Synthesis and Dimroth rearrangement of 3-amino-4-(5-amino-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazoles

Vladimir Yu. Rozhkov, Lyudmila V. Batog,* Elena K. Shevtsova and Marina I. Struchkova

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: mnn@ioc.ac.ru

10.1070/MC2004v014n02ABEH001891

The cycloaddition of 4-amino-3-azido-1,2,5-oxadiazole to nitriles with activated methylene groups has been studied, and 3-amino-4-(5-amino-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazoles and the products of their Dimroth rearrangement, *viz.*, *N*-(4-R-1*H*-1,2,3-triazol-5-yl)-1,2,5-oxadiazole-3,4-diamines, have been synthesised.

Previously,[1–3] we reported the synthesis of (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles (triazolylfurazans) by cycloaddition of azidofurazans to acetylenes, morpholinonitroethylene, and 1,3-dicarbonyl compounds. The resulting triazolylfurazans contained various substituents in both heterocycles. We also found[4] that an NH_2 group can be introduced at the 4-position of the triazole ring of triazolylfurazans using the Curtius and Hofmann rearrangements in the appropriate 4-CON_3 and 4-$CONH_2$ derivatives. The triazolylfurazans with an NH_2 group at the 5-position of the triazole ring were not described previously; however, it is known[5,6] that some derivatives of 5-amino-1,2,3-triazoles and their transformation products display various types of pharmacological activity. Thus, it seemed promising to synthesise triazolylfurazans with an NH_2 group at the 5-position of the triazole ring and to study their reactivity and biological activity.

5-Amino-1,2,3-triazoles[7–11] are usually obtained in the reactions of azides with nitriles containing an activated methylene group. The reactions occur regiospecifically to give only 5-amino derivatives; they are usually carried out in alcohols in the presence of sodium alkylates.[5,7–9] Cottrell *et al.*[10] successfully used K_2CO_3 in DMSO to obtain 1-substituted 5-amino-1,2,3-triazoles.

In order to obtain triazolylfurazans **1a–e** with an NH_2 group at the 5-position of the triazole ring and an NH_2 group at the furazan ring, we studied the cycloaddition of 4-amino-3-azidofurazan **2** to nitriles **3a–e** with an activated methylene group (Scheme 1, i–v). These reactions were carried out with a small excess of the nitrile component in water, MeOH, EtOH and MeCN at room temperature or on heating (30–50 °C) in the presence of basic catalysts (K_2CO_3, $MgCO_3$, EtONa or Et_3N; **2**:**3**:catalyst molar ratio of ~1:1:0.1) or without catalysts. The catalyst and solvent were varied in the reaction of azidoaminofurazan **2** with dinitrile **3a** as an example. This reaction was found to occur regiospecifically. Compound **1a** is formed in high yield (77–92%) at room temperature in the presence of K_2CO_3 in water as a solvent. If the reaction is carried out without a catalyst or with catalysts other than EtONa, the yield of compound **1a** decreases (23–30%); the decomposition of azide **2** occurs in the presence of EtONa, like in the reaction with 1,3-dicarbonyl compounds.[3] An increase in the reaction temperature to 50 °C increases the yield of compound **1a** to 94.6%. The reaction of compound **2** with nitrile **3a** does not occur in MeCN. We found conditions for the synthesis of the target diamines.† Compound **1d** is formed in high yield under the same conditions as compound **1a**, provided that MeOH is used instead of water. The reaction of azide **2** with nitriles **3b**,**c**,**e** under the conditions found gave corresponding triazolylfurazans **1b**,**c**,**e** in lower yields (30–44%) (Scheme 1, ii, iii, v), even though reactions iii and v were performed at 40–50 °C.

A study of the properties of triazolylfurazans **1a–e** showed that compound **1c** remained unchanged on heating (85–95 °C) in DMF for 1 h, whereas compounds **1a**,**b**,**d**,**e** underwent the Dimroth rearrangement[7] to give hitherto unknown monosubstituted diaminofurazans **4a–d**‡ (Scheme 1, vi). Compound **1a** also undergoes this rearrangement on heating in DMSO or on prolonged exposure of solutions of **1a** in [$^2H_6$]DMSO at room temperature.

The structures of compounds **1a–e** and triazoles **4a–d**, which are isomeric to **1a**,**b**,**d**,**e**, were found using elemental analysis and spectroscopic techniques (IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry).§ The ^{1}H NMR spectra of compounds **1a–d** contain two singlets, which, according to their integral intensities, correspond to the protons of NH_2 groups; the chemical shifts of protons in the NH_2 group bound to the furazan ring are observed upfield (δ 6.13–6.61 ppm) of those for protons in the NH_2 group bound to the triazole ring (δ 6.89–8.32 ppm). Unlike compounds **1a–d**, diamine **1e** gives one signal in the ^{1}H NMR spectrum (δ 6.58 ppm) corresponding to the protons

† *General preparation procedure for triazoles* **1a–e**. A mixture of azide **2** and nitrile compound **3a–e** in water or an alcohol was stirred in the presence of a catalyst at room temperature or on slightly heating until vigorous precipitation. The precipitate was filtered off, washed with water and dried in air.

‡ *General preparation procedure for diaminofurazans* **4a–d**. Triazoles **1a–e** were heated for 1 h in DMF at 90 °C; water was added, the precipitate was filtered off, washed with water and dried in air.

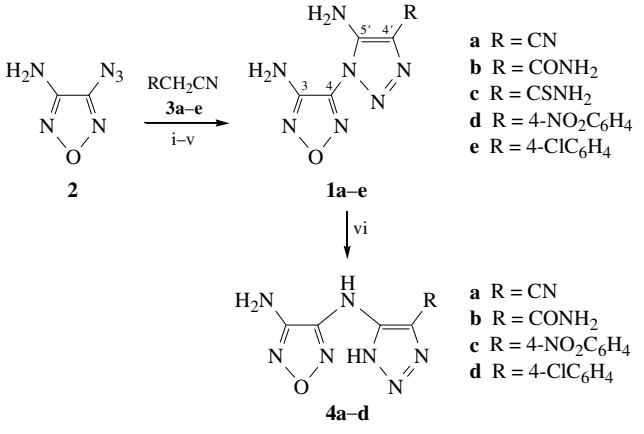
§ All new compounds exhibited satisfactory elemental analysis data. The ^{13}C and ^{1}H NMR spectra of compounds were measured on a Bruker AM-300 spectrometer (75.5 MHz for ^{13}C and 300 MHz for ^{1}H) in a Fourier transform pulse mode as solutions in [$^2H_6$]DMSO (δ^{13}C 39.5, δ^1H 2.5). The IR spectra were recorded on a Specord M80 instrument in KBr pellets. The mass spectra of reaction products were recorded on a Varian MAT CH6 spectrometer. TLC monitoring was performed using Silufol UV-254 plates (Czech Republic) using ethyl acetate as an eluent.

5-Amino-1-(4-amino-1,2,5-oxadiazol-3-yl)-1H-1,2,3-triazol-4-yl carbonitrile **1a**: 95% yield, mp 268 °C, R_f 0.84. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.60 (s, 2H, NH_2 of furazan ring), 7.80 (s, 2H, NH_2 of triazole ring). ^{13}C NMR ([$^2H_6$]DMSO) δ: 100.72 (C-4′), 112.66 (CN), 141.3 (C-3), 149.03 (C-5′), 152.40 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3460, 3420, 3324, 3192 (NH_2), 2252 (CN), 1640, 1628, 1600, 1572, 1484, 1440, 1380, 1340, 1256, 1092, 1068, 1004, 976, 860, 796, 732, 668. MS, *m*/*z* (%): 192 (M^+, 20).

5-Amino-1-(4-amino-1,2,5-oxadiazol-3-yl)-1H-1,2,3-triazole-4-carboxamide **1b**: 30% yield, mp 310 °C (decomp.), R_f 0.63. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.53 (s, 2H, NH_2 of furazan ring), 6.89 (s, 2H, NH_2 of triazole ring), 7.29 (s, 1H, CONH), 7.67 (s, 1H, CONH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 142.02 (C-3), 145.87 (C-4′), 150.0 (C-5′), 152.0 (C-4), 163.58 ($CONH_2$). IR (KBr, ν_{max}/cm^{-1}): 3464, 3424, 3344, 3192 (NH_2), 1684 (CO), 1648, 1612, 1588, 1560, 1540, 1500, 1428, 1352, 1312, 1276, 1196, 1004, 976, 872, 760, 736, 704, 656. MS, *m*/*z* (%): 210 (M^+, 80).

5-Amino-1-(4-amino-1,2,5-oxadiazol-3-yl)-1H-1,2,3-triazole-4-carbothioamide **1c**: 39% yield, mp 273 °C (decomp.), R_f 0.73. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.13 (s, 2H, NH_2 of furazan ring), 7.92 (s, 1H, CSNH), 8.32 (s, 2H, NH_2 of triazole ring), 8.63 (s, 1H, CSNH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 134.29 (C-5′), 152.55 (C-4), 154.27 (C-4′), 156.46 (C-3), 166.39 ($CSNH_2$). IR (KBr, ν_{max}/cm^{-1}): 3608, 3444, 3400, 3288 (NH_2), 1636, 1576, 1552, 1520, 1504, 1368, 1320, 1256, 996, 916, 888, 848, 808, 636. MS, *m*/*z* (%): 226 (M^+, 45).

4-[5-Amino-4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl]-1,2,5-oxadiazol-3-amine **1d**: 92% yield, mp 212 °C, R_f 0.80. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.61 (s, 2H, NH_2 of furazan ring), 6.95 (s, 2H, NH_2 of triazole ring), 8.06 (d, 2H, Ph, *J* 8.56 Hz), 8.29 (d, 2H, Ph, *J* 8.56 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 124.02 ($C_{o\text{-Ph}}$), 124.37 ($C_{i\text{-Ph}}$), 124.94 ($C_{m\text{-Ph}}$), 137.66 (C-5′), 141.98 (C-3), 142.26 (C-4′), 145.05 ($C_{p\text{-Ph}}$), 152.27 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3476, 3400, 3364, 3308 (NH_2), 2880 (Ph), 1652, 1624, 1604, 1580, 1500, 1432, 1416, 1392, 1336, 1268, 1112, 972, 872, 856, 760, 716. MS, *m*/*z* (%): 288 (M^+, 25).



Scheme 1 *Reagents and conditions*: i, **3a**, H_2O, K_2CO_3, 55 °C; ii, **3b**, H_2O, K_2CO_3, 20 °C; iii, **3c**, H_2O, K_2CO_3, 40 °C; iv, **3d**, MeOH, K_2CO_3, 20 °C; v, **3e**, MeOH, K_2CO_3, 50 °C, vi, **1a**,**b**,**d**,**e**, DMF, 90 °C, 1 h.

*4-[5-Amino-4-(4-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-1,2,5-oxadiazol-3-amine* **1e**: 44% yield, mp 210 °C, R_f 0.78. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.58 (s, 4H, 2NH_2 of furazan and triazole rings), 7.51 (d, 2H, Ph, *J* 8.52 Hz), 7.82 (d, 2H, Ph, *J* 8.52 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 125.27 ($C_{i\text{-Ph}}$), 126.63 ($C_{o\text{-Ph}}$), 128.66 ($C_{m\text{-Ph}}$), 129.75 ($C_{p\text{-Ph}}$), 130.89 (C-4′), 140.82 (C-5′), 142.21 (C-3), 152.07 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3468, 3372, 3320 (NH_2), 1612, 1584, 1568, 1504, 1440, 1404, 1388, 1316, 1300, 1252, 1220, 1104, 1068, 1012, 964, 876, 828, 724. MS, *m*/*z* (%): 277 (M^+, 19).

*5-(4-Amino-1,2,5-oxadiazol-3-ylamino)-1*H*-1,2,3-triazol-4-yl carbonitrile* **4a**: 87% yield, mp 275 °C, R_f 0.56. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.20 (s, 2H, NH_2 of furazan ring), 9.95 (s, 1H, NH), 15.7 (s, 1H, NH of triazole ring). ^{13}C NMR ([$^2H_6$]DMSO) δ: 107.97 (C-4′), 112.26 (CN), 145.09 (C-5′), 146.91 (C-3), 149.80 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3588, 3400, 3332, 3280, 3188 (NH_2, NH), 2252 (CN), 1656, 1620, 1572, 1536, 1476, 1428, 1400, 1328, 1292, 1260, 1248, 1184, 1136, 984, 828, 720, 700. MS, *m*/*z* (%): 192 (M^+, 25).

*5-(4-Amino-1,2,5-oxadiazol-3-ylamino)-1*H*-1,2,3-triazole-4-carboxamide* **4b**: 52% yield, 337 °C (decomp.), R_f 0.44. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.19 (s, 2H, NH_2 of furazan ring), 7.50 (s, 1H, CONH), 7.81 (s, 1H, CONH), 8.73 (s, 1H, NH), 14.95 (s, 1H, NH of triazole ring). ^{13}C NMR ([$^2H_6$]DMSO) δ: 126.60 (C-4′), 144.34 (C-3), 145.58 (C-5′), 150.05 (C-4), 163.18 (CO). IR (KBr, ν_{max}/cm^{-1}): 3452, 3360, 3192 (NH_2, NH), 1680 (CO), 1620, 1600, 1568, 1496, 1452, 1360, 1228, 1124, 1008, 988, 832, 788, 696, 668. MS, *m*/*z* (%): 210 (M^+, 75).

N-*[4-(4-Nitrophenyl)-1*H*-1,2,3-triazol-5-yl]-1,2,5-oxadiazole-3,4-diamine* **4c**: 57% yield, mp 253 °C, R_f 0.67. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.05 (s, 2H, NH_2 of furazan ring), 7.98 (d, 2H, Ph, *J* 8.50 Hz), 8.32 (d, 2H, Ph, *J* 8.50 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 124.00 ($C_{m\text{-Ph}}$), 127.12 ($C_{o\text{-Ph}}$), 134.01 ($C_{i\text{-Ph}}$), 136.42 (C-5′), 141.91 (C-4′), 146.68 ($C_{p\text{-Ph}}$), 147.59 (C-3), 149.71 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3624, 3472, 3375, 3125 (NH, NH_2), 1640, 1560, 1508, 1500, 1468, 1424, 1336, 1292, 1236, 1176, 1112, 1076, 1040, 992, 860, 836, 760, 720, 692. MS, *m*/*z* (%): 288 (M^+, 80).

N-*[4-(4-Chlorophenyl)-1*H*-1,2,3-triazol-5-yl]-1,2,5-oxadiazole-3,4-diamine* **4d**: 73% yield, mp 223 °C, R_f 0.70. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.02 (s, 2H, NH_2 of furazan ring), 7.50 (d, 2H, Ph, *J* 8.51 Hz), 7.74 (d, 2H, Ph, *J* 8.51 Hz), 8.64 (s, 1H, NH), 14.88 (s, 1H, NH of triazole ring). ^{13}C NMR ([$^2H_6$]DMSO) δ: 128.02 ($C_{m\text{-Ph}}$), 128.81 ($C_{o\text{-Ph}}$), 129.00 ($C_{i\text{-Ph}}$), 132.80 ($C_{p\text{-Ph}}$), 136.48 (C-4′), 141.52 (C-3), 147.94 (C-5′), 149.65 (C-4). IR (KBr, ν_{max}/cm^{-1}): 3448, 3348, 3228, 3032 (NH_2, NH), 2868, 2788 (Ph), 1648, 1624, 1600, 1580, 1492, 1436, 1400, 1320, 1280, 1256, 1220, 1196, 1144, 1096, 1040, 1012, 996, 836, 816, 732, 704, 668. MS, *m*/*z* (%): 277 (M^+, 20).

of both amino groups. A comparison of the ^{1}H NMR spectra of triazolylfurazans **1a**,**b**,**d**,**e** and diaminofurazans **4a**–**d** showed the singlets of protons in NH_2 groups at furazan rings of the latter compounds to be shifted upfield (δ 6.02–6.20 ppm). The ^{1}H NMR spectra of compounds **4a**,**b**,**d** contain the singlets of 5-NH group protons (δ 8.64–9.95 ppm) and the downfield shifted broadened singlets of triazole ring protons (δ 14.88–15.70 ppm). The ^{1}H NMR spectrum of diamine **4c** does not display similar signals, probably, because of the high mobility of these protons and their exchange with water that was present in the [$^2H_6$]DMSO used. The assignment of signals in the ^{1}H and ^{13}C NMR spectra of compounds **1a**–**e** and **4a**–**d** was carried out using data for a series of triazolylfurazans obtained previously[1–3] and the ^{13}C NMR spectra of aryl-substituted azoles.[12] The mass spectra of all the compounds contain the peaks of molecular ions.

Thus, we found that the reaction of 4-amino-3-azidofurazan **2** with nitriles containing an activated methylene group can be used for the synthesis of (1,2,3-triazol-1-yl)furazans along with the approaches developed previously.[1–3] We proposed a simple general method for the synthesis of hitherto unknown 3-amino-4-(5-amino-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazoles **1a**–**e** and performed their Dimroth rearrangements to give *N*-(4-R-1*H*-1,2,3-triazol-5-yl)-1,2,5-oxadiazole-3,4-diamines **4a**–**d**. The synthesis of compounds **1a**–**e** and **4a**–**d** incorporating several potentially reactive functional groups opens new prospects for synthesising new structures of furazan and triazole series based on these compounds.

References

1 L. V. Batog, L. S. Konstantinova, V. Yu. Rozhkov, Ya. A. Strelenko, O. V. Lebedev and L. I. Khmel'nitskii, *Khim. Geterotsikl. Soedin*., 2000, 100 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 2000, **36**, 91].
2 L. V. Batog, V. Yu. Rozhkov, Ya. A. Strelenko, O. V. Lebedev and L. I. Khmel'nitskii, *Khim. Geterotsikl. Soedin*., 2000, 406 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 2000, **36**, 343].
3 L. V. Batog, V. Yu. Rozhkov and M. I. Struchkova, *Mendeleev Commun*., 2002, 159.
4 E. K. Shevtsova, V. Yu. Rozhkov, L. V. Batog and M. I. Struchkova, *V Molodezhnaya nauchnaya shkola-konferentsiya po organicheskoi khimii* (*5th School-Conference on Organic Chemistry for Young Scientists*), Ekaterinburg, April 22–26, 2002, p. 487 (in Russian).
5 A. Da Settimo, O. Livi, P. L. Ferrarini and G. Primofiore, *Il Farmaco Ed. Sci.*, 1980, **35**, 298.
6 P. G. Baraldi, B. Cacciari, G. Spalluto, M. J. P. De Las Infants, C. Zocchi, S. Ferrara and S. Dionisotti, *Il Farmaco Ed. Sci*., 1996, **51**, 297.
7 O. Dimroth, *Liebigs Ann. Chem*., 1909, **364**, 183.
8 Ch. Westerlund, *J. Heterocycl. Chem.*, 1980, **17**, 1765.
9 J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc*., 1956, **78**, 5832.
10 F. Cottrell, D. Hands, P. G. Houghton, G. R. Humphrey and S. H. B. Wright, *J. Heterocycl. Chem*., 1991, **28**, 301.
11 A. Albert, *Adv. Heterocycl. Chem*., 1986, **40**, 129.
12 M. Begtrup, *Acta Chem. Scand*., 1973, **27**, 3101.

Received: 19th January 2004; Com. 04/2217