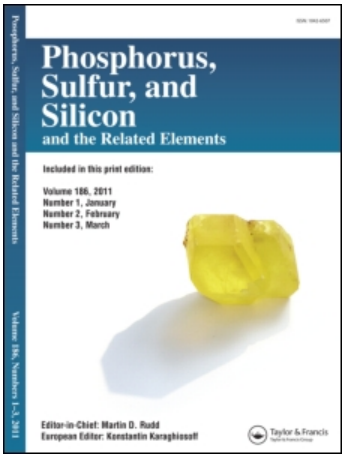

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Synthesis of Novel [1,2,4]triazolo[3,2-b][2,4,6]benzothiadiazocin-11(5H,10H)-One Derivatives

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SYNTHESIS OF NOVEL [1,2,4]TRIAZOLO[3,2-b][2,4,6]BENZOTHIADIAZOCIN-11 (5H,10H)-ONE DERIVATIVES

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*Several [1,2,4]triazolobenzothiadiazocin-11-ones **3** were prepared via ring expansion of [1,2,4]triazolo[3,2-b][2,4]benzothiazepin-10(5H)-ones **1** in presence of sodium azide. The reaction intermediate was isolated and characterized as an aryl isocyanate **2b**. A possible pathway for formation of novel triazolobenzothiadiazocin-11-one **3** is described.*

Keywords: Isocyanate; ring expansion; sodium azide; triazolobenzothiadiazocinone; triazolobenzothiazepinone; Tricyclic heterocycles

Triazolobenzothiadiazocines are a class of heterocycles which have not received much attention. A literature search revealed that very little was known about the synthesis and chemistry of these compounds and there is only one reference dealing with the synthesis of some [1,2,4]triazolo[3,4-b][1,3,4]benzothiadiazocines.[1]

In connection with our program of preparing new heterocyclic compounds which might exhibit potential biological activity, we have recently described the synthesis of some [1,2,4]triazolo[3,2-b][2,4]benzothiazepin-10(5H)-ones **1** members of a new heterocyclic ring system.[2] Pursuing our interest in novel fused heterocycles,[3–8] in this article we report the synthesis and the structure elucidation of some novel [1,2,4]triazolo[3,2-b][2,4,6]benzothiadiazocin-11(5H,10H)-ones **3a–c**. Thus, when the triazolobenzothiazepinones **1a–c** were allowed to interact with sodium azide in refluxing acetone, ring

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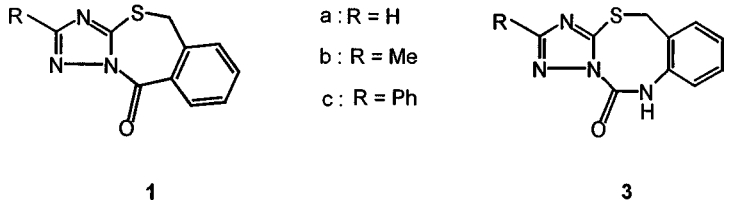
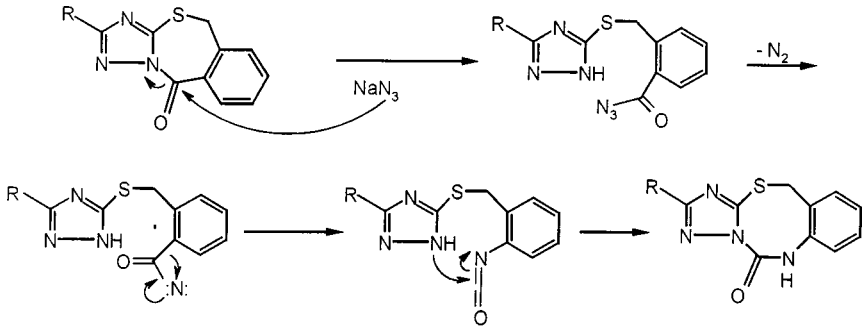


FIGURE 1

expansion reaction occured, giving the triazolobenzothiadiazocin-11-ones **3a–c** (Figure 1).

The structural assignment of novel compounds **3a–c** was based on the analytical and spectral data. The IR spectra was devoid of the keto C=O absorption band at 1700 cm^{-1} of the precursor but instead showed a band at 1640 cm^{-1} for amide C=O absorption and N–H band at 3300 cm^{-1}. The ^1H NMR spectra showed a singlet (1H, δ 8.50) for the N–H proton and a singlet (2H, δ 4.36–4.49) for the CH_2 protons, indicating the formation of a thiadiazocinone ring.

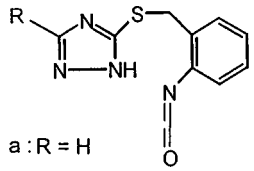
Compounds **3a–c** are considered to be produced by the intramolecular cyclisation of the NH nitrogen of the triazole ring of the intermediate **2a–c**, prepared from **1a–c** and sodium azide by a Curtius rearrangement,[9] to the isocyanate group accompanied by hydrogen migration (Scheme 1).



SCHEME 1

This hypothesis was substantiated by isolation of the crystalline arylisocyanate **2b** as the sole reaction intermediate, when **1b** treated with sodium azide in acetone at room temperature and the filtrate was kept refrigerated for 3 days (Figure 2).

The structure of the intermediate **2b** is based upon IR, ^1H NMR, CHN analysis and mass spectral data. The presence of a NH group in ^1H NMR



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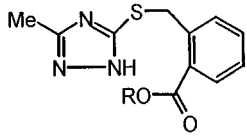

R=Me, Et, n-Pr

4

FIGURE 2

spectrum at δ 13.7 (in DMSO-d_6 solution) and a –N=C=O group[10] in IR spectrum at ν 2240 cm^{-1} are in agreement with the structure described. This intermediate was then converted to **3b** when heated under reflux in acetone.

The susceptibility of the thiazepinone ring toward cleavage with nucleophiles was demonstrated while attempting to purify **1b** on a silica column using MeOH as the eluent or when we tried to recrystallise it from EtOH. In both cases ring cleaved products **4** (R = Me, Et) were obtained. In a typical procedure, when we heated triazolobenzothiazepinon **1b** with several alcohols under reflux, we obtained the corresponding ring cleaved products **4** (R = Me, Et, n-Pr) in high yields (Figure 2).

In conclusion, the reaction of **1** with sodium azide in acetone, undergo ring cleavage to give an arylisocyanate **2** as the intermediate via a Curtius rearrangement. The intramolecular cyclisation of the intermediate afforded the ring expanded product **3**.

EXPERIMENTAL SECTION

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Mass spectra were scanned on a Varian CH-7 instrument at 70 ev. Microanalysis were performed by Tarbiat Modarres University, Tehran, Iran.

General Procedure for the Preparation of Triazolobenzothiadiazocinones 3a–c

Sodium azide (0.2 g, 3 mmol) in water (10 ml) was added to a suspension of triazolobenzothiazepinone **1a–c** (1.7 mmol) in acetone (15 ml). The mixture was refluxed for 1.5 h. The precipitate was filtered off and

recrystallized from a suitable solvent to give **3a–c** in 58, 56, and 52% yield respectively.

[1,2,4]Triazolo[3,2-b][2,4,6]benzothiadiazocin-11 (5H,10H)-one(3a)

This compound was obtained as white crystals (ethanol-water), m.p. 208–210°C.

Anal. Calcd. for $C_{10}H_8N_4OS$: C, 51.71; H, 3.47; N, 24.12; S, 13.80, Found: C, 51.45; H, 3.41; N, 24.29; S, 13.86.

^{1}H NMR: δ (d_6-DMSO), 4.41 (s, 2H, S—CH_2), 6.9–7.9 (m, 4H, C_6H_4), 8.42 (s, 1H, N=CH), 8.50 (s, 1H, NH).

IR (KBr disc): ν, C=O, 1640 cm^{-1}; NH, 3295 cm^{-1}.

MS: m/z (%) 232(2), 231(16), 202(10), 129(73), 104(100), 76(16).

2-Methyl[1,2,4]triazolo[3,2-b][2,4,6]benzothiadiazocin-11 (5H,10H)-one (3b)

This compound was obtained as white crystals (acetone), m.p. 223–225°C.

Anal. Calcd. for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75; S, 13.02, Found: C, 53.71; H, 4.13; N, 22.69; S, 13.11.

^{1}H NMR: δ (d_6-DMSO), 2.30 (s, 3H, Me), 4.36 (s, 2H, S—CH_2), 6.9–7.8 (m, 4H, C_6H_4), 8.57 (s, 1H, NH).

IR (KBr disc): ν, C=O, 1640 cm^{-1}; NH, 3300 cm^{-1}.

MS: m/z (%) 246(2), 245(4), 244(15), 216(10), 129(100), 104(97), 76(78).

2-Phenyl[1,2,4]triazolo[3,2-b][2,4,6]benzothiadiazocin-11 (5H,10H)-one (3c)

This compound was obtained as white crystals (acetonitrile), m.p. 229–231°C.

Anal. Calcd. for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17; S, 10.39, Found: C, 62.28; H, 3.84; N, 18.14; S, 10.44.

^{1}H NMR: δ (d_6-DMSO), 4.49 (s, 2H, S—CH_2), 6.9–8.2 (m, 9H, Ph, and C_6H_4), 8.50 (s, 1H, NH).

IR (KBr disc): ν, C=O, 1640 cm^{-1}; NH, 3305 cm^{-1}.

MS: m/z (%) 308(4), 307(13), 306(22), 279(13), 129(52), 104(100), 76(22).

Preparation of 5-(2-Isocyanatobenzylsulfanyl)-3-methyl-1H-[1,2,4]triazole (2b)

Sodium azide (0.7 g, 10 mmol) in water (8 ml) was added to a suspension of **1b** (0.7 g, 3 mmol) in acetone (25 ml). The mixture was stirred at room temperature for 3 h. The filtrate was refrigerated for 3 days. The

crystalline compound was collected with no further purification, yield 40%, m.p. 210–212°C.

Anal. Calcd. for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75; S, 13.02, Found: C, 53.68; H, 4.05; N, 22.71; S, 13.10.

^{1}H NMR: δ (d_6-DMSO), 2.30 (s, 3H, Me), 4.63 (s, 2H, S—CH_2), 7.1–8.1 (m, 4H, C_6H_4), 13.7 (broad, 1H, NH).

IR (KBr disc): ν, —N=C=O, 2240 cm^{-1}.

MS: m/z (%) 246(2), 245(6), 244(22), 210(6), 200(4), 129(100), 102(18), 77(20), 76(54).

General Procedure for the Preparation of 2-(5-Methyl-2H-[1,2,4]triazol-3-ylsulfanylmethyl)-benzoic Acid Alkyl Ester, 4 (R = Me, Et, n-Pr)

Triazolobenzothiazepin **1b** (0.3 g) was refluxed with different alcohols for 1 h. The solvent was evaporated under reduced pressure. The residue was recrystallized from water to afford 4 (R = Me, Et, n-Pr).

2-(5-Methyl-2H-[1,2,4]triazol-3-ylsulfanylmethyl)-benzoic Acid Methyl Ester 4 (R = Me)

This compound was obtained as white crystals, yield 89%, m.p. 131–133°C.

^{1}H NMR: δ ($CDCl_3$), 2.40 (s, 3H, Me), 3.90 (s, 3H, MeO), 4.69 (s, 2H, S—CH_2), 7.2–8.0 (m, 4H, C_6H_4), 12.30 (broad, 1H, NH); IR (KBr disc), ν, C=O, 1727 cm^{-1}; NH, 3192 cm^{-1}; MS m/z, M^+263.

2-(5-Methyl-2H-[1,2,4]triazol-3-ylsulfanylmethyl)-benzoic Acid Ethyl Ester 4 (R = Et)

This compound was obtained as white crystals, yield 92%, mp 124–126°C.

^{1}H NMR: δ ($CDCl_3$), 1.37 (t, j = 7 Hz, 3H, Me), 2.38 (s, 3H, Me), 4.34 (q, j = 7 Hz, 2H, CH_2), 4.68 (s, 2H, S—CH_2), 7.2–8.0 (m, 4H, C_6H_4), 12.56 (broad, 1H, NH); IR (KBr disc), ν, C=O, 1703 cm^{-1}; NH, 3174 cm^{-1}; MS m/z, M^+277.

2-(5-Methyl-2H-[1,2,4]triazol-3-ylsulfanylmethyl)-benzoic Acid n-Propyl Ester 4 (R = n-Pr)

This compound was obtained as white crystals, yield 85%, m.p. 116–118°C.

^{1}H NMR: δ ($CDCl_3$), 0.90 (t, j = 7 Hz, 3H, Me), 1.64 (m, 2H, CH_2), 2.29 (s, 3H, Me), 4.16 (t, j = 7 Hz, 2H, CH_2O), 4.59 (s, 2H, S—CH_2),

7.2–8.0 (m, 4H, C_6H_4), 11.78 (broad, 1H, NH); IR (KBr disc), ν, C=O, 1709 cm^{-1}; NH, 3174 cm^{-1}; MS m/z, M^+291.

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