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Ring formation and ring opening reactions of a dihydrothiadiazine cycle fused to 1,2,4-triazole

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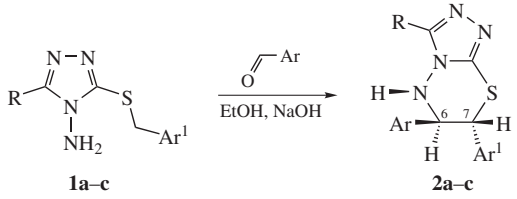
A new method of dihydrothiadiazine cycle annelation to 1,2,4-triazole derivatives is suggested and a ring opening reaction of the obtained dihydrothiadiazine cycle is found, leading to a substituted desoxybenzoine; the structures of both reaction products are supported by X-ray analysis.

Recently,[1] we reported a new intramolecular cyclization of S-methylene derivatives of *N*-imidazolylimines giving 3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazines through the C–C bond formation at thiadiazine ring closing. Here we show that a similar reaction with 4-amino-3-nitrobenzylthio-1,2,4-triazole derivatives can be used as a new route for the synthesis of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines. High interest in the fused triazolo[3,4-*b*][1,3,4]thiadiazine systems is stimulated by their broad biological activity, whereas their syntheses are mainly based on the cyclocondensation of 5-substituted 4-amino-1,2,4-triazole-3-thiones with α-halocarbonyl compounds.[2]

By the condensation of 5-substituted 4-amino-3-nitrobenzylthio-1,2,4-triazoles **1a–c**† with benzaldehydes under base catalysis conditions, triazolo[3,4-*b*][1,3,4]thiadiazines **2**‡ were obtained (Scheme 1). This method of formation of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines has not been described before.



1a–c **2a–c**

a R = Ph, Ar = 4-ClC_6H_4, Ar^1 = 4,5-$(MeO)_2$-2-$NO_2C_6H_2$
b R = Ph, Ar = 4-ClC_6H_4, Ar^1 = 4-$NO_2C_6H_4$
c R = 2-furyl, Ar = 3-$NO_2C_6H_4$, Ar^1 = 4-$NO_2C_6H_4$

Scheme 1

The ^{1}H NMR spectra of thiadiazines **2** contain two single-proton doublets of the N(5)H and C(7)H at 7.6 and 5.2 ppm, as well as a doublet of doublets of the C(6)H group at 5.0 ppm. The spin–spin coupling constant of H(6) and H(7) (*J* 10 Hz) evidences their pseudoaxial *trans*-position with respect to the thiadiazine cycle. Good resolution of all signals and the absence of doubling suggest that thiadiazines **2** constitute a racemic compound and not a mixture of the four possible stereoisomers due to the presence of the two asymmetric centers C(6) and C(7). Thus, the reaction of the thiadiazine cycle formation is diastereoselective.

† Initial 4-amino-5-R-1,2,4-trialoze-3-thiones and their benzylthio derivatives **1a–c** were obtained according to known methods.[3,4]

The structure of compound **2b** was confirmed by X-ray analysis§ (Figure 1). According to X-ray diffraction (XRD) studies, **2b** crystallizes in centrosymmetric space group (*C*2/*c*) with a different configuration of the asymmetric atoms resulting in the presence of two corresponding enantiomers in the crystal. The examination of molecular geometry revealed that the bond lengths and angles do not significantly deviate from the typical values accepted for them. The conformation of the thiadiazine cycle in **3** can be described as a slightly distorted sofa with the C(6) atom deviating by 0.64 Å from the plane formed by other atoms of the cycle. The aromatic substituents at the chiral C(6) and C(7) atoms are both in the equatorial position relative to the mean plane of the thiadiazine fragment; the angles between the latter and the C(6)–C(16) and C(7)–C(23) bond lines are 91(1) and 114(1)°, respectively.

‡ *General procedure for the synthesis of* **2a–c**. Equimolar quantities (5 mmol) of compound **1** and aromatic aldehyde were refluxed for 1–1.5 h in EtOH (10 ml) in the presence of NaOH (5 mmol). The precipitate was filtered and recrystallized from MeCN.

*6-(4-Chlorophenyl)-7-(4,5-dimethoxy-2-nitrophenyl)-3-phenyl-6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine* **2a**: yield 81%, mp 305 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.77, 3.90 (2s, 3H, OMe), 5.22 [dd, 1H, C(6)H, *J* 10.3 and 10.4 Hz], 5.71 [d, 1H, C(7)H, *J* 10.0 Hz], 7.24 (d, 2H, 4-ClC_6H_4, *J* 8.8 Hz), 7.33 (d, 3H, 4-ClC_6H_4, *J* 8.8 Hz), 7.44–7.49 (m, 4H, Ph, H_{Ar}), 7.25 (d, 1H, NH, *J* 11.1 Hz), 7.87–7.97 (m, 2H, Ph). MS, *m*/*z* (%): 463 (17), 326 (4), 258 (1), 196 (5), 177 (70), 152 (13), 136 (48), 103 (100), 77 (63). Found (%): C, 56.32; H, 3.44; N, 13.29. Calc. for $C_{24}H_{20}ClN_5O_4S$ (%): C, 56.52; H, 3.95; N, 13.73.

*6-(4-Chlorophenyl)-7-(4-nitrophenyl)-3-phenyl-6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine* **2b**: yield 58%, mp 285 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.97 [dd, 1H, H(6), *J* 10.1 and 10.2 Hz], 5.19 [d, 1H, H(7), *J* 9.8 Hz], 7.29 (s, 4H, Ar), 7.42–7.45 (d, 3H, Ph), 7.49 (d, 1H, NH, *J* 10.5 Hz), 7.68 (d, 2H, Ar, *J* 8.8 Hz), 7.92 (m, 2H, Ph), 8.08 (d, 2H, Ar, *J* 8.8 Hz). MS, *m*/*z* (%): 310 (3), 273 (10), 259 (11), 192 (14), 177 (29), 152 (41), 138 (34), 103 (85), 89 (100), 77 (86). Found (%): C, 58.84; H, 3.91; N, 15.41. Calc. for $C_{22}H_{16}ClN_5O_2S$ (%): C, 58.73; H, 3.58; N, 15.57.

*3-(2-Furyl)-6-(3-nitrophenyl)-7-(4-nitrophenyl)-6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine* **2c**: yield 45%, mp 248–250 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.24 [dd, 1H, C(6)H, *J* 9.2 and 10.2 Hz], 5.37 [d, 1H, C(7)H, *J* 10.5 Hz], 6.63 (dd, 1H, H_{furyl}, *J* 0.8 and 1.8 Hz), 7.04 (d, 1H, H_{furyl}, *J* 3.3 Hz), 7.57 (dd, 1H, 3-$NO_2C_6H_4$, *J* 8.3 and 7.9 Hz), 7.67 (d, 1H, NH, *J* 9.7 Hz), 7.73 (d, 3H, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, *J* 8.8 Hz), 7.89 (s, 1H, H_{furyl}), 8.09 (d, 1H, 3-$NO_2C_6H_4$, *J* 7.8 Hz), 8.12 (d, 2H, 4-$NO_2C_6H_4$, *J* 8.3 Hz), 8.29 (s, 1H, 3-$NO_2C_6H_4$). MS, *m*/*z* (%): 228 (2), 210 (3), 176 (4), 165 (16), 133 (11), 121 (15), 109 (16), 93 (100), 89 (50), 77 (63). Found (%): C, 53.57; H, 3.71; N, 18.22. Calc. for $C_{20}H_{14}N_6O_5S$ (%): C, 53.33; H, 3.13; N, 18.66.

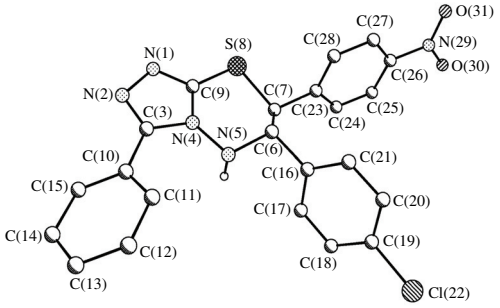


Figure 1 General view of compound **2b**. Hydrogen atoms are omitted for clarity.

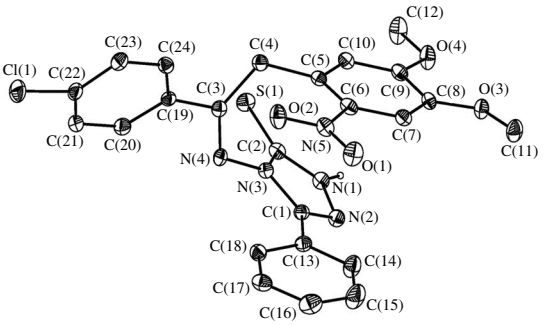
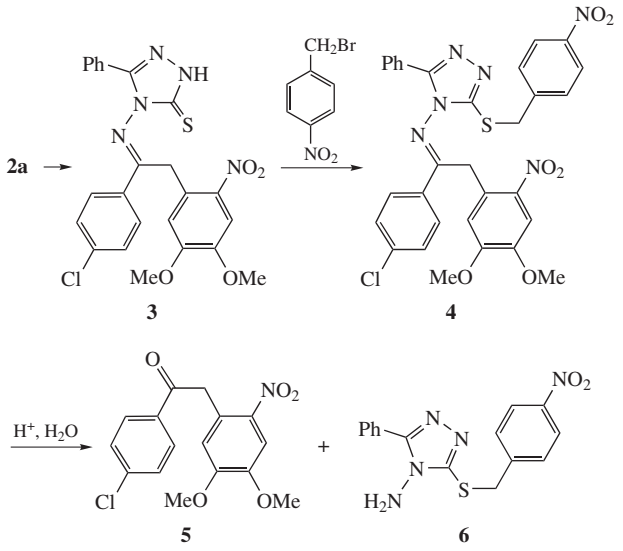


Figure 2 General view of compound **3** in representation of atoms *via* thermal ellipsoids (P = 50%). Hydrogen atoms are omitted for clarity.

In the course of our investigations of **2a**, a dihydrothiadiazine ring opening reaction going through the S–C bond cleavage has been found, which led to the formation of compound **3** (Scheme 2).¶ The ^{1}H NMR spectrum of **3** contains an AB-quartet of the prochiral methylene group at 4.3–4.9 ppm. The structure of **3** was confirmed by X-ray analysis§ (Figure 2). In line with XRD data, the geometrical parameters for the molecule of **3** are also close to the standard ones for this type of compounds. The mutual disposition of the heterocyclic and nitroaryl residues is a cisoid one. Although the smallest interatomic distance between them was found to be approximately 3.0 Å, the corresponding dihedral angle of 23(1)° prevents them from exhibiting the stacking interaction. On the other hand, such an arrangement of substituents results in the formation of centrosymmetric dimers *via* H-bonding between the NH group of the heterocycle and the oxygen atom of the methoxy group [N···O 3.037(2) Å, NHO 171(1)°].



Scheme 2

The thio group alkylation of compound **3** by *p*-nitrobenzylbromide leads to the formation of corresponding sulfide **4**,¶ the hydrolysis of which results in desoxybenzoine **5** and 4-amino-3-(4-nitrobenzylthio)-5-phenyl-1,2,4-triazole **6**, which is identical to initial substance **1b** in physico-chemical and spectral characteristics.

Therefore, the formation and further thiadiazine ring opening reactions enable obtaining desoxybenzoine derivatives from initial aromatic aldehyde and benzylhalogenide by their addition to the 5-substituted 4-amino-3-thio-1,2,4-triazole functional groups.

Online Supplementary Materials

Supplemetary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.09.008.

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§ *Crystallographic data*. Crystals of **2b** ($C_{22}H_{16}ClN_5O_2S$, M = 349.91) are monoclinic, space group $C2/c$, at 100 K: a = 27.4221(12), b = = 8.6924(5) and c = 20.7520(12) Å, β = 124.784(5)°, V = 4062.6(4) Å^3, Z = 8 (Z' = 1), d_{calc} = 1.471 g cm^{-3}, μ(MoKα) = 3.22 cm^{-1}, F(000) = 1856. Crystals of **3** ($C_{24}H_{20}ClN_5O_4S$, M = 509.96) are triclinic, space group $P\bar{1}$, at 100 K: a = 8.4216(6), b = 11.0433(8) and c = 12.4718(9) Å, α = = 93.573(2), β = 90.349(2), γ = 96.911(2)°, V = 1149.13(14) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.474 g cm^{-3}, μ(MoKα) = 3.00 cm^{-1}, F(000) = 528. Intensities of 18241 (**2b**) and 15115 (**3**) reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 60°$] and 5399 independent reflections [R_{int} = 0.0352] for **2b** and 6679 [R_{int} = 0.0319] for **3** were used in a further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms of NH groups were located from the Fourier synthesis of the electron density. Positions of H(C) atoms were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model. For **2b** the refinement converged to wR_2 = 0.1094 and GOF = 1.007 for all independent reflections [R_1 = 0.0366 was calculated against F for 4430 observed reflections with $I > 2\sigma(I)$]. For **3** the refinement converged to wR_2 = 0.0978 and GOF = 1.010 for all independent reflections [R_1 = = 0.0411 was calculated against F for 5041 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[5]

CCDC 701622 and 701623 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

¶ *4-[1-(4-Chlorophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethylideneamino]-2,4-dihydro-3*H*-5-phenyl-1,2,4-triazole-3-thione* **3**. Thiadiazine **2a** (1 mmol) was dissolved in 5 ml DMF and added dropwise the EtONa solution (4 mmol) in 3 ml EtOH. After 15 min, the reaction mixture was diluted with water and neutralized with dilute AcOH. Recrystallized from MeOH, yield 62%, mp 236 °C.

N-*[1-(4-Chlorophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethylideneamino]-3-(4-nitrobenzyl)thio-4*H*-5-phenyl-1,2,4-triazole-4-amine* **4**. Triazolethione **3** was alkylated analogously to the obtaining method of compounds **1**. Recrystallized from the mixture of benzene/hexane (3:1). Yield 67%, mp 127 °C.

1-(4-Chlorophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethanone **5**. Compound **4** was refluxed for 2 h in 40% HCl solution. Extracted with $CHCl_3$, evaporated to dryness. The substance was isolated by column chromatography [Al_2O_3 (III); eluent, $CHCl_3$]. Yield 30%, mp 185 °C.

For spectral characteristics of compounds **3**–**5**, see Online Supplementary Materials.