benzyltetrazole (**7**) (46%) (Scheme 2). The spectral characteristics of compounds **6** and **7** were in agreement with previously published data.[8,10]

The developed methodology was extended to a series of ketals (Table 2).

It was found that the ring size (5–7 atoms) and the character of ketone group in dimethyl ketals **1a**–**e** did not have a strong effect on the effectiveness of this three-component process – the respective tetrazoles **3a**–**e** were obtained in good to high yields (Table 2, entries 1–5). The nature of isonitrile had a more significant effect – yields in the range from good to high were observed for the reactions of benzyl isonitrile (**2a**) and *p*-methoxyphenyl isonitrile (**2c**) (entries 1, 2, 5 and 7, 9, 11, respectively), while the yields were substantially lower for aromatic isonitriles that did not contain electron-donating groups (nitriles **2b** and **2d**) (entries 6, 8, 10, 12). Analogous results were obtained in the reaction of isonitriles **2a**,**c**,**d** and trimethylsilyl azide with diethyl ketal **1f** (entries 13–15).

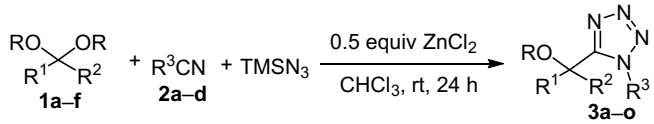
Scheme 2



Entirely different results were observed after reacting the aromatic isonitrile **2e** containing an ester group at the *ortho* position with ketal **1e** (Scheme 3). Instead of the respective tetrazole, the isolated product turned out to be amide **8**, which was apparently formed as a result of hydrolysis during the silica gel chromatography of compound **9**, the product of formal isonitrile insertion at the ketal **1e** C–O bond.[11,12] The formation of the insertion product in this case was probably facilitated by coordination between Zn(OMe)Cl and the oxygen atom of ester group in nitrilium salt **10**.

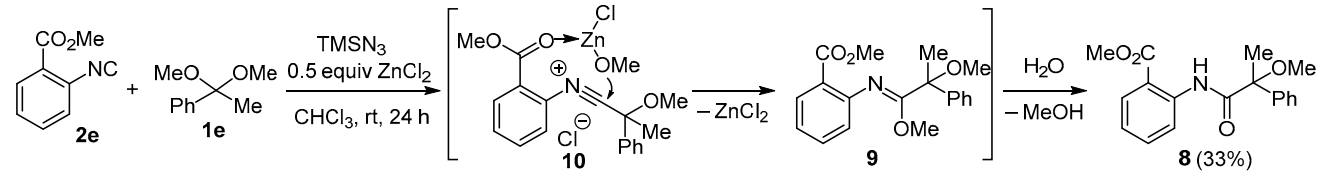
The approach that we developed was applied to the reaction of 2-methoxytetrahydropyran (**11**), which can be viewed as a cyclic acetal. Achieving acceptable yields in this case required an increased amount of catalyst and longer reaction time (Scheme 4). The obtained products **12** were of interest as analogs of nucleosides.

Table 2. The conditions for reactions between ketals **1a**–**f**, isonitriles **2**–**d**, and $TMSN_3$ and the yields of tetrazoles **3a**–**o**

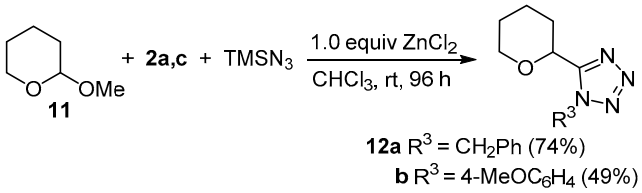


Entry	Ketal	Isonitrile	Tetrazole	R	R^1	R^2	R^3	Yield, %
1	**1a**	**2a**	**3a**	Me	Cyclohexyl		$PhCH_2$	76
2	**1b**	**2a**	**3b**	Me	Cyclopentyl		$PhCH_2$	84
3	**1c**	**2a**	**3c**	Me	Cycloheptyl		$PhCH_2$	78
4	**1d**	**2a**	**3d**	Me	Bu	Et	$PhCH_2$	80
5	**1e**	**2a**	**3e**	Me	Ph	Me	$PhCH_2$	76
6	**1a**	**2b**	**3f**	Me	Cyclohexyl		Ph	35
7	**1a**	**2c**	**3g**	Me	Cyclohexyl		$4\text{-}MeOC_6H_4$	82
8	**1a**	**2d**	**3h**	Me	Cyclohexyl		$4\text{-}ClC_6H_4$	41
9	**1b**	**2c**	**3i**	Me	Cyclopentyl		$4\text{-}MeOC_6H_4$	66
10	**1b**	**2d**	**3j**	Me	Cyclopentyl		$4\text{-}ClC_6H_4$	29
11	**1e**	**2c**	**3k**	Me	Ph	Me	$4\text{-}MeOC_6H_4$	54
12	**1e**	**2d**	**3l**	Me	Ph	Me	$4\text{-}ClC_6H_4$	43
13	**1f**	**2a**	**3m**	Et	Cyclohexyl		$PhCH_2$	72
14	**1f**	**2c**	**3n**	Et	Cyclohexyl		$4\text{-}MeOC_6H_4$	80
15	**1f**	**2d**	**3o**	Et	Cyclohexyl		$4\text{-}ClC_6H_4$	26

Scheme 3



Scheme 4



Thus, we have demonstrated that ketals of aromatic and aliphatic ketones participate in a three-component reaction with isonitriles and trimethylsilyl azide in the presence of the readily available and cheap $ZnCl_2$ catalyst, leading to the formation of 1,5-disubstituted tetrazoles.

Experimental

IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer in thin film (diamond ATR accessory, 4000–400 cm^{-1} range). ^1H and ^{13}C NMR spectra were recorded on a Bruker-400 instrument (400 and 100 MHz, respectively) in $CDCl_3$, with the residual solvent protons as internal standard (7.26 and 77.2 ppm, respectively). The LC-MS analysis was performed on a system consisting of an Agilent 1100 Series liquid chromatograph, Agilent Technologies LC/MSD VL mass spectrometer (electrospray ionization), and a Sedex 75 ELSD detector. Elemental analysis was performed on a EuroVector EA-3000 elemental analyzer. Melting points were determined in capillaries on an SMP 10 apparatus. Sorbfil plates were used for thin-layer chromatography (visualization with iodine vapor), while silica gel from Macherey Nagel GmbH & Co (0.04–0.06 mm / 230–400 mesh, 60 Å) was used for column chromatography. The solvents were purified according to standard procedures. Ketals **1a-f**,[18,19] isonitriles **2a-d**,[16,20] and 2-methoxypyran (**11**)[21] were synthesized according to published procedures.

Synthesis of tetrazoles 3a-o (General method). The appropriate isonitrile **2** (1.6 mmol), trimethylsilyl azide (184 mg, 0.211 ml, 1.6 mmol), and anhydrous $ZnCl_2$ (80 mg, 0.6 mmol) were added to a solution of ketal **1** (1.2 mmol) in anhydrous $CHCl_3$ (1.8 ml). The reaction mixture was stirred for 24 h at room temperature, diluted with CH_2Cl_2 (20 ml), washed with 5% aqueous NaOH solution (2×10 ml), saturated NaCl solution (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure, and the residue was separated by silica gel column chromatography, eluting with a 5:1 mixture of hexane–ethyl acetate.

1-Benzyl-5-(1-methoxycyclohexyl)-1*H*-tetrazole (3a). Yield 248 mg (76%), yellowish crystals, mp 72–73°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 2935, 2858, 2207, 1707, 1498, 1455, 1411, 1150, 1068, 934, 723, 694. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24–1.36 (1H, m, H Cy); 1.51–1.65 (5H, m, H Cy); 1.84–1.94 (4H, m, H Cy); 2.87 (3H, s, OCH_3); 5.73 (2H, s, NCH_2); 7.21–7.25 (2H, m, H Ph); 7.27–7.35 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 21.2 (2C); 25.1; 33.8 (2C); 51.0; 51.7; 75.1; 127.8 (2C); 128.6; 128.9 (2C); 134.5; 157.5. Mass spectrum, *m*/*z*: 273 $[M+H]^+$. Found, %: C 66.32; H 7.46; N 20.53. $C_{15}H_{20}N_4O$. Calculated, %: C 66.15; H 7.40; N 20.57.

1-Benzyl-5-(1-methoxycyclopentyl)-1*H*-tetrazole (3b). Yield 260 mg (84%), yellowish crystals, mp 59–60°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3067, 3031, 2976, 2945, 2872, 2835, 1497, 1454, 1421, 1072, 965, 730, 693. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.69–1.83 (4H, m, H Cyp); 2.05–2.13 (2H, m, H Cyp); 2.13–2.21 (2H, m, H Cyp); 2.85 (3H, s, OCH_3); 5.69 (2H, s, NCH_2); 7.26–7.30 (2H, m, H Ph); 7.30–7.36 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 23.6 (2C); 36.3 (2C); 51.6; 52.0; 83.5; 128.0 (2C); 128.7; 129.0 (2C); 134.3; 156.7. Mass spectrum, *m*/*z*: 259 $[M+H]^+$. Found, %: C 65.32; H 7.09; N 21.53. $C_{14}H_{18}N_4O$. Calculated, %: C 65.09; H 7.02; N 21.69.

1-Benzyl-5-(1-methoxycycloheptyl)-1*H*-tetrazole (3c). Yield 268 mg (78%), colorless oil. IR spectrum, ν, cm^{-1}: 3034, 2928, 2858, 2828, 1497, 1455, 1409, 1073, 722, 700. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.45–1.69 (8H, m, H cycloheptyl); 2.04–2.16 (4H, m, H cycloheptyl); 2.87 (3H, s, OCH_3); 5.69 (2H, s, NCH_2); 7.23–7.27 (2H, m, H Ph); 7.27–7.34 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 21.8 (2C); 29.4 (2C); 37.3 (2C); 51.5; 51.8; 79.3; 128.0 (2C); 128.6; 129.0 (2C); 134.4; 158.3. Mass spectrum, *m*/*z*: 287 $[M+H]^+$. Found, %: C 67.32; H 7.78; N 19.53. $C_{16}H_{22}N_4O$. Calculated, %: C 67.11; H 7.74; N 19.56.

1-Benzyl-5-(1-ethyl-1-methoxypentyl)-1*H*-tetrazole (3d). Yield 276 mg (80%), colorless oil. IR spectrum, ν, cm^{-1}: 3034, 2957, 2873, 2832, 1498, 1456, 1409, 1163, 1066, 721, 702. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.57 (3H, t, *J* = 7.5, CH_3); 0.69 (3H, t, *J* = 7.3, CH_3); 0.77–0.86 (2H, m); 0.96–1.12 (2H, m); 1.74–1.82 (1H, m); 1.87–1.97 (2H, m) and 1.99–2.08 (1H, m, $4CH_2$); 3.05 (3H, s, OCH_3); 5.68–5.76 (2H, m, NCH_2); 7.17–7.22 (2H, m, H Ph); 7.22–7.30 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 13.9; 17.2; 22.5; 25.0; 27.8; 34.8; 49.5; 52.4; 80.5; 127.8 (2C); 128.4; 128.7 (2C); 135.1; 156.8. Mass spectrum, *m*/*z*: 289 $[M+H]^+$. Found, %: C 66.77; H 8.43; N 19.38. $C_{16}H_{24}N_4O$. Calculated, %: C 66.64; H 8.39; N 19.43.

1-Benzyl-5-(1-methoxy-1-phenylethyl)-1*H*-tetrazole (3e). Yield 268 mg (76%), white crystals, mp 67–68°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 2992, 2937, 1495, 1456, 1448, 1371, 1133, 1104, 1072, 1040, 877, 768, 722, 698. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (3H, s, CCH_3); 2.95 (3H, s, OCH_3); 5.05 (1H, d, *J* = 14.9) and 5.28 (1H, d, *J* = 14.9, CH_2); 6.95–6.99 (2H, m, H Ph); 7.16–7.23 (5H, m, H Ph); 7.23–7.30 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 25.9; 51.5; 51.6; 76.9; 124.9 (2C); 128.1; 128.3; 128.4 (2C); 128.5 (2C); 128.8 (2C); 133.6; 143.0; 156.6. Mass spectrum, *m*/*z*: 295 $[M+H]^+$. Found, %: C 69.48; H 6.18; N 18.95. $C_{17}H_{18}N_4O$. Calculated, %: C 69.37; H 6.16; N 19.03.

5-(1-Methoxycyclohexyl)-1-phenyl-1*H*-tetrazole (3f). Yield 108 mg (35%), yellowish crystals, mp 56–58°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3061, 2936, 2858, 2831, 1595, 1501, 1455, 1417, 1153, 1072, 769, 691. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25–1.37 (1H, m, H Cy); 1.40–1.47 (2H, m, H Cy); 1.47–1.58 (3H, m, H Cy); 1.87–2.03 (4H, m, H Cy); 3.03 (3H, s, OCH_3); 7.42–7.46 (2H, m, H Ph); 7.49–7.57 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 21.6 (2C); 25.2; 33.6 (2C); 50.8; 74.8; 126.4 (2C); 129.4 (2C); 130.6; 135.6; 157.0. Mass spectrum, *m*/*z*: 259 $[M+H]^+$. Found, %: C 65.32; H 7.09; N 21.53. $C_{14}H_{18}N_4O$. Calculated, %: C 65.09; H 7.02; N 21.69.

5-(1-Methoxycyclohexyl)-1-(4-methoxyphenyl)-1*H*-tetrazole (3g). Yield 283 mg (82%), yellowish oil. IR spectrum, ν, cm^{-1}: 3078, 2939, 2857, 1609, 1590, 1516, 1461, 1254, 1172, 1156, 1071, 1026, 837, 623. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26–1.37 (1H, m, H Cy); 1.41–1.48 (2H, m, H Cy); 1.48–1.60 (3H, m, H Cy); 1.90–2.02 (4H, m, H Cy); 3.04 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 7.00 (2H, d, *J* = 8.9, H Ar); 7.35 (2H, d, *J* = 8.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.5 (2C); 25.0; 33.3 (2C); 50.6; 55.6; 74.6; 114.3 (2C); 127.5 (2C); 128.0; 156.9; 160.9. Mass spectrum, *m*/*z*: 289 $[M+H]^+$. Found, %: C 62.70; H 7.01; N 19.36. $C_{15}H_{20}N_4O_2$. Calculated, %: C 62.48; H 6.99; N 19.43.

1-(4-Chlorophenyl)-5-(1-methoxycyclohexyl)-1*H*-tetrazole (3h). Yield 144 mg (41%), amber colored crystals, mp 80–81°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 2944, 2864, 2854, 1495, 1458, 1411, 1242, 1157, 1084, 1012, 926, 830, 561. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29–1.38 (1H, m, H Cy); 1.44–1.52 (2H, m, H Cy); 1.52–1.63 (3H, m, H Cy); 1.90–1.98 (2H, m, H Cy); 1.98–2.05 (2H, m, H Cy); 3.04 (3H, s, OCH_3); 7.44 (2H, d, *J* = 8.8, H Ar); 7.52 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.6 (2C); 25.1; 33.6 (2C); 50.8; 74.8; 127.6 (2C); 129.7 (2C); 134.1; 136.8; 157.2. Mass spectrum, *m*/*z*: 293 $[M+H]^+$. Found, %: C 57.42; H 5.91; N 19.03. $C_{14}H_{17}ClN_4O$. Calculated, %: C 57.44; H 5.85; N 19.14.

5-(1-Methoxycyclopentyl)-1-(4-methoxyphenyl)-1*H*-tetrazole (3i). Yield 217 mg (66%), yellowish crystals, mp 74–76°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3088, 3012, 2947, 2876, 2842, 2828, 1609, 1590, 1516, 1464, 1253, 1177, 1095, 1067, 837, 625. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.63–1.76 (4H, m, H Cyp); 1.99–2.07 (2H, m, H Cyp); 2.08–2.16 (2H, m, H Cyp); 3.02 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 7.00 (2H, d, *J* = 8.8, H Ar); 7.40 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.2 (2C); 35.9 (2C); 51.5; 55.7; 82.6; 114.4 (2C); 127.4 (2C); 127.7; 156.6; 161.1. Mass spectrum, *m*/*z*: 275 $[M+H]^+$. Found, %: C 61.19; H 6.64; N 20.37. $C_{14}H_{18}N_4O_2$. Calculated, %: C 61.30; H 6.61; N 20.42.

1-(4-Chlorophenyl)-5-(1-methoxycyclopentyl)-1*H*-tetrazole (3j). Yield 97 mg (29%), yellowish oil. IR spectrum, ν, cm^{-1}: 3098, 2949, 2873, 2826, 1497, 1407, 1197, 1091, 1068, 1013, 955, 832, 528. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67–1.80 (4H, m, H Cyp); 2.02–2.10 (2H, m, H Cyp); 2.12–2.19 (2H, m, H Cyp); 3.04 (3H, s, OCH_3); 7.49–7.53 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.3 (2C); 36.1 (2C); 51.6; 82.7; 127.4 (2C); 129.7 (2C); 133.6; 136.8; 156.7. Mass spectrum, *m*/*z*: 279 $[M+H]^+$. Found, %: C 55.94; H 5.46; N 20.03. $C_{13}H_{15}ClN_4O$. Calculated, %: C 56.02; H 5.42; N 20.10.

1-(4-Methoxyphenyl)-5-(1-methoxy-1-phenylethyl)-1*H*-tetrazole (3k). Yield 201 mg (54%), white crystals, mp 112–113°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3052, 2997, 2963, 2935, 2834, 1610, 1593, 1516, 1467, 1446, 1369, 1308, 1256, 1183, 1127, 1106, 1073, 1044, 826, 703, 624. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.05 (3H, s, CCH_3); 3.18 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 6.70 (2H, d, *J* = 9.1, H Ar); 6.74 (2H, d, *J* = 9.1, H Ar); 7.05–7.09 (2H, m, H Ph); 7.16–7.20 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 25.9; 51.4; 55.6; 76.8; 113.7 (2C); 125.0 (2C); 127.3 (3C); 127.7; 128.3 (2C); 143.2; 157.5; 160.6. Mass spectrum, *m*/*z*: 311 $[M+H]^+$. Found, %: C 65.68; H 5.88; N 17.97. $C_{17}H_{18}N_4O_2$. Calculated, %: C 65.79; H 5.85; N 18.05.

1-(4-Chlorophenyl)-5-(1-methoxy-1-phenylethyl)-1*H*-tetrazole (3l). Yield 162 mg (43%), white crystals, mp 120–121°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3068, 2997, 2970, 2933, 2836, 1496, 1449, 1367, 1248, 1196, 1123, 1095, 1075, 1035, 1012, 830, 776, 752, 704, 600. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (3H, s, CCH_3); 3.20 (3H, s, OCH_3); 6.82 (2H, d, *J* = 8.8, H Ar); 7.05–7.10 (2H, m, H Ar); 7.18–7.22 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 25.9; 51.5; 76.9; 125.0 (2C); 127.4 (2C); 128.0; 128.5 (2C); 128.9 (2C); 133.2; 136.4; 143.0; 157.5. Mass spectrum, *m*/*z*: 315 $[M+H]^+$. Found, %: C 59.89; H 4.81; N 17.78. $C_{16}H_{15}ClN_4O$. Calculated, %: C 61.05; H 4.80; N 17.80.

1-Benzyl-5-(1-ethoxycyclohexyl)-1*H*-tetrazole (3m). Yield 247 mg (72%), white crystals, mp 61–63°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3036, 2983, 2941, 2880, 2863, 1607, 1497, 1445, 1422, 1314, 1150, 1061, 980, 904, 774, 736, 691. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.26–1.37 (1H, m, H Cy); 1.51–1.68 (5H, m, H Cy); 1.88–1.96 (2H, m, H Cy); 2.01–2.10 (2H, m, H Cy); 3.12 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 5.79 (2H, s, NCH_2); 7.16–7.21 (2H, m, H Ph); 7.29–7.37 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 15.4; 21.4 (2C); 25.2; 34.3 (2C); 51.5; 58.6; 74.5; 127.3 (2C); 128.0 (2C); 128.5; 134.6; 157.9. Mass spectrum, *m*/*z*: 287 $[M+H]^+$. Found, %: C 67.30; H 7.78; N 19.49. $C_{16}H_{22}N_4O$. Calculated, %: C 67.11; H 7.74; N 19.56.

5-(1-Ethoxycyclohexyl)-1-(4-methoxyphenyl)-1*H*-tetrazole (3n). Yield 290 mg (80%), yellowish crystals, mp 78–79°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 2986, 2937, 2901, 2858, 1610, 1515, 1453, 1306, 1254, 1173, 1153, 1063, 1029, 903, 835, 622. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.29–1.39 (1H, m, H Cy); 1.40–1.65 (5H, m, H Cy); 1.95–2.05 (4H, m, H Cy); 3.22 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 3.89 (3H, s, OCH_3); 7.01 (2H, d, *J* = 8.9, H Ar); 7.39 (2H, d, *J* = 8.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 15.3; 21.8 (2C); 25.3; 34.1 (2C); 55.8; 58.1; 74.3; 114.5 (2C); 127.7 (2C); 128.4; 157.2; 161.0. Mass spectrum, *m*/*z*: 303 $[M+H]^+$. Found, %: C 63.61; H 7.35; N 18.49. $C_{16}H_{22}N_4O_2$. Calculated, %: C 63.55; H 7.33; N 18.53.

1-(4-Chlorophenyl)-5-(1-ethoxycyclohexyl)-1*H*-tetrazole (3o). Yield 95 mg (26%), yellowish crystals, mp 90–91°C (EtOAc–hexane). IR spectrum, ν, cm^{-1}: 3074, 2972, 2963, 2934, 1497, 1451, 1271, 1153, 1093, 1064, 1006, 978, 903, 836, 746. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.31–1.40 (1H, m, H Cy); 1.42–1.50 (2H, m, H Cy); 1.50–1.64 (3H, m, H Cy); 1.94–2.07 (4H,

m, H Cy); 3.21 (2H, q, J = 7.0, $C\underline{H}_2CH_3$); 7.48 (2H, d, J = 8.7, H Ar); 7.52 (2H, d, J = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 15.2; 21.7 (2C); 25.2; 34.1 (2C); 58.2; 74.3; 127.6 (2C); 129.6 (2C); 134.1; 136.7; 157.0. Mass spectrum, *m/z*: 307 $[M+H]^+$. Found, %: C 58.71; H 6.29; N 18.28. $C_{15}H_{19}ClN_4O$. Calculated, %: C 58.73; H 6.24; N 18.26.

Reaction of cyclohexanone with benzyl isonitrile (2a) and trimethylsilyl azide. Benzyl isonitrile (**2a**) (152 mg, 1.3 mmol), trimethylsilyl azide (150 mg, 0.17 ml, 1.3 mmol), and anhydrous $ZnCl_2$ (68 mg, 0.5 mmol) were added to a solution of cyclohexanone (98 mg, 1.0 mmol) in anhydrous $CHCl_3$ (1.5 ml). The reaction mixture was stirred at room temperature for 24 h, diluted with CH_2Cl_2 (20 ml), washed with 5% NaOH solution (2×10 ml), saturated NaCl solution (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure, the residue was separated by silica gel column chromatography, eluting with 3:1 hexane–EtOAc mixture. The isolated products were 1-(1-benzyl-1*H*-tetrazol-5-yl)cyclohexanol (**6**) (59 mg, 23%) and 1-benzyl-1*H*-tetrazole (**7**) (74 mg, 46%), with spectral characteristics that matched the literature data.[8,10]

Methyl 2-[(2-methoxy-2-phenylpropane)amido]benzoate (8). The compound was obtained according to the general method for the synthesis of tetrazoles **3a**–**o**, except that $TMSN_3$ did not participate in this reaction. Yield 124 mg (33%), yellowish oil. IR spectrum, ν, cm^{-1}: 3265 (br.), 2986, 2952, 2832, 1694, 1585, 1516, 1449, 1266, 1137, 1086, 1049, 756, 699. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.89 (3H, s, CCH_3); 3.39 (3H, s, OCH_3); 3.96 (3H, s, OCH_3); 7.04–7.09 (1H, m, H Ar); 7.26–7.31 (1H, m, H Ar); 7.33–7.38 (2H, m, H Ar); 7.46–7.52 (1H, m, H Ar); 7.56–7.60 (2H, m, H Ar); 8.03 (1H, dd, J = 1.7, J = 8.0, H Ar); 8.72 (1H, dd, J = 1.7, J = 8.6, H Ar); 12.10 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 20.6; 51.8; 52.4; 82.7; 116.0; 120.4; 122.7; 126.3 (2C); 127.9; 128.5 (2C); 131.0; 134.5; 141.0; 141.1; 168.2; 172.9. Mass spectrum, *m/z*: 314 $[M+H]^+$. Found, %: C 69.23; H 6.08; N 4.53. $C_{18}H_{19}NO_4$. Calculated, %: C 69.00; H 6.11; N 4.47.

1-Benzyl-5-(tetrahydro-2*H*-pyran-2-yl)-1*H*-tetrazole (12a). Benzyl isonitrile (**2a**) (200 mg, 1.7 mmol), trimethylsilyl azide (196 mg, 0.223 ml, 1.7 mmol), and anhydrous $ZnCl_2$ (177 mg, 1.3 mmol) were added to a solution of 2-methoxytetrahydropyran (**11**) (150 mg, 1.3 mmol) in anhydrous $CHCl_3$ (1.8 ml). The reaction mixture was stirred at room temperature for 96 h, diluted with CH_2Cl_2 (20 ml), washed with 5% NaOH solution (2×20 ml), saturated NaCl solution (10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was separated by silica gel column chromatography, eluting with hexane–EtOAc mixture. Yield 235 mg (74%), yellowish oil. IR spectrum, ν, cm^{-1}: 2942, 2852, 1455, 1203, 1086, 1045, 911, 721, 695. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.70 (3H, m, H pyran); 1.77–1.88 (1H, m, H pyran); 1.89–1.99 (1H, m, H pyran); 1.99–2.09 (1H, m, H pyran); 3.49–3.60 (1H, m, H pyran); 3.98–4.08 (1H, m, H pyran); 4.57 (1H, dd, J = 2.8, J = 10.7, H pyran); 5.63 (1H, d, J = 15.0) and 5.73 (1H, d, J = 15.0, NCH_2); 7.22–7.30 (2H, m, H Ph); 7.31–7.42 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 22.4; 25.4; 29.3; 51.9; 68.6; 70.7; 128.2 (2C); 128.8; 129.0 (2C); 134.1; 154.2. Mass spectrum, *m/z*: 245 $[M+H]^+$. Found, %: C 63.99; H 6.64; N 22.89. $C_{13}H_{16}N_4O$. Calculated, %: C 63.91; H 6.60; N 22.93.

1-(4-Methoxyphenyl)-5-(tetrahydro-2*H*-pyran-2-yl)-1*H*-tetrazole (12b) was obtained analogously to compound **12a**. Yield 166 mg (49%), yellowish oil. IR spectrum, ν, cm^{-1}: 2939, 2844, 1609, 1508, 1443, 1250, 1172, 1083, 1043, 1023, 834, 637, 546. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47–1.59 (2H, m, H pyran); 1.59–1.71 (1H, m, H pyran); 1.80–1.89 (1H, m, H pyran); 1.92–2.03 (1H, m, H pyran); 2.08–2.22 (1H, m, H pyran); 3.43–3.52 (1H, m, H pyran); 3.85 (3H, s, OCH_3); 3.93–4.00 (1H, m, H pyran); 4.52 (1H, dd, J = 2.6, J = 10.8, H pyran); 7.01 (2H, d, J = 9.0, H Ar); 7.46 (2H, d, J = 9.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.5; 25.2; 28.8; 55.7; 68.6; 69.0; 114.7 (2C); 126.4 (2C); 126.8; 154.2; 161.0. Mass spectrum, *m/z*: 261 $[M+H]^+$. Found, %: C 60.32; H 6.28; N 21.45. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.99; H 6.20; N 21.52.

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