JOC The Journal of Organic Chemistry

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1-Alkyl-5-((di)alkylamino) Tetrazoles: Building Blocks for Peptide Surrogates

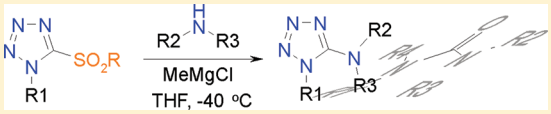
Andriy V. Tymtsunik,[†,‡] Vitaliy A. Bilenko,[‡] Serhiy O. Kokhan,[†,‡] Oleksandr O. Grygorenko,*[,†,‡] Dmitriy M. Volochnyuk,[‡] and Igor V. Komarov[†,‡]

[†]Kyiv National Taras Shevchenko University, Volodymyrska Street 64, Kyiv 01601, Ukraine

[‡]Enamine Ltd., Alexandra Matrosova Street 23, Kyiv 01103, Ukraine

Supporting Information

ABSTRACT: An approach to the synthesis of 1-alkyl-5-((di)-alkylamino)tetrazoles by nucleophilic substitution in 1-alkyl-5-sulfonyl-tetrazoles with anions generated from the primary or secondary amines was developed. Tolerance of the method to the presence of some functional groups (i.e., protected amine) in both components of the reaction was demonstrated. Obtained tetrazoles are promising building blocks for the design of peptide surrogates, in particular, for replacement approaches of alkyl urea derivatives.



Tetrazole derivatives have attracted close attention in bioorganic and medicinal chemistry in recent years.[1] The tetrazole moiety is a well-known nonclassical bioisostere for the carboxylate,[2] whereas 1,5-disubstituted tetrazoles are considered as a replacement for the *cis*-peptide bonds (Figure 1).[3]

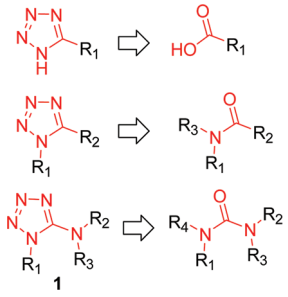


Figure 1. Tetrazoles as potential surrogates of functional groups.

Tetrazole derivatives were used in the discovery of cephalosporin antibiotics (e.g., Cefoperazone). Recently, the 1,5-disubstituted tetrazole moiety was incorporated into the molecule of Smac peptidomimetic, a potential anticancer agent.[4]

1-Alkyl-5-((di)alkylamino)tetrazoles **1** represent a promising chemotype for the design of the peptide surrogates and other molecules of potential interest to bioorganic and medicinal chemistry. Favorable physicochemical properties of these tetrazole derivatives, their remarkable metabolic stability, and multiple possibilities for the interaction with the biological targets provide unique means for that. In particular, the 1-alkyl-5-(alkylamino)tetrazole moiety might be considered as a potential replacement of an alkyl urea derivatives, which themselves are peptide isosteres used in the discovery of human soluble epoxide inhibitors hydrolase,[5] calcitonin mimetics,[6] cathepsin inhibitors,[7] β_1 adrenergic receptor ligands (Xamoterol **2** and Landiolol **3**), and HIV-1 protease inhibitors (Ritonavir **4**) (Figure 2). This suggestion is supported by the fact that

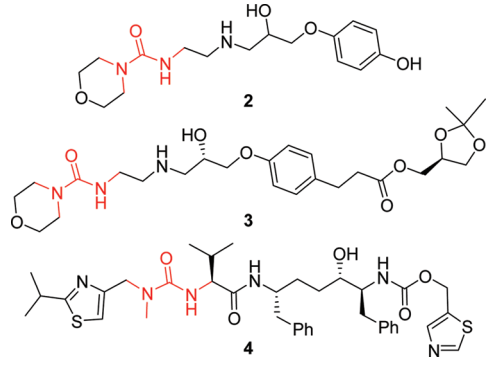


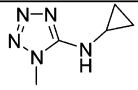
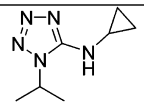
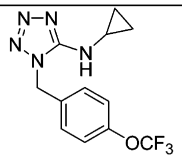
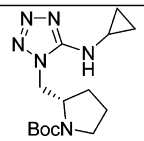
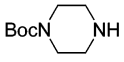
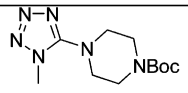
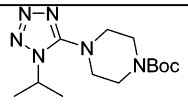
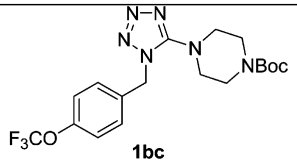
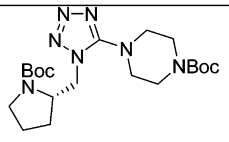
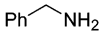
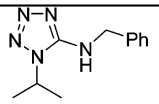
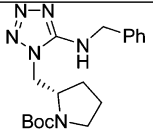
Figure 2. Marketed drugs having an alkyl urea fragment.

some other aminoheterocycles were already considered as urea surrogates.[8]

Most of the known methods for the preparation of 1-alkyl-5-((di)alkylamino)tetrazoles rely on the cyclization or cycloaddition of the properly substituted precursor.[9] Functionalization of the synthetic intermediates that already contain the tetrazole fragment is an alternative and powerful approach that has been scarcely exploited to date. Alkylation of 5-((di)-alkylamino)tetrazoles at the N-1 atom is one of the methods to achieve this; however, this reaction often leads to the mixtures of products.[10] Another approach includes functionalization of 1-alkyl tetrazoles bearing a leaving group (e.g., halo or sulfonyl) at the C-5 atom. Unlike their more reactive 1-aryl counterparts,[11] these tetrazoles have been only scarcely used in nucleophilic substitution reactions to date. The known isolated

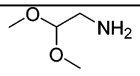
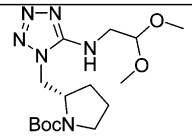
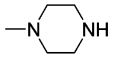
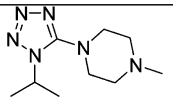
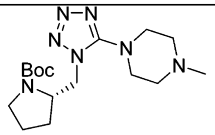
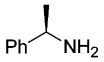
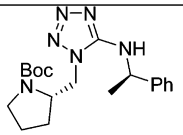
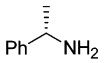
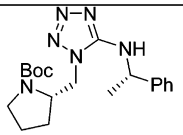
Received: October 29, 2011
Published: December 15, 2011

Table 1. Amination of Tetrazoles 5a−d

Entry No.	Amine	Tetrazole	Product	Yield, %
1	 **6a**	**5a**	 **1aa**	76
2		**5b**	 **1ab**	85
3		**5c**	 **1ac**	82
4		**5d**	 **1ad**	92
5	 **6b**	**5a**	 **1ba**	73
6		**5b**	 **1bb**	78
7		**5c**	 **1bc**	77
8		**5d**	 **1bd**	80
9	 **6c**	**5b**	 **1cb**	82
10		**5d**	 **1cd**	85

dx.doi.org/10.1021/jo2022235 | *J. Org. Chem.* 2012, 77, 1174−1180

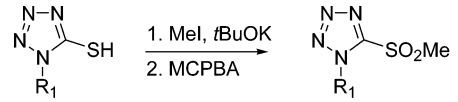
Table 1. continued

Entry No.	Amine	Tetrazole	Product	Yield, %
11	 **6d**	**5b**	–	–
12		**5d**	 **1dd**	77
13	 **6e**	**5b**	 **1eb**	62
14		**5d**	 **1ed**	58
15	 **6f**	**5d**	 **1fd**	83
16	 **6g**	**5d**	 **1gd**	80
17	 **6h**	**5b**	–	–

examples of using amines as nucleophiles in the reaction with 1-alkyl tetrazoles bearing a leaving group differ significantly in the reaction conditions and hence lack generality.[12] In particular, reaction of 1-benzyl-5-bromotetrazole with benzylamine gave the substitution product in good yield.[13] Nucleophilic substitution in 1-methyl-5-(methylsulfonyl)tetrazole (**5a**) using azole anions as the *N*-nucleophiles has been described.[14] Amination of **5a** with a primary amine was also reported; however, the corresponding product was obtained in 22% yield.[15] An interesting transformation of the properly functionalized 1-alkyl-5-(alkylsulfonyl)tetrazoles to **1** through intramolecular nucleophilic substitution can also be mentioned.[15]

In this work, we wish to report a convenient approach to the synthesis of 1-alkyl-5-((di)alkylamino)tetrazoles by nucleophilic substitution in 1-alkyl-5-sulfonyltetrazoles. We have turned our attention to these compounds as they are readily available in a few steps from common starting materials, either through sulfur alkylation−oxidation of 1-alkyltetrazole-5-thiols[15,16] or by [3 + 2] cycloaddition of alkyl azides and tosyl cyanide.[17] Apart from the simplest representatives **5a** and **5b**, a fluorine-containing tetrazole **5c** and a proline-derived tetrazole **5d** were included in this study (Table 1), keeping in mind the potential use of the final products as the building blocks for the peptide surrogates. Compounds **5a−d** were prepared using the general methods mentioned above (Schemes 1−3).

Scheme 1

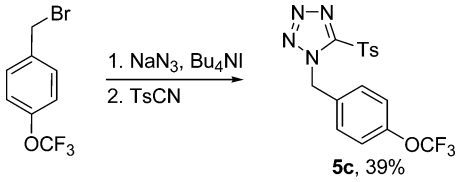


5a, R_1 = Me, 52%
5b, R_1 = *i*Pr, 59%

As it turned out soon, tetrazoles **5** are not sufficiently reactive toward amine nucleophiles at reasonable reaction conditions. In particular, no product **1ab** was detected by LC−MS and NMR in the reaction of the compound **5b** and cyclopropylamine **6a**

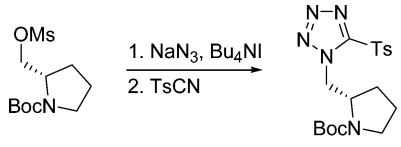
dx.doi.org/10.1021/jo2022235 | *J. Org. Chem.* 2012, 77, 1174−1180

Scheme 2



5c, 39%

Scheme 3



5d, 43%

even upon heating of the starting materials without solvent in a sealed tube at 100 °C for 48 h. We have found that deprotonation of **6a** by action of the methyl magnesium chloride in THF solves the reactivity problem: the corresponding anion and **5b** smoothly reacted at −40 °C to rt overnight.[18] To demonstrate the utility of this procedure, tetrazoles **5a−d** were tested in the reaction with **6a**, as well as *N*-Boc-piperazine **6b** containing an additional protected amino function (Table 1). It was found that tetrazoles **5a−d** showed similar reactivity toward anions generated from **6a** and **6b**; the corresponding products **1aa−1bd** were obtained in 73−92% yields.

In addition to **6a** and **6b**, amines **6c−6h** containing aromatic substituents, a hidden aldehyde moiety, or a basic tertiary amine center were also tested in the reaction with tetrazoles **5b** and **5d**. It was found that the anions formed from the amines **6a−6c**, **6e**, and **6f** smoothly reacted with the tetrazoles **5** to give the corresponding products **1cb−1fd** in good yields (58−92%). Under the same reaction conditions, yields of the tetrazoles **1eb** and **1ed** were diminished due to incomplete conversion. Nevertheless, **1eb** and **1ed** were obtained in 58−62% yields after a prolonged reaction time. We attribute this fact to lower nucleophilicity of the anion formed from **6e**, which is related to its relatively tight chelation with the magnesium ion. Moreover, the anion generated from the amine **6d** also showed low reactivity in these transformations. In particular, less than 10% yield of the corresponding tetrazole was detected in the crude product only when 10-fold excess of the reagent was used in the reaction with **5b**. It should be noted that the products presumably arising from the deprotonation of **5b** at the methylsulfonyl moiety were detected by LC−MS and NMR in this case. The reaction with **5d** was also slower, although the corresponding product **1bd** still was obtained in 80% yield. As in the case of **6e**, we attribute lowered reactivity of the anion of **6d** to its chelation with the magnesium ion. These results allow the assumption that the tosyl-substituted tetrazoles are a better choice as the substrates for the preparation of **1** if reactivity problems are expected.

The sterically hindered anion generated from the amine **6h** was unreactive toward nucleophilic substitution in the tetrazole **5b**; in this case, no traces of the corresponding product were detected in the crude product.

To prove that in the case of the optically active tetrazole **5d** the final products were obtained as single stereoisomers, reaction with both enantiomers **6f** and **6g** was performed. ^{1}H NMR spectra of **1fd** and **1gd** were remarkably similar; nevertheless, they did not contain any trace signals of the corresponding diastereomers.

In conclusion, a simple and effective procedure was developed for the amination of 5-sulfonyltetrazoles. The 1-alkyl-5-((di)alkylamino)tetrazoles obtained by this reaction are promising building blocks for the design of peptidomimetics and other molecules of potential interest to drug discovery and, in particular, as a potential replacement for the alkyl urea derivatives.

EXPERIMENTAL SECTION

General Methods. Solvents were purified according to the standard procedures. 1-Methyl-1*H*-tetrazole-5-thiol,[19] 1-isopropyl-1*H*-tetrazole-5-thiol,[20] 1-(bromomethyl)-4-(trifluoromethoxy)-benzene,[21] and *tert*-butyl (2*S*)-2-{[(methylsulfonyl)oxy]methyl}-pyrrolidine-1-carboxylate[22] were prepared using the procedures reported in the literature. All other starting materials were purchased from the commercial sources. Melting points were measured on an automated melting point system. Column chromatography was performed using silica gel (230−400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz NMR spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13 and 470.3 for fluorine-19) and 400 MHz NMR spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as an internal standard. HPLC−MS analyses were done on a LC−MS instrument (chemical ionization (CI) and electrospray ionization (ESI)) or a GC−MS instrument (electron impact ionization (EI)). Flash chromatography was performed on an automated flash chromatography system.

1-Methyl-5-(methylsulfonyl)-1*H*-tetrazole 5a. To a solution of 1-methyl-1*H*-tetrazole-5-thiol (11.6 g, 0.1 mol) in THF (300 mL) was added *t*BuOK (33.7 g, 0.3 mol) at rt. The resulting mixture was stirred for 10 min, and MeI (18.4 g, 0.130 mol) was added dropwise. The mixture was stirred for 36 h, evaporated to dryness, diluted with 10% aq citric acid (300 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL), and MCPBA (51.8 g, 0.3 mol) was added. The reaction mixture was refluxed for 10 h, then cooled to rt and washed with 1 M aq K_2CO_3 (150 mL). The organic phase was separated, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to give the crude compound **5a**, which was purified by column chromatography. Yield 52%. R_f = 0.82 (hexanes−EtOAc (2:1)). White crystals. Mp 70−72 °C (lit. 72−73 °C).[23] MS (*m*/*z*, EI): 162 (M^+), 119, 79 ($CH_3SO_2^+$). Anal. Calcd for $C_3H_6N_4O_2S$: C 22.22, H 3.73, N 34.55, S 19.77. Found: C 22.54, H 4.01, N 34.51, S 19.80. ^{1}H NMR ($CDCl_3$) δ 4.35 (s, 3H), 3.28 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.1 (C), 43.7 (CH_3), 36.1 (CH_3).

1-Isopropyl-5-(methylsulfonyl)-1*H*-tetrazole 5b. Prepared from 1-isopropyl-1*H*-tetrazole-5-thiol analogously to **5a**. Yield 11 g (59%). R_f = 0.55 (hexanes−EtOAc (2:1)). White crystals. Mp 69−70 °C. MS (*m*/*z*, EI): 190 (M^+), 147, 121, 79 ($CH_3SO_2^+$). Anal. Calcd for $C_5H_{10}N_4O_2S$: C 31.57, H 5.30, N 29.45, S 16.86. Found: C 31.79, H 5.16, N 29.48, S 17.10. ^{1}H NMR ($CDCl_3$) δ 5.28 (sept, J = 6.6 Hz, 1H), 3.60 (s, 3H), 1.68 (d, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) 153.4 (C), 54.5 (CH), 43.8 (CH_3), 22.6 (CH_3).

5-[(4-Methylphenyl)sulfonyl]-1-[4-(trifluoromethoxy)-benzyl]-1*H*-tetrazole 5c. 1-(Bromomethyl)-4-(trifluoromethoxy)-benzene (0.10 mol) was dissolved in DMF (250 mL). NaN_3 (19.5 g, 0.30 mol) and $Bu_4N^+ I^-$ (3.7 g, 0.01 mol) were added subsequently, and the resulting mixture was stirred at 80 °C for at 24 h, then cooled, evaporated under reduced pressure, diluted with water (250 mL), and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give the corresponding azide (16 g) pure enough for the further use. A mixture of this compound and toluenesulfonyl cyanide (0.074 mol) was heated in a sealed tube at 80 °C for 48 h. The crude

dx.doi.org/10.1021/jo2022235 | J. Org. Chem. 2012, 77, 1174−1180

mixture was subjected to column chromatography to give **5c**. Yield 12.9 g (39%). Yellowish crystals. R_f = 0.70 (hexanes−EtOAc (2:1)). Mp 76−77 °C. MS (*m*/*z*, EI): 370 ($M^+ - N_2$), 217, 175 ($CF_3OC_6H_4CH_2^+$), 155, 91 ($C_7H_7^+$). MS (*m*/*z*, ESI): 399 (MH^+). Anal. Calcd for $C_{16}H_{13}F_3N_4O_3S$: C 48.24, H 3.29, N 14.06, S 8.05. Found: C 47.94, H 3.63, N 13.74, S 8.41. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.93 (s, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 155.0 (C), 150.1 (C), 149.8 (C), 134.4 (C), 131.5 (C), 130.49 (CH), 130.46 (CH), 129.3 (CH), 121.6 (CH), 120.4 (q, *J* = 257 Hz, CF_3), 52.1 (CH_2), 22.0 (CH_3). ^{19}F NMR ($CDCl_3$) δ −58.4.

***tert*-Butyl (2*S*)-2-({5-[(4-Methylphenyl)sulfonyl]-1*H*-tetrazol-1-yl}methyl)pyrrolidine-1-carboxylate 5d.** Prepared from *tert*-butyl (2*S*)-2-{[(methylsulfonyl)oxy]methyl}pyrrolidine-1-carboxylate analogously to **5c**. Yield 13.3 g (43%). Yellowish crystals. R_f = 0.43 (hexanes−EtOAc (2:1)). Mp 201−202 °C (dec). Anal. Calcd for $C_{18}H_{25}N_5O_4S$: C 53.06, H 6.18, N 17.19, S 7.87. Found: C 53.37, H 5.90, N 16.89, S 8.06. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.42 (br s, 2H), 4.84 (br s, 1.5H), 4.7 (br s, 0.5H), 4.49 (br m, 1H), 3.32−3.52 (m, 2H), 2.48 (s, 3H), 1.79−2.03 (m, 4H), 1.39 (s, 4.5H), 1.32 (s, 4.5H). ^{13}C NMR ($CDCl_3$) δ 155.5 (C), 154.8 and 154.4 (C), 147.5 (C), 134.7 (C), 130.4 (CH), 129.5 (CH), 80.7 and 80.2 (C), 57.0 and 56.2 (CH), 52.0 (CH_2), 46.8 and 46.6 (CH_2), 29.1 and 28.2 (CH_2), 28.4 (CH_3), 22.7 and 22.8 (CH_2), 22.0 (CH_3).

General Procedure for the Preparation of 1. A solution of the amine **6** (10 mmol) in dry THF (100 mL) was cooled to −10 °C, and MeMgCl (3 M in THF, 4 mL) was added dropwise under argon atmosphere. The obtained mixture was stirred at −10 °C for 1 h, and then cooled to −40 °C. The solution of the compound **5** (5 mmol) in THF (50 mL) was added dropwise at this temperature. The resulting mixture was stirred at −40 °C for 2 h, then slowly warmed to rt, and left for 18−72 h. Silica gel (15 g) was added, and the mixture was stirred at rt for 2 h. SiO_2 was filtered off and washed with MeOH (3 × 30 mL). The combined filtrates were evaporated to give the crude compound **1**, which was purified by column, preparative thin-layer, or flash chromatography.

***N*-Cyclopropyl-1-methyl-1*H*-tetrazol-5-amine, 1aa.** Yield 0.65 g (76%). White crystals. R_f = 0.57 (EtOAc). Mp 138−140 °C. MS (*m*/*z*, ESI): 140 (M^+). Anal. Calcd for $C_5H_9N_5$: C 43.16, H 6.52, N 50.33. Found: C 43.47, H 6.46, N 50.03. ^{1}H NMR ($CDCl_3$) δ 4.76 (br s, 1H), 3.78 (s, 3H), 2.81−2.86 (m, 1H), 0.86 (dd, *J* = 11.9 and 6.5 Hz, 2H), 0.65−0.68 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 156.2 (C), 32.1 (CH_3), 26.0 (CH), 7.8 (CH_2).

***N*-Cyclopropyl-1-isopropyl-1*H*-tetrazol-5-amine, 1ab.** Yield 0.75 g (85%). White crystals. R_f = 0.53 (EtOAc). Mp 82−83 °C. MS (*m*/*z*, EI): 167 (M^+), 138, 124 (c-$C_3H_5NHCN_4^+$), 69, 43 ($(CH_3)_2CH^+$). Anal. Calcd for $C_7H_{13}N_5$: C 50.28, H 7.84, N 41.88. Found: C 50.05, H 8.11, N 42.17. ^{1}H NMR ($CDCl_3$) δ 4.93 (br s, 1H), 3.22 (sept, *J* = 6.6 Hz, 1H), 2.81−2.85 (m, 1H), 1.52 (d, *J* = 6.6 Hz, 6H), 0.82 (dd, *J* = 13.1 and 5.5 Hz, 2H), 0.62−0.65 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.1 (C), 49.0 (CH), 26.0 (CH), 21.8 (CH_3), 7.6 (CH_2).

***N*-Cyclopropyl-1-[4-(trifluoromethoxy)benzyl]-1*H*-tetrazol-5-amine, 1ac.** Yield 0.61 g (82%). White crystals. R_f = 0.54 (EtOAc). Mp 130−131 °C. MS (*m*/*z*, EI): 299 (M^+), 270, 175 ($CF_3OC_6H_4CH_2^+$), 124 (c-$C_3H_5NHCN_4^+$), 69. Anal. Calcd for $C_{12}H_{12}F_3N_5O$: C 48.16, H 4.04, N 23.40. Found: C 48.47, H 3.87, N 23.25. ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 4H), 5.33 (s, 2H), 4.76 (br s, 1H), 2.72−2.76 (m, 1H), 0.78 (dd, *J* = 12.8 and 6.4 Hz, 2H), 0.53−0.56 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 156.0 (C), 149.6 (C), 132.0 (C), 129.0 (CH), 121.8 (CH), 120.5 (q, J = 258 Hz, CF_3), 48.6 (CH_2), 26.0 (CH_3), 7.7 (CH_2). ^{19}F NMR ($CDCl_3$) δ −58.4.

***tert*-Butyl (2*S*)-2-{[5-(Cyclopropylamino)-1*H*-tetrazol-1-yl]methyl}pyrrolidine-1-carboxylate, 1ad.** Yield 0.70 g (92%). White crystals. R_f = 0.54 (EtOAc). Mp 158−160 °C. $[\alpha]_D$ = −19.3 (*c* 0.5, MeOH). MS (*m*/*z*, ESI): 309 (MH^+). Anal. Calcd for $C_{14}H_{24}N_6O_2$: C 54.53, H 7.84, N 27.25. Found: C 54.28, H 7.99, N 27.45. ^{1}H NMR ($CDCl_3$) δ 6.46 (br s, 1H), 4.25−4.29 (m, 1H), 4.05 (d, J = 14.2 Hz, 1H), 3.78 (br s, 1H), 3.21−3.32 (m, 2H), 2.81−2.86 (m, 1H), 2.07 (br s, 1H), 1.93−2.01 (m, 1H), 1.76−1.89 (m, 2H), 1.48 (s, 9H), 0.79−0.85 (m, 2H), 0.62−0.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 156.5 (C), 155.7 (C), 80.9 (C), 56.6 (CH), 48.2 (CH_2), 47.0 (CH_2), 29.5 (CH_2), 28.5 (CH_3), 25.6 (CH), 23.5 (CH_2), 7.3 (CH_2), 7.1 (CH_2).

***tert*-Butyl 4-(1-Methyl-1*H*-tetrazol-5-yl)piperazine-1-carboxylate, 1ba.** Yield 1.21 g (73%). White crystals. R_f = 0.64 (EtOAc). Mp 89−90 °C. MS (*m*/*z*, EI): 268 (M^+), 212, 195, 168, 112, 69, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_{11}H_{20}N_6O_2$: C 49.24, H 7.51, N 31.32. Found: C 49.51, H 7.83, N 31.07. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.58 (t, *J* = 4.9 Hz, 4H), 3.25 (t, *J* = 4.9 Hz, 4H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) 159.0 (C), 154.7 (C), 80.6 (C), 49.6 (CH_2), 43.1 (CH_2), 33.8 (CH_3), 28.49 (CH_3).

***tert*-Butyl 4-(1-Isopropyl-1*H*-tetrazol-5-yl)piperazine-1-carboxylate, 1bb.** Yield 1.22 g (78%). White crystals. R_f = 0.82 (EtOAc). Mp 160−162 °C. MS (*m*/*z*, EI): 296 (M^+), 223, 140, 57 ($(CH_3)_3C^+$). Anal. Calcd for $C_{13}H_{24}N_6O_2$: C 52.68, H 8.16, N 28.36. Found: C 52.95, H 7.05, N 28.03. ^{1}H NMR ($CDCl_3$) δ 4.47 (sept, *J* = 6.7 Hz, 1H), 3.60 (t, *J* = 4.8 Hz, 4H), 3.19 (t, *J* = 4.8 Hz, 4H), 1.59 (d, *J* = 6.7 Hz, 6H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) 158.4 (C), 154.7 (C), 80.6 (C), 50.7 (CH_2), 50.2 (CH), 43.2 (CH_2), 28.5 (CH_3), 22.6 (CH_3).

***tert*-Butyl 4-{1-[4-(Trifluoromethoxy)benzyl]-1*H*-tetrazol-5-yl}piperazine-1-carboxylate, 1bc.** Yield 0.82 g (77%). White crystals. R_f = 0.75 (hexanes−EtOAc (5:1)). Mp 133−134 °C. MS (*m*/*z*, ESI): 429 (MH^+), 373 ($MH^+ - (CH_3)_2C{=}CH_2$). Anal. Calcd for $C_{18}H_{23}F_3N_6O_3$: C 50.46, H 5.41, N 19.62. Found: C 50.29, H 5.37, N 19.66. ^{1}H NMR ($CDCl_3$) δ 7.24−7.29 (m, 4H), 5.42 (s, 2H), 3.50 (t, *J* = 4.7 Hz, 4H), 3.19 (t, *J* = 4.7 Hz, 4H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 158.7 (C), 154.5 (C), 149.5 (C), 132.2 (C), 128.8 (CH), 121.6 (CH), 120.4 (q, *J* = 258 Hz, CF_3), 80.5 (C), 50.01 (CH_2), 49.97 (CH_2), 42.8 (CH_2), 28.4 (CH_3). ^{19}F NMR ($CDCl_3$) δ −58.4.

***tert*-Butyl 4-(1-{[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]methyl}-1*H*-tetrazol-5-yl)piperazine-1-carboxylate, 1bd.** Yield 0.85 g (80%). Yellowish crystals. R_f = 0.78 (EtOAc). Mp 107−109 °C. $[\alpha]_D$ = −8.8 (*c* 0.5, MeOH). MS (*m*/*z*, ESI): 460 (MNa^+), 438 (MH^+). Anal. Calcd for $C_{20}H_{35}N_7O_4$: C 54.90, H 8.06, N 22.41. Found: C 55.17, H 7.93, N 22.40. ^{1}H NMR ($CDCl_3$) δ 4.47 (br d, *J* = 11.7 Hz, 0.8H), 4.33 (br s, 0.4H), 4.08−4.18 (m, 1.8H), 3.60 (s, 4H), 3.22−3.47 (m, 6H), 1.73−2.04 (m, 4H), 1.48 (s, 9H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$) 159.1 (C), 154.9 (C), 154.7 (C), 80.3 (C), 80.2 (C), 55.8 (CH), 49.8 (CH_2), 48.6 (CH_2), 47.0 (CH_2), 43.2 (CH_2), 28.57 (CH_3), 28.51 (CH_3), 28.3 (CH_2), 23.5 (CH_2).

***N*-Benzyl-1-isopropyl-1*H*-tetrazol-5-amine, 1cb.** Yield 0.94 g (82%). White crystals. R_f = 0.77 (EtOAc). Mp 138−140 °C. MS (*m*/*z*, CI): 218 (MH^+), 176, 91 ($C_7H_7^+$). Anal. Calcd for $C_{11}H_{15}N_5$: C 60.81, H 6.96, N 32.23. Found: C 60.99, H 7.15, N 32.36. ^{1}H NMR ($CDCl_3$) δ 7.31−7.39 (m, 5H), 4.65 (d, *J* = 5.4 Hz, 2H), 4.25 (br s, 1H), 4.25 (sept, *J* = 6.6 Hz, 1H), 1.54 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) 154.5 (C), 137.9 (C), 129.0 (CH), 128.2 (CH), 128.2 (CH), 49.1 (CH), 48.9 (CH_2), 21.8 (CH_3).

***tert*-Butyl (2*S*)-2-{[5-(Benzylamino)-1*H*-tetrazol-1-yl]methyl}-pyrrolidine-1-carboxylate, 1cd.** Yield 0.74 g (85%). White crystals. R_f = 0.82 (EtOAc). Mp 166−168 °C. $[\alpha]_D$ = −8.4 (*c* 0.5, MeOH). MS (*m*/*z*, ESI): 359 (MH^+). Anal. Calcd for $C_{18}H_{26}N_6O_2$: C 60.32, H 7.31, N 23.45. Found: C 60.12, H 7.70, N 23.58. ^{1}H NMR ($CDCl_3$) δ 7.42 (d, *J* = 6.0 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 6.64 (br s, 1H), 4.61−4.70 (m, 2H), 4.26−4.32 (m, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.80 (br s, 1H), 3.32 (br s, 1H), 3.23 (br s, 1H), 2.03−2.10 (m, 1H), 1.93−2.01 (m, 1H), 1.79−1.91 (m, 2H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) 156.1 (C), 155.5 (C), 138.1 (C), 128.7 (CH), 128.0 (CH), 127.6 (CH), 80.9 (C), 56.8 (CH), 48.3 (CH_2), 46.9 (CH_2), 29.6 (CH_2), 28.4 (CH_3), 23.7 (CH_2).

***tert*-Butyl (2*S*)-2-({5-[(2,2-Dimethoxyethyl)amino]-1*H*-tetrazol-1-yl}methyl)pyrrolidine-1-carboxylate, 1dd.** Yield 0.67 g (77%). Yellowish crystals. R_f = 0.61 (EtOAc). Mp 135−136 °C. $[\alpha]_D$ = −26.0 (*c* 0.5, MeOH). MS (*m*/*z*, ESI): 357 (MH^+). Anal. Calcd for $C_{15}H_{28}N_6O_4$: C 50.55, H 7.92, N 23.58. Found: C 50.29, H 7.67, N 23.40. ^{1}H NMR ($CDCl_3$) δ 6.20 (br s, 1H), 4.59 (br s, 1H), 4.19−4.26 (br s, 1H), 4.10 (d, *J* = 14.5 Hz, 1H), 3.80 (br s, 1H), 3.53−3.64 (m, 2H), 3.39 (s, 6H), 3.32−3.41 (m, 1H), 3.22 (br s, 1H), 1.79−

dx.doi.org/10.1021/jo2022235 | *J. Org. Chem.* 2012, 77, 1174−1180

2.04 (m, 4H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) 156.1 (C), 155.5 (C), 102.1 (CH), 80.8 (C), 56.6 (CH), 54.1 (CH_3), 53.8 (CH_3), 48.3 (CH_2), 46.9 (CH_2), 45.6 (CH_2), 29.4 (CH_2), 28.5 (CH_3), 23.6 (CH_2).

1-(1-Isopropyl-1*H*-tetrazol-5-yl)-4-methylpiperazine, 1eb. Yield 0.68 g (62%). Yellowish crystals. R_f = 0.46 (MeOH). Mp 149−151 °C (dec). MS (*m*/*z*, EI): 210 (M^+), 140, 98, 83, 71, 56, 43. Anal. Calcd for $C_9H_{18}N_6$: C 51.41, H 8.63, N 39.97. Found: C 51.50, H 8.86, N 40.09. ^{1}H NMR ($CDCl_3$) δ 4.45 (sept, J = 6.6 Hz, 1H), 3.30−3.34 (m, 4H), 2.64−2.68 (m, 4H), 2.40 (s, 3H), 1.57 (d, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) 158.3 (C), 54.1 (CH_2), 50.4 (CH_2), 50.2 (CH), 46.0 (CH_3), 22.6 (CH_3).

***tert*-Butyl (2*S*)-2-{[5-(4-Methylpiperazin-1-yl)-1*H*-tetrazol-1-yl]methyl}pyrrolidine-1-carboxylate, 1ed.** Yield 0.50 g (58%). White crystals. R_f = 0.42 (MeOH). Mp 235−237 °C. $[\alpha]_D$ = +12.0 (*c* 0.42, MeOH). Anal. Calcd for $C_{16}H_{29}N_7O_2$: C 54.68, H 8.32, N 27.90. Found: C 54.86, H 8.24, N 28.13. ^{1}H NMR ($CDCl_3$) δ 4.04−4.44 (br m, 3H), 3.25−3.54 (br m, 6H), 2.60 (br s, 4H), 2.34 (s, 3H), 1.72−1.98 (br m, 4H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$) 158.8 (C), 154.8 (C), 80.0 and 80.6 (C), 56.1 and 55.6 (CH), 54.2 (CH_2), 49.9 and 49.3 (CH_2), 48.6 (CH_2), 47.0 and 46.6 (CH_2), 46.0 (CH_3), 29.7 and 29.0 (CH_2), 28.5 (CH_3), 23.4 and 22.7 (CH_2).

***tert*-Butyl (2*S*)-2-[(5-{[(1*R*)-1-Phenylethyl]amino}-1*H*-tetrazol-1-yl)methyl]pyrrolidine-1-carboxylate, 1fd.** Yield 0.76 g (83%). White crystals. R_f = 0.82 (EtOAc). Mp 187−188 °C. $[\alpha]_D$ = +32.5 (*c* 0.26, MeOH). MS (*m*/*z*, ESI): 373 (M^+). Anal. Calcd for $C_{19}H_{28}N_6O_2$: C 61.27, H 7.58, N 22.56. Found: C 61.14, H 7.90, N 22.51. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 6.99 (br s, 1H), 5.02 (quint, J = 7.2 Hz, 1H), 4.22 (dd, J = 14.3 and 8.4 Hz, 1H), 4.11 (d, J = 14.3 Hz, 1H), 3.70 (br s, 1H), 3.40 (br s, 1H), 3.22 (br s, 1H), 1.96−2.02 (m, 1H), 1.90 (br s, 3H), 1.62 (d, J = 7.5 Hz, 3H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$) 155.6 (C), 155.3 (C), 144.0 (C), 128.7 (CH), 127.4 (CH), 126.4 (CH), 81.0 (C), 57.0 (CH), 54.3 (CH), 48.8 (CH_2), 46.8 (CH_2), 29.8 (CH_2), 28.6 (CH_3), 23.8 (CH_2), 23.6 (CH_3).

***tert*-Butyl (2*S*)-2-[(5-{[(1*S*)-1-Phenylethyl]amino}-1*H*-tetrazol-1-yl)methyl]pyrrolidine-1-carboxylate, 1gd.** Yield 0.73 g (80%). White crystals. R_f = 0.81 (EtOAc). Mp 173−175 °C. $[\alpha]_D$ = −21.3 (*c* 0.08, MeOH). MS (*m*/*z*, ESI): 373 (M^+). Anal. Calcd for $C_{19}H_{28}N_6O_2$: C 61.27, H 7.58, N 22.56. Found: C 61.46, H 7.25, N 22.49. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 6.95 (br s, 1H), 5.05 (quint, J = 6.8 Hz, 1H), 4.22 (dd, J = 14.6 and 8.4 Hz, 1H), 4.07 (d, J = 14.6 Hz, 1H), 3.82 (br s, 1H), 3.40 (br s, 1H), 3.20−3.26 (m, 1H), 1.85−2.07 (m, 4H), 1.62 (d, J = 6.8 Hz, 3H), 1.49 (s, 9H). It is interesting to note that ^{1}H NMR spectra of **1fd** and **1gd** differ significantly by a single signal (at 3.70 and 3.82 ppm, respectively). This is clearly seen in a spectrum of their mixture. ^{13}C NMR ($CDCl_3$) 155.6 (C), 155.4 (C), 144.0 (C), 128.7 (CH), 127.4 (CH), 126.3 (CH), 81.1 (C), 57.0 (C), 54.4 (CH), 48.9 (CH), 46.8 (CH_2), 29.8 (CH_2), 28.5 (CH_3), 23.8 (CH_2), 23.4 (CH_3).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gregor@univ.kiev.ua.

■ ACKNOWLEDGMENTS

The authors thank Olga V. Manoylenko for the chromatographic separations, Vitaly Polovinko for NMR spectra measurements, and Valentin Tkachenko for LC−MS measurements.

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