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Synthesis of 1,2,4-oxadiazole-, pyrrole- and 1,2,3-triazole-substituted (1,2,3-triazol-1-yl)furazans

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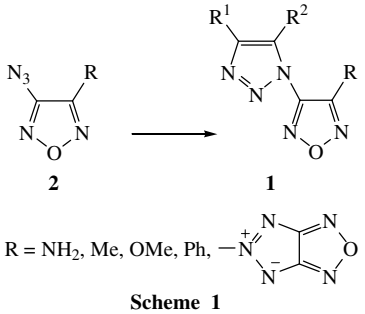
The synthesis of tricyclic compounds with hitherto unknown combinations of heterocycles (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles with 1,2,4-oxadiazol-3-yl, pyrrol-1-yl or 1,2,3-triazol-1-yl substituents at the furazan ring, was developed by interaction of corresponding substituted azidofurazans with 1,3-dicarbonyl compounds, and pyrrolyl derivatives were also synthesised by condensation of amino(1,2,3-triazol-1-yl)furazans with 2,5-dimethoxytetrahydrofuran.

Previously,[1–5] we have synthesised (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles (triazolylfurazans) **1** with various substituents at both rings by 1,3-dipolar cycloaddition of azidofurazans **2** to acetylenes,[1] morpholinonitroethylene,[2] 1,3-dicarbonyl compounds[3,4] and methylene-active nitriles.[5] Azidofurazans with NH_2, Me, OMe, Ph and triazoloxadiazole substituents were used (Scheme 1).[1–5] The synthesis of new triazolylfurazans based on reactions of aminoazidofurazan **2a** ($R = NH_2$) with chloroacetoacetic ester and studies on the chemical transformations[4,6,7] of functional groups in the resulting products expanded considerably the range of these compounds. Studies on the biological activity of triazolylfurazans revealed that some of the compounds have a selective potentiating effect on the NO-dependent activation of sGC (a soluble form of guanylate cyclase[8]) or can act as selective inhibitors of glycogen-synthase kinase-3.[6]

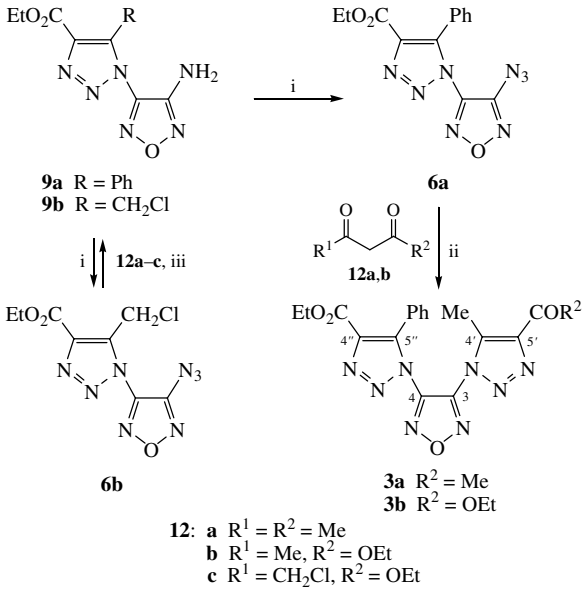
Note that, of triazolylfurazans **1** (Scheme 1), only one compound contains a heteroaromatic substituent at the furazan ring. It was of interest to synthesise compounds of the triazolylfurazan series containing other aromatic heterocycles at the furazan ring, *e.g.*, 1,2,4-oxadiazole, pyrrole or 1,2,3-triazole, which occur in various biologically active compounds. The compounds thus obtained might be more promising as a result of acquiring a new set of properties.



Scheme 1

The purpose of this study was to synthesise new triazolylfurazan derivatives representing the following tricyclic structures: bis(1,2,3-triazol-1-yl)furazans **3**, (1,2,4-oxadiazol-3-yl)- **4** and (pyrrol-1-yl)- **5** triazolylfurazans (Schemes 2–4). No compounds with such a combination of heterocycles as in **3**–**5** have been reported before.

By analogy with the methods we established previously for the syntheses of triazolylfurazans,[3,4] a possible way to synthesise compounds **3**–**5** might involve cycloaddition of azidofurazans

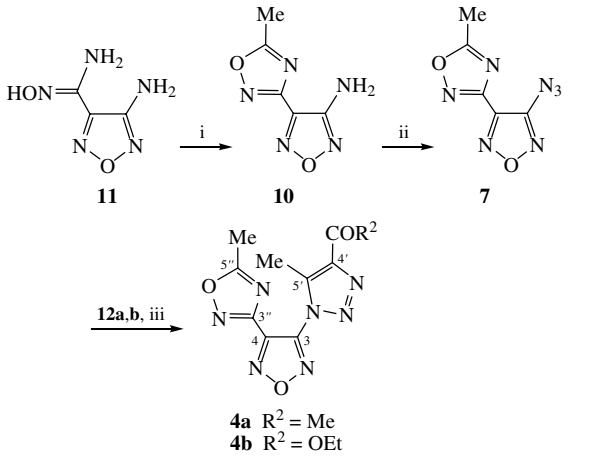


Scheme 2 *Reagents and conditions*: i, $NaNO_2$, H_2SO_4, 2–5 °C, H_3PO_4, 1 h, NaN_3, H_2O; ii, **12a**,**b** (1.2 equiv.), EtOH, EtOH–H_2O (1:1), Et_3N (2 equiv.), 20 °C, 1–8 h, H_2O; iii, acetone–H_2O (1:1), K_2CO_3 (0.6 equiv.), 20 °C.

containing a 1,2,3-triazole (**6**), 1,2,4-oxadiazole (**7**) or pyrrole (**8**) ring as the second substituent to dipolarophiles, *e.g.* to 1,3-dicarbonyl compounds. With this in mind, we developed methods to obtain the hitherto unknown (1,2,3-triazol-1-yl)- (**6a**,**b**), (1,2,4-oxadiazol-3-yl)- (**7**) and (pyrrol-1-yl)- (**8**) azidofurazans (Schemes 2–4).†

Compounds **6a**,**b** and **7** were synthesised under the conditions used to obtain the known azidofurazans from aminofurazans,[9] namely, by diazotization of the appropriate amines (**9a**,**b** and **10**) with nitrosylsulfuric acid in a mixture of concentrated H_2SO_4 and H_3PO_4, followed by treatment of the resulting diazonium ions with sodium azide (Schemes 2, 3). To produce amine **10**, amidoxime **11** was refluxed in AcOH. Azidofurazan **8** was obtained by condensation of azidoaminofurazan **2a** with 2,5-dimethoxytetrahydrofuran (DMT) in refluxing AcOH (Scheme 4). The condensation of primary amines with DMT (Clauson–Kaas reaction[10]) that is successfully used to

† The carbon atoms in compounds **3** (Scheme 2) and **4** (Scheme 3) are numbered arbitrarily (see the signal assignments in the ^{13}C NMR spectra of these compounds).

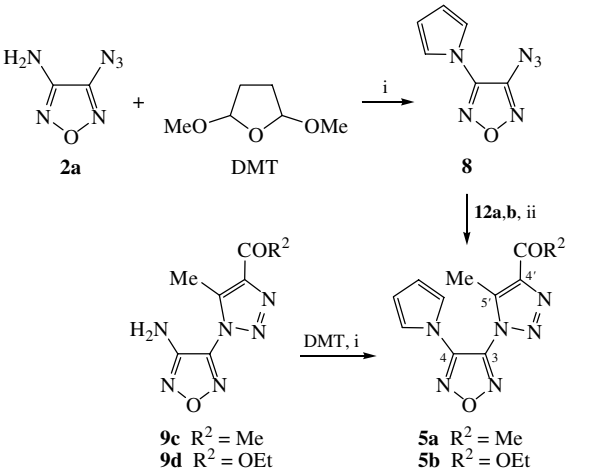


Scheme 3 *Reagents and conditions*: i, AcOH, 118 °C, 1 h, H_2O; ii, $NaNO_2$, H_2SO_4, 2–5 °C, H_3PO_4, NaN_3, H_2O; iii, acetone–H_2O (1:1, 2:1), K_2CO_3 (0.3–0.5 equiv.), 20 °C, 1–8 h, H_2O.

synthesise N-alkyl- and N-arylpyrroles was expanded for 3-amino-4-R-furazans.[11] We have shown that this technique is also suitable for synthesising azidopyrrolylfurazan **8** in 88% yield.

We have studied whether it is possible to synthesise compounds **3**–**5** by the 1,3-dipolar cycloaddition of azidofurazans **6a**,**b**, **7** and **8** to 1,3-dicarbonyl compounds **12a**–**c** (Schemes 2–4). The reactions were carried out in EtOH, EtOH–H_2O or acetone–H_2O with a small excess of a dipolarophile **12** in the presence of Et_3N or K_2CO_3. We found that the interactions of azides **6a**, **7** and **8** with acetylacetone **12a** and acetoacetic ester **12b** led to target compounds **3a**,**b** (Scheme 2), **4a**,**b** and **5a**,**b** in high yields (Schemes 3, 4). Conversely, reactions of azide **6b** with compounds **12a**–**c** gave amine **9b** under the conditions studied (Scheme 2). Examples are known[12,13] where reactions of aromatic azides, including azidofurazans,[3] with 1,3-dicarbonyl compounds gave products of formal reduction of azide groups into amino ones.

To synthesise pyrrole-containing compounds **5**, we studied the formation of a pyrrole ring at (1,2,3-triazol-1-yl)furazan by condensation of aminotriazolylfurazans **9c**,**d** with DMT, similarly to the syntheses of (pyrrol-1-yl)furazans from aminofurazans.[11] The study resulted in the high-yield production of target compounds **5a**,**b** (Scheme 4) that are identical to those obtained in the reaction of azide **8** with compounds **12a**,**b** (Scheme 4). Both approaches were found to be acceptable for obtaining compounds **5a**,**b**.



Scheme 4 *Reagents and conditions*: i, DMT (1.2 equiv.), AcOH, 118 °C, 1 h, H_2O; ii, **12a**,**b** (1 equiv.), acetone–H_2O (1:1, 2:1), K_2CO_3 (0.4 equiv.), 20 °C, 1–8 h, H_2O.

The structures of the compounds synthesised were established from the data of elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry.‡ All target compounds (**3a**,**b**, **4a**,**b** and **5a**,**b**) had molecular ions in mass spectra. The attribution of carbon atom signals of furazan and triazole rings in ^{13}C NMR spectra was carried out based on previous data.[1,3] The chemical shifts of the carbon atoms C(3) and C(4) of the furazan ring in compounds **3a** and **3b** are at 145 ppm. The chemical shifts of analogous carbon atoms in compounds **4a**,**b** and **5a**,**b** are at 143 and 148 ppm, respectively. In the triazole rings of compounds **3a**,**b**, **4a**,**b** and **5a**,**b** the chemical shifts of carbon atoms C(4′), C(4″) and C(5′), C(5″) occur at 136–142 and 141–143 ppm, respectively. The chemical shifts of carbon atoms C(2″) and C(3″) of pyrrole ring in compounds **5a** and **5b** are at 121 and 112 ppm, respectively, and those of carbon atoms C(3″) and C(5″) of 1,2,4-oxadiazole ring in compounds **4a** and

‡ The ^{13}C and ^1H NMR spectra were measured in [$^2H_6$]DMSO in the pulse mode on a Bruker AM-300 spectrometer (^{13}C, 75.5 MHz; ^1H, 300 MHz). IR spectra were obtained on a Specord M-80 instrument in KBr pellets. Chromatographic monitoring was carried out on Silufol UV-254 plates.

3a: yield 70%, mp 167–168 °C (EtOH–H_2O, 1:2), R_f 0.55 ($CHCl_3$–AcOEt, 9:1). IR (KBr, ν_{max}/cm^{-1}): 2992, 1732 (CO), 1696 (CO), 1600, 1556, 1420, 1180, 980, 704. ^1H NMR, δ: 1.17 (t, 3H, Me, *J* 7.1 Hz), 2.43 (s, 3H, Me), 2.62 (s, 3H, Me), 4.26 (q, 2H, CH_2, *J* 7.1 Hz), 7.36 (m, 5H, Ph). ^{13}C NMR, δ: 9.3 (Me), 13.8 (CH_2*Me*), 27.9 (CO*Me*), 61.3 (CH_2), 122.5 (Ph), 128.5 (Ph), 129.7 (Ph), 130.9 (Ph), 136.4 [C(4″)], 140.0 [C(4′)], 142.8 [C(5′)], 142.9 [C(5″)], 145.0 [C(3)], 145.3 [C(4)], 159.3 (CO), 192.5 (*C*OMe). MS, *m*/*z* (%): 408 (M^+, 8), 380 ($M^+ - N_2$, 2), 352 ($M^+ - 2N_2$, 2), 337 ($M^+ - N_2$ – COMe, 2), 43 (100). Found (%): C, 52.91; H, 4.04; N, 27.61. Calc. for $C_{18}H_{16}N_8O_4$ (%): C, 52.94; H, 3.92; N, 27.45.

3b: yield 84%, mp 191–192 °C (EtOH–H_2O, 1:2), R_f 0.61 ($CHCl_3$–AcOEt, 9:1). IR (KBr, ν_{max}/cm^{-1}): 2980, 1744 (CO), 1728 (CO), 1576, 1280, 1176, 980, 704. ^1H NMR, δ: 1.17 (t, 3H, Me, *J* 7.0 Hz), 1.34 (t, 3H, Me, *J* 7.0 Hz), 2.45 (s, 3H, Me), 4.25 (q, 2H, CH_2, *J* 7.0 Hz), 4.37 (q, 2H, CH_2, *J* 7.0 Hz), 7.38 (m, 5H, Ph). ^{13}C NMR, δ: 9.4 (Me), 13.7 (CH_2*Me*), 14.0 (CH_2Me), 61.2 (CH_2), 61.3 (CH_2), 122.6 (Ph), 128.4 (Ph), 129.7 (Ph), 130.9 (Ph), 136.4 [C(4′)], 136.5 [C(4″)], 141.7 [C(5′)], 142.9 [C(5″)], 145.1 [C(3)], 145.2 [C(4)], 159.3 (CO), 159.8 (CO). MS, *m*/*z* (%): 438 (M^+, 10), 410 ($M^+ - N_2$, 2), 77 (45), 102 (100). Found (%): C, 51.69; H, 4.18; N, 25.76. Calc. for $C_{19}H_{18}N_8O_5$ (%): C, 52.05; H, 4.11; N, 25.57.

4a: yield 72%, mp 135–136 °C (MeOH–H_2O, 1:1), R_f 0.44 ($CHCl_3$–AcOEt, 9:1). IR (KBr, ν_{max}/cm^{-1}): 3020, 1688 (CO), 1584, 1564, 1552, 1252, 1172, 952. ^1H NMR, δ: 2.64 (s, 3H, Me), 2.68 (s, 3H, Me), 2.72 (s, 3H, Me). ^{13}C NMR, δ: 9.1 [C(5′)*Me*], 11.9 [C(5″)*Me*], 27.7 (CO*Me*), 140.9 [C(5′)], 142.0 [C(4′)], 142.7 [C(3)], 148.2 [C(4)], 157.1 [C(3′)], 179.2 [C(5″)], 192.5 (*C*OMe). MS, *m*/*z* (%): 275 (M^+, 25), 247 ($M^+ - N_2$, 10), 205 (30), 190 (13), 172 (25), 43 (100). Found (%): C, 43.57; H, 3.38; N, 35.44. Calc. for $C_{10}H_9N_7O_3$ (%): C, 43.64; H, 3.30; N, 35.62.

4b: yield 78%, mp 152–153 °C (EtOH–H_2O, 1:1), R_f 0.53 ($CHCl_3$–AcOEt, 9:1). IR (KBr, ν_{max}/cm^{-1}): 3000, 1736 (CO), 1584, 1564, 1416, 1256, 1184, 884. ^1H NMR, δ: 1.37 (t, 3H, Me, *J* 7.0 Hz), 2.65 (s, 3H, Me), 2.72 (s, 3H, Me), 4.39 (q, 2H, CH_2, *J* 7.0 Hz). ^{13}C NMR, δ: 9.3 (Me), 12.0 (Me), 14.0 (CH_2*Me*), 61.0 (CH_2), 136.2 [C(4′)], 142.2 [C(3)], 142.6 [C(5′)], 148.3 [C(4)], 157.2 [C(3″)], 160.1 (CO), 179.3 [C(5″)]. MS, *m*/*z* (%): 305 (M^+, 2), 110 (10), 83 (10), 43 (100). Found (%): C, 43.21; H, 3.72; N, 32.27. Calc. for $C_{11}H_{11}N_7O_4$ (%): C, 43.28; H, 3.83; N, 32.12.

5a: yield 74% (i), 55% (ii), mp 65–66 °C, R_f 0.71 (C_6H_6). IR (KBr, ν_{max}/cm^{-1}): 3136, 1692 (CO), 1600, 1564, 1416, 1256, 1076, 752. ^1H NMR, δ: 2.65 (s, 3H, Me), 2.67 (s, 3H, Me), 6.39 (br. s, 2H, 2CH), 7.05 (br. s, 2H, 2CH). ^{13}C NMR, δ: 9.3 (Me), 27.9 (*Me*CO), 112.8 (CH), 121.1 ($CHN_{pyrr.}$), 141.3 [C(4′)], 143.0 [C(5′)], 143.5 [C(3)], 148.8 [C(4)], 192.8 [*C*OMe]. MS, *m*/*z* (%): 258 (M^+, 5), 230 ($M^+ - N_2$, 5), 43 (100). Found (%): C, 50.82; H, 3.72; N, 32.40. Calc. for $C_{11}H_{10}N_6O_2$ (%): C, 51.16; H, 3.90; N, 32.54.

5b: yield 82% (i), 65% (ii), mp 74–75 °C, R_f 0.66 (C_6H_6). IR (KBr, ν_{max}/cm^{-1}): 3148, 2996, 1736 (CO), 1600, 1476, 1256, 1204, 752. ^1H NMR, δ: 1.37 (t, 3H, Me, *J* 7.1 Hz), 2.64 (s, 3H, Me), 4.37 (q, 2H, CH_2, *J* 7.1 Hz), 6.40 (br. s, 2H, 2CH), 7.03 (br. s, 2H, 2CH). ^{13}C NMR, δ: 9.3 (Me), 14.0 (CH_2*Me*), 61.0 (CH_2), 112.7 (CH), 121.0 (CHN), 136.5 [C(4′)], 142.7 [C(3)], 143.5 [C(5′)], 148.7 [C(4)], 160.1 (CO). Found (%): C, 49.62; H, 4.09; N, 29.01. Calc. for $C_{12}H_{12}N_6O_3$ (%): C, 50.00; H, 4.16; N, 29.16.

4b, at 157 and 179 ppm, respectively, which are consistent with published data.[11,14]

Thus, we synthesised azidofurazans with 1,2,3-triazole, 1,2,4-oxadiazole and pyrrole rings as substituents, studied their reactions with 1,3-dicarbonyl compounds (acetylacetone and acetoacetic ester) and found methods to obtain tricyclic compounds with hitherto unknown combinations of heterocycles. In addition, a method for incorporating a pyrrole ring at a carbon atom of the furazan ring in amino(1,2,3-triazol-1-yl)furazans by condensation of the latter with DMT has been developed.

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6a: yield 88%, mp 87–88 °C (EtOH–H_2O, 1:1), R_f 0.27 (C_6H_6). IR (KBr, ν_{max}/cm^{-1}): 2984, 2168 (N_3), 2148 (N_3), 1720 (CO), 1544, 1260, 1192, 1060, 984, 764, 696. ^{1}H NMR, δ: 1.15 (t, 3H, Me, *J* 6.9 Hz), 4.25 (q, 2H, CH_2, *J* 6.9 Hz), 7.53 (s, 5H, Ph). ^{13}C NMR, δ: 13.8 (Me), 61.2 (CH_2O), 123.6 ($C_{ipso\text{-}Ph}$), 128.3 ($C_{m\text{-}Ph}$), 130.4 ($C_{o\text{-}Ph}$), 130.9 ($C_{p\text{-}Ph}$), 136.8 [C(5′)], 142.9 [C(4′)], 143.8 (CN_{1tr}), 150.3 (CN_3), 159.4 (CO).

6b: yield 99%, oil. IR (KBr, ν_{max}/cm^{-1}): 2988, 2148 (N_3), 1724 (CO), 1552, 1352, 1272, 1176, 1156, 992, 744. ^{1}H NMR, δ: 1.38 (t, 3H, Me, *J* 7.1 Hz), 4.44 (q, 2H, CH_2, *J* 7.1 Hz), 5.17 (s, 2H, CH_2). ^{13}C NMR, δ: 14.9 (CH_2*Me*), 32.4 (CH_2Cl), 63.6 (CH_2O), 139.1, 142.2, 145.2, 152.0, 161.5 (CO). MS, *m*/*z* (%): 298 (M^+, 35), 253 (M^+ – OEt, 25), 113 (50), 52 (100).

7: yield 81%, oil. IR (KBr, ν_{max}/cm^{-1}): 2160 (N_3), 1588, 1528, 1456, 1264, 1200, 784.

8: yield 88%, mp 79–80 °C, R_f 0.85 (C_6H_6). IR (KBr, ν_{max}/cm^{-1}): 3144, 3124, 2148 (N_3), 1596, 1556, 1532, 1336, 1068, 740. ^{1}H NMR, δ: 6.44 (s, 2H, 2CH), 7.38 (s, 2H, 2CH). ^{13}C NMR, δ: 112.7 (CH), 120.1 (CHN), 145.6 (CN_3), 147.4 ($CN_{pyrr.}$). Found (%): C, 41.04; H, 2.33; N, 47.57. Calc. for $C_6H_4N_6O$ (%): C, 40.91; H, 2.27; N, 47.72.

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