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Mendeleev Commun., 2016, **26**, 375–377
Mendeleev Communications

Tandem A_N–A_N reactions in the synthesis of tetrahydrothiazolo[4,5-*e*][1,2,4]triazines

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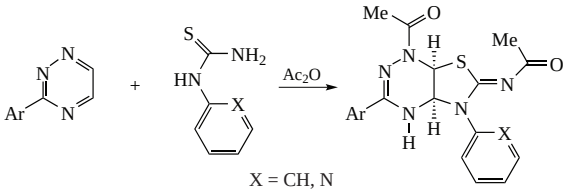
DOI: 10.1016/j.mencom.2016.09.002

Reaction of 3-aryl-1,2,4-triazines with S,N-dinucleophilic *N*-(het)arylthioureas in acetic anhydride at room temperature affords the cyclization products, tetrahydrothiazolo[4,5-*e*]-[1,2,4]triazines in good yields. The structure of the heterocyclic system thus formed was confirmed by X-ray diffraction analysis.



The tandem addition of bifunctional nucleophilic reagents at two adjacent carbon atoms of π-deficient azaaromatics (pyrazines, 1,2,4-triazines, and their benzo analogues) is in attention as an efficient route to fused heterocyclic systems.[1–7]

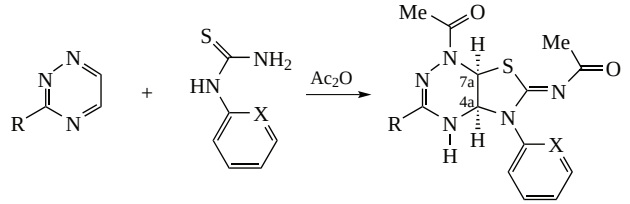
We have reported earlier, that the tandem A_N–A_N reactions of 3-aryl-1,2,4-triazines with a number of S,N-dinucleophilic reagents, such as arylthioamides and 4-arylthiosemicarbazides result in annelation of the thiazole ring,[8,9] while cyclizations of *N*(1)-alkyl-5-methoxy-1,2,4-triazinium salts with unsubstituted thiosemicarbazide, proceeding as the A_N–S_N^{ipso} tandem reaction, afford imidazo annelated triazines.[10] Thioureas in the reaction with 5-metoxy-1,2,4-triazines in acetic anhydride produce only imidazo annelated triazines.[10] In principle, thioureas can represent not only N,N-dinucleophilic but also S,N-dinucleophilic reagents, and, therefore, their cyclizations with 1,2,4-triazines can give rise to annelation of imidazole or thiazole rings.

Herein we have found that cyclizations of 3-aryl-1,2,4-triazines **1a**–**c** with (het)arylthioureas **2** in acetic anhydride at room temperature result in annelation of the thiazole ring to form tetrahydrothiazolo[4,5-*e*][1,2,4]triazines **3a**–**d** (Scheme 1).†

The evidence for the structure of cycloadducts **3a**–**d** was provided by the data of two-dimensional ^{1}H and ^{13}C NMR spectroscopy (2D HMBS, 2D HSQC and 2D NOESY procedures), and the X-ray diffraction analysis.

The resonance signals of two bridgehead H^{4a} and H^{7a} hydrogen atoms in the ^{1}H NMR spectrum of compound **3a** are in a full agreement with the formation of this cyclic system. The signal of H^{7a} is observed at δ 6.59 as a doublet with a vicinal coupling constant $J_{H^{4a},H^{7a}}$ 6.5 Hz, whereas the signal of H^{4a} is observed at δ 6.33 as a doublet of doublets with two vicinal constants $J_{H^{4a},H^{7a}}$ 6.5 Hz and J_{H^{4a},N^4H} 1.8 Hz. Value of 6.5 Hz corresponds to the *cis* orientation of the bridgehead protons. Also it indicates annelation of a five-membered ring to the 1,2,4-triazine ring.[11] The signal of NH group appears as a broad singlet at δ 7.90. All other resonance signals can easily be assigned: multiplets of phenyl protons at δ 7.37–7.46 and 7.90–7.93, multiplets of the pyridine ring protons at δ 7.33, 7.93, 8.10 and 8.53, and singlets of two acetyl groups at δ 2.12 and 2.32 (see Figures S1 and S2, Online Supplementary Materials).

Similar patterns have been revealed in ^{1}H NMR spectra of compounds **3b–d**, which have characteristic signals of the bridgehead protons H^{7a} (a doublet at δ 6.57–6.67 with $^3J_{H^{4a},H^{7a}}$ 6.3–6.4 Hz) and H^{4a} (a doublet of doublets at δ 6.16–6.23 with $^3J_{H^{4a},H^{7a}}$



1a R = Ph
1b R = 4-MeC_6H_4
1c R = 4-$MeOC_6H_4$

2a X = N
2b X = CH

3a R = Ph, X = N
3b R = Ph, X = CH
3c R = 4-MeC_6H_4, X = N
3d R = 4-$MeOC_6H_4$, X = N

Scheme 1

† *Synthesis of tetrahydrothiazolo[4,5-*e*][1,2,4]triazines* **3a**–**d** (*general procedure)*. Arylthiourea **2** (1 mmol) was added to a solution (in case of **1a**) or suspension (for **1b**,**c**) of 3-substituted 1,2,4-triazine **1** (1 mmol) in acetic anhydride. The reaction mixture was stirred at room temperature for 7–27 h. The precipitate obtained was filtered and washed with a small amount of acetic anhydride, diethyl ether and dried in air. For the analytical data, see Online Supplementary Materials.

(Z)-N-*[1-Acetyl-3-phenyl-5-(pyridin-2-yl)-1,4a,5,7a-tetrahydrothiazolo-[4,5-*e*][1,2,4]triazin-6(4*H*)-ylidene]acetamide* **3a**. The reaction was carried out in 1 ml of acetic anhydride for 7 h. Yield 0.79 g (72%), mp 181–182 °C. ^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 3H, C^6=NCOMe), 2.32 (s, 3H, N^1COMe), 6.33 (dd, 1H, H^{4a}, *J* 6.5, 1.8 Hz), 6.59 (d, 1H, H^{7a}, *J* 6.5 Hz), 7.33 (ddd, 1H, $H^{5''}_{Py}$, *J* 7.3, 4.9, 1.0 Hz), 7.40 (m, 2H, $H^{3'}_{Ph}$ and $H^{5'}_{Ph}$), 7.46 (t, 1H, $H^{4'}_{Ph}$, *J* 7.2 Hz), 7.62 (dd, 2H, $H^{2'}_{Ph}$ and $H^{6'}_{Ph}$, *J* 8.3, 1.5 Hz), 7.90 (br.s, 1H, NH, *J* 1.8 Hz), 7.93 (ddd, 1H, $H^{4''}_{Py}$, *J* 8.4, 7.3, 1.9 Hz), 8.10 (ddd, 1H, $H^{3''}_{Py}$, *J* 8.4, 1.0, 0.9 Hz), 8.53 (ddd, 1H, $H^{6''}_{Py}$, *J* 4.9, 1.9, 0.9 Hz). ^{13}C NMR (DMSO-d_6) δ: 20.96 (q, 1C, N^1CO*Me*, *J* 129.4 Hz), 27.27 (q, 1C, C^6=NCO*Me*, *J* 127.7 Hz), 52.16 (dd, 1C, C^{7a}, *J* 166.5, 2.9 Hz), 65.19 (d, 1C, C^{4a}, *J* 171.6 Hz), 119.78 (ddd, 1C, $C^{3''}_{Py}$, *J* 172.7, 6.6, 1.2 Hz), 121.30 (dt, 1C, $C^{5''}_{Py}$, *J* 166.3, 7.4 Hz), 126.16 (ddd, 2C, $C^{2'}_{Ph}$ and $C^{6'}_{Ph}$, *J* 159.2, 7.6, 5.8 Hz), 128.29 (dd, 2C, $C^{3'}_{Ph}$ and $C^{5'}_{Ph}$, *J* 160.4, 7.5 Hz), 130.28 (dt, 1C, $C^{4'}_{Ph}$, *J* 162.0, 7.8 Hz), 132.20 (t, 1C, $C^{1'}_{Ph}$, *J* 7.5 Hz), 138.03 (ddd, 1C, $C^{4''}_{Py}$, *J* 166.4, 6.6, 1.7 Hz), 145.10 (m, 1C, C^3), 147.77 (ddd, 1C, $C^{6''}_{Py}$, *J* 180.80, 7.6, 3.7 Hz), 150.93 (dd, 1C, $C^{2''}_{Py}$, *J* 12.4, 9.3 Hz), 166.38 (d, 1C, C^6, *J* 5.5 Hz), 170.69 (qd, N^1*C*OMe, *J* 6.3, ~0.6 Hz), 182.08 (q, C^6=N*C*OMe, *J* 6.4 Hz). MS, *m/z* (%):

6.3–6.4 Hz and J_{H^{4a},N^4H} 1.3–1.7 Hz). Values of the vicinal coupling constants between bridgehead protons ($^3J_{H^{4a},H^{7a}}$ 6.3–6.4 Hz) indicate annelation of a five-membered ring to the 1,2,4-triazine ring (see Figures S3–S8, Online Supplementary Materials).

The data of the ^{13}C NMR spectra are in agreement with the structure of thiazolo annelated 1,2,4-triazines. The informative part of the ^{13}C NMR spectra is presented by the resonance signals of carbons at δ 166.38, 170.69 and 182.08. Based on the literature data, the signal at δ 182.08 might be assigned to either C=O of an acetyl fragment or C=S of the imidazole ring annelated to the 1,2,4-triazine ring.[11–13] However, in the HMBC spectra of **3a**, two carbon resonances with chemical shifts δ 170.69 and 182.08 have cross-peaks with protons of acetyl fragments, thus indicating that they belong to C=O carbon resonances of these acetyl groups (see Figures S9 and S10, Online Supplementary Materials). Moreover, these cross-peaks in the HMBC spectra confirm that the reaction of 1,2,4-triazine with arylthioureas results in annelation of the thiazole ring. At the same time, the data of the ^{13}C NMR spectra are not sufficient to distinguish unambiguously the heterocycle fusion pattern.

In the ^{13}C NMR spectra of **3a** the bridgehead carbon atoms C^{4a} and C^{7a} can be identified on the basis of the literature data, as signals at δ 65.19 and 52.16, respectively (see Figures S10–S12, Online Supplementary Materials).

The unequivocal evidence for mutual orientation of heterocyclic rings in compound **3a** has been obtained by means of the X-ray diffraction analysis. It is worth noting that this case is the first successful example of X-ray analysis of such type of cyclic adducts in the series of 1,2,4-triazines. The geometry of **3a** is shown in Figure 1.‡

According to the X-ray diffraction analysis data, compound **3a** is crystallized in the form of centrosymmetrical spatial group of the monoclinic system. The axis lengths *a* and *b* of the primitive cell of **3a** are nearly 10 times of difference, being 44.495(13) and 4.7093(5) Å, respectively (Figures 1, 2).

All atoms of the triazine ring, with the exception of C(15) (deviation 0.45 Å), lay in the same plane within 0.02 Å. The phenyl group is nearly coplanar with the triazine ring [the angle of rotation relative to C(6)–C(12) is 2.6°]. The thiazole ring is not planar, atoms S(1) and C(14) (Figure 2) are located at one side of the mean-square plane S(1)C(15)C(14)N(4)C(13), while three other atoms of the ring are localized at the other side of this plane. The bicyclic system has U-shaped configuration with

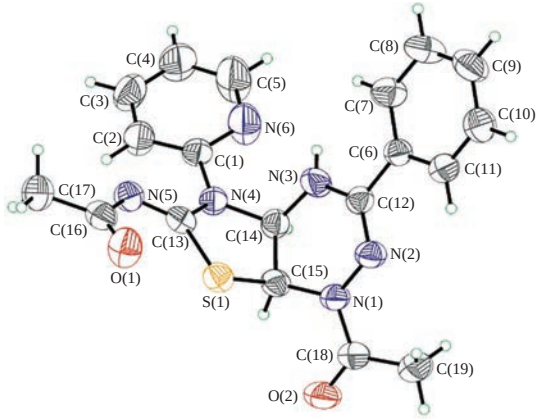


Figure 1 Overall view of molecule **3a**.

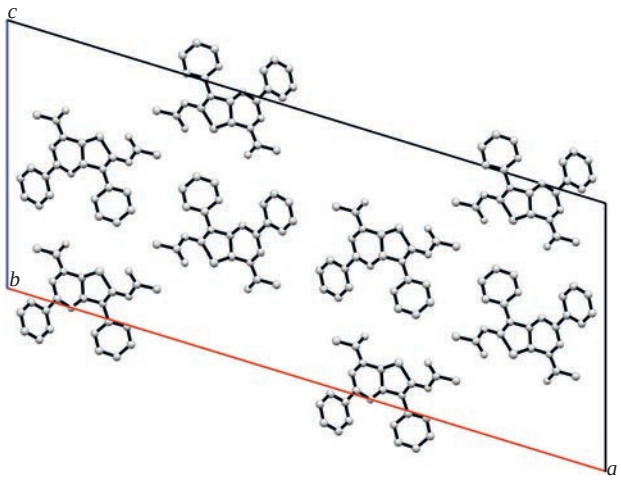


Figure 2 Molecular packing in the crystal of **3a**.

394 (7) $[M]^+$, 195 (15), 194 (100), 159 (17), 158 (62), 152 (45), 137 (8), 120 (29), 104 (41), 94 (18), 78 (30), 77 (14), 43 (40). Found (%): C, 57.99; H, 4.78; N, 21.28. Calc. for $C_{19}H_{18}N_6O_2S$ (%): C, 57.85; H, 4.60; N, 21.31.

(Z)-N-*[1-Acetyl-3,5-diphenyl-1,4a,5,7a-tetrahydrothiazolo[4,5*-e*]-[1,2,4]triazin-6(4*H*)-ylidene]acetamide* **3b**. The reaction was carried out in 1.1 ml of acetic anhydride for 24 h. Yield 0.79 g (17%), mp 169–170 °C. ^{1}H NMR (DMSO-d_6) δ : 2.24 (s, 3H, C^6=NCOMe), 2.56 (s, 3H, N^1COMe), 6.16 (dd, 1H, H^{4a}, *J* 6.4, 1.7 Hz), 6.67 (d, 1H, H^{7a}, *J* 6.4 Hz), 6.84–6.87 (m, 2H, Ph), 7.05–7.08 (m, 1H, Ph), 7.24–7.29 (m, 2H, Ph), 7.38–7.45 (m, 3H, Ph), 7.80–7.84 (m, 2H, Ph) , 7.97 (br. s, 1H, NH). MS, *m*/*z* (%): 393 (26) $[M]^+$, 258 (19), 216 (26), 193 (12), 191 (14), 173 (18), 159 (50), 158 (71), 151 (12), 135 (11), 119 (14). Found (%): C, 61.08; H, 4.81; N, 17.84. Calc. for $C_{20}H_{19}N_5O_2S$ (%): C, 61.05; H, 4.87; N, 17.80.

(Z)-N-*[1-Acetyl-5-(pyridin-2-yl)-3-(*p*-tolyl)-1,4a,5,7a-tetrahydrothiazolo-[4,5*-e*][1,2,4]triazin-6(4*H*)-ylidene]acetamide* **3c**. The reaction was carried out in 1.5 ml of acetic anhydride for 10 h. Yield 0.79 g (72%), mp 192–193 °C. ^{1}H NMR (DMSO-d_6) δ: 2.14 (s, 3H, C^6=NCOMe), 2.33 (s, 3H, C_6H_4*Me*), 2.36 (s, 3H, N^1COMe), 6.23 (dd, 1H, H^{4a}, *J* 6.3, 1.3 Hz), 6.59 (d, 1H, H^{7a}, *J* 6.3 Hz), 7.16 (d, 2H, Tol, *J* 8.0 Hz), 7.27 (ddd, 1H, $H^{5''}_{Py}$, *J* 7.3, 5.0, 0.6 Hz), 7.54 (br. s, 1H, NH), 7.54 (d, 2H, Tol, *J* 8.0 Hz), 7.86 (ddd, 1H, $H^{4''}_{Py}$, *J* 8.3, 7.3, 1.7 Hz), 8.13 (dd, 1H, $H^{3''}_{Py}$, *J* 8.3, 0.6 Hz), 8.46 (dd, 1H, $H^{6''}_{Py}$, *J* 5.0, 1.7 Hz). MS, *m*/*z* (%): 408 (5) $[M]^+$, 195 (14), 194 (100), 173 (17), 172 (70), 152 (38), 120 (26), 118 (37), 94 (14), 78 (25), 43 (35). Found (%): C, 58.57; H, 4.94; N, 20.56. Calc. for $C_{20}H_{20}N_6O_2S$ (%): C, 58.81; H, 4.93; N, 20.58.

(Z)-N-*[1-Acetyl-3-(4-methoxyphenyl)-5-(pyridin-2-yl)-1,4a,5,7a-tetra-hydrothiazolo[4,5*-e*][1,2,4]triazin-6(4*H*)-ylidene]acetamide* **3d**. The reaction was carried out in 0.8 ml of acetic anhydride for 27 h. Yield 0.79 g (16%), mp 170–171 °C. ^{1}H NMR (DMSO-d_6) δ: 2.14 (s, 3H, C^6=NCOMe), 2.32 (s, 3H, N^1COMe), 3.80 (s, 1H, OMe), 6.23 (dd, 1H, H^{4a}, *J* 6.4, 1.7 Hz), 6.57 (d, 1H, H^{7a}, *J* 6.4 Hz), 6.88 (d, 2H, C_6H_4, *J* 8.8), 7.27 (dd, 1H, $H^{5''}_{Py}$, *J* 7.0, 4.9 Hz), 7.54 (br. s, 1H, NH), 7.58 (d, 2H, C_6H_4, *J* 8.8 Hz), 7.86 (ddd, 1H, $H^{4''}_{Py}$, *J* 8.4, 7.0, 1.4 Hz), 8.11 (d, 1H, $H^{3''}_{Py}$, *J* 8.4 Hz), 8.47 (dd, 1H, $H^{6''}_{Py}$, *J* 4.9, 1.4 Hz). MS, *m*/*z* (%): 424 (3) $[M]^+$, 195 (12), 194 (100), 189 (20), 188 (60), 152 (33), 134 (27), 133 (13), 120 (24), 94 (10), 78 (22), 43 (43). Found (%): C, 56.43; H, 4.67; N, 19.84. Calc. for $C_{20}H_{20}N_6O_3S$ (%): C, 56.60; H, 4.75; N, 19.80.

‡ *Crystal data for* **3a**. The colorless needle crystal is monoclinic, space group *C*2/*c*, a = 44.495(13), b = 4.7093(5) and c = 18.976(2) Å, β = 106.991(19) °, V = 3802.6(13) Å, Z = 8, d_{calc} = 1.378 g cm^{-3}, μ = 0.199 mm^{-1}. On the angles 2.87 < θ < 26.38° 10480 reflections were collected, 3786 independent reflection (R_{int} = 0.0440), 2046 reflection with $I > 2\sigma(I)$. Completeness 97.4%. The final parameters of the refinement: R_1 = 0.0460, wR_2 = 0.1026 with $I > 2\sigma(I)$, R_1 = 0.1002, wR_2 = 0.1131 (all data), GOOF = 1.002, $\Delta\rho_e$ = 0.285/–0.192 eÅ^{-3}. The XRD analysis was accomplished on an Xcalibur 3 automated four-circled diffractometer with CCD-detector using standard procedure [295(2) K, MoKα-irradiation, graphite monochromator, ω-scans with 1° steps], absorption correction was not applied. The solution and refinement of the structure were performed using the program package SHELX97.[14] All non-hydrogen atoms were refined in anisotropic approximation, the H-atoms were placed in the calculated positions and refined in the 'riding' model with dependent isotropic displacement parameters.

CCDC 1430835 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

synclinal location of protons at C(14) and C(15) carbon atoms. Bond lengths correspond to the structure given in Figure 1. Indeed, the distance between C(13) and N(5) atoms (1.293 Å) is significantly shorter than the standard value for C–N single bond. Also the length of C(12)–N(2) bond is 1.284 Å, thus corresponding to the double C=N bond (see Tables S1 and S2, Online Supplementary Materials).

The molecule contains NH-proton at N(3), which can be involved in hydrogen bonding. Actually, intramolecular N(3)–H···N(6) hydrogen bond is observed in crystals, fixing N(6) nitrogen atom of the pyridine ring. The length of H···N bond is 2.296 Å, while the angle N(3)–H···N(6) is 121.74°.

Note that aryl substituted thioureas are similar to aryl substituted thioamides and thiosemicarbazides as S,N-dinucleophiles in the reactions with 3-aryl-1,2,4-triazines under closed reaction conditions with the formation of thiazolo[4,5-*e*]-annelated adducts.[8,9]

In summary, the reaction of 3-aryl-1,2,4-triazines with *N*-(het)-arylthioureas occurring at room temperature under activation with acetic anhydride can be regarded as a convenient procedure for the preparation of tetrahydrothiazolo[4,5-*e*][1,2,4]triazines.

This work was supported by the Russian Science Foundation (grant no. 15-13-00077).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.09.002.

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Received: 4th March 2016; Com. 16/4864