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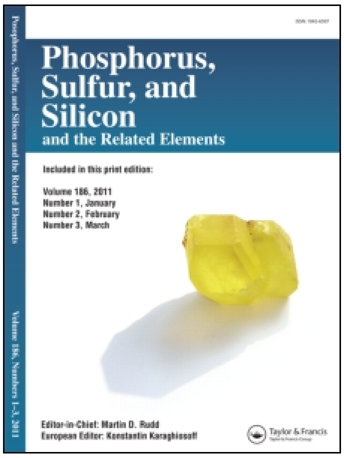

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Synthesis of 3-Substituted (6-[(*E*)-2-(1-Benzofuran-2-yl)ethenyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles

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Synthesis of 3-Substituted (6-[(*E*)-2-(1-Benzofuran-2-yl)ethenyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles

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*The reaction of (2*E*)-3-(1-benzofuran-2-yl)-2-propenoic acid with 4-amino-5-R-1,2,4-triazole-3-thioles has been investigated. It has been established, that 6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazole were formed as the result of heterocyclization.*

Keywords 1,3,4-thiadiazole; 1,2,4-triazole;; [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole; 4-amino-4*H*-1,2,4-triazole-3-thiol; benzofuran derivates; heterocyclization

INTRODUCTION

A large number of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles show a broad spectrum of biological activity—ntibacterial,[1–5] antimicrobial,[6–8] antifungal,[5,9–11] antihelmintic,[12,13] anticancer,[14–16] antiviral.[17]

The *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system (**I**) can be successfully synthesized by the following routes. The first one is the cyclocondensation of 4-amino-5-aryl-1,2,4-triazole-3-thiones **II** (Scheme 1) with acids in the presence of phosphorus oxychloride.[8–10,14,15,17–20] The second route involves a ring formation by the 5-substituted 2-hydrazino-1,3,4-thiadiazole **III** reaction with acids by reflux in methanol or xylene[11] (Scheme 1).

As a rule, 4-amino-5-aryl-1,2,4-triazole-3-thiones are used. They easily can be prepared from respective acids using previously reported methods.[5,18]

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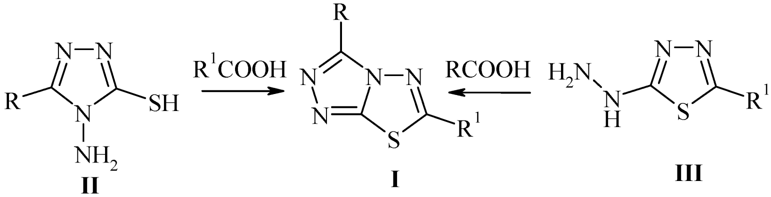


SCHEME 1

On the other hand heterocyclic compounds of the benzofuran and benzopyran series are important aromatic rings.[21–25] They occur in nature and exhibit wide range of valuable pharmacological properties. So, we decided to combine benzofuran heterocycle with 1,3,4-triazolo[3,4-*b*]-1,3,4-thiadiazole ring in order to obtain new heterocyclic compounds exhibiting biological activity.

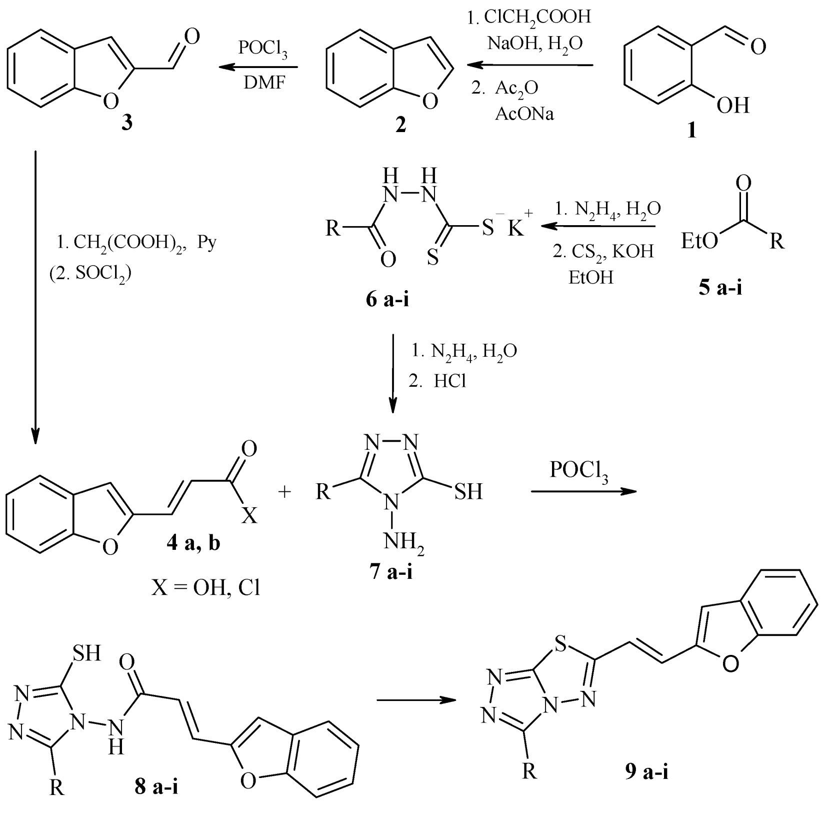
RESULTS AND DISCUSSION

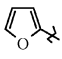
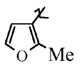
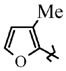
We have synthesized (2*E*)-3-(1-benzofuran-2-yl)-2-propenoic acid **4** (Scheme 2) in general good yield. Formylation of the 1-benzofuran **2**, which was prepared according to literature procedure[26] from salicylaldehyde by Vilsmeier–Haack reagent, afforded the 1-benzofuran-2-carbaldehyde[27] **3** in 71% yield. By the reaction of aldehyde **3** with malonic acid the corresponding (2*E*)-3-(1-benzofuran-2-yl)-2-propenoic acid **4** was obtained.

A new efficient synthesis of heterocycles that contain 1-benzofuran and triazolo[3,4-*b*][1,3,4]thiadiazole cycle compounds **9a–h** was developed by the cyclocondensation of the 5-substituted-4-amino-4H-1,2,4-triazole-3-thiol **7a–h** with acid **4a** or acid chloride **4b**. The first step of synthesis involves the reaction acylation of aminotriazole, the second one—intramolecular ring formation as shown in Scheme 2. Although compounds **8a–h** can be isolated and characterized, it is more convenient to treat them without isolating.

The structures of compounds **9a–i** were substantiated from microanalytical and spectral data. Analytical, ^{1}H-NMR, ^{13}C-NMR and mass spectral data are in agreement with the proposed structures. In ^{1}H-NMR spectrum compounds **9a–i** benzofuranethenyle fragments are showed as two triplets, two doublets and singlet (3-H) of benzofurane and two doublets ($J \approx 16$ Hz) of protons of the external double bond.

As a result we have developed a new method for the synthesis of 6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles by the cycloaddition of (1-benzofuran-2-yl)-2-propenoic acid and 4-amino-5-aryl-1,2,4-triazole-3-thiones derivatives. The convenient



9	a	b	c	d	e	f	g	h	i
R	Me	Pr	PhCH$_2$	3-MePh	4-MePh	4-BrPh			

SCHEME 2

synthesis provides access to polynuclear heterocycles which contain the basic ring structure found in molecules that exhibit biological activity.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were run on a Mercury 400 MHz and Bruker 200 (200 MHZ) instruments respectively using TMS as an internal reference and DMSO-d$_6$ sas solvent. The mass spectra were performed on a Agilent 1100 chromatomass spectrometer at 70 eV. The starting materials were commercially available and/or prepared in accordance to literature procedures **7a–h**.[5,18] Yields of products were not optimized.

Synthesis of 4-Amino-5-R-4*H*-1,2,4-triazole-3-thioles 7a–h

Acid ester **5** (0.01 mol) was refluxed with 20 ml of 85% $NH_2NH_2{\cdot}H_2O$ for 2 h; it was then cooled and diluted with water. Solid collected by filtration and dried. To 250 ml KOH (0.015 mol) absolute ethanol solution acid hydrazide (0.01 mol) and CS_2 (0.015 mol) were added. The solution was stirred at room temperature for 24 h, and then absolute ether (50 mL) was added to it and left as such for 2 h. The residue was filtered, washed (with ethanol and ether), and dried. This solid was dissolved in excess hydrazine hydrate (85%). The mixture was heated and refluxed for 6 h, cooled and poured into acidic ice water ($pH = 2$) to give solid which was filtered, dried and recrystallized.

Compounds **7a–h** were prepared as a white powdered solid in 56–74% yields count on acid ester: **7a**, m.p. 192–193°C (ethanol–H_2O), yield 56%; **7b**, m.p. 112–113°C (ethanol–H_2O), yield 58%; **7c**, m.p. 180°C (ethanol), yield 62%; **7d**, m.p. 148–149°C (ethanol) yield 67%; **7e**, m.p. 188°C (ethanol) yield 74%; **7f**, m.p. 194°C (ethanol) yield 69%; **7g**, m.p. 197°C (ethanol) yield 60%; **7h**, m.p. 214°C (ethanol) yield 71%; **7i**, m.p. 127–128°C (ethanol), yield 60%.

(2*E*)-3-(1-Benzofuran-2-yl)-2-propenoic Acid 4a

In a 100-ml round-bottomed flask, fitted with a reflux condenser, are placed 10.4 g (0.1 mol) of malonic acid, 14.6 g (0.1 mol) of 1-benzofuran-2-carbaldehyde **3**, and 40 ml of pyridine. Piperidine (0.7 ml) is then added and the mixture is heated to 80°. An internal temperature of 80–85° is maintained for 1 hour, and the material is finally heated under reflux 109–115°C for an additional 3 h. After being cooled the reaction mixture is poured into a large beaker containing 200 ml of cold water. The mixture is acidified by adding with stirring 50 ml of concentrated hydrochloric acid; it should be strongly acidic at this point. The crystals are separated by suction filtration and washed 4 times with 15 ml portions of cold water. The product is dried at 60–70°C. M.p. 221–222°C; yield 15,7 g. (84%). ^1H NMR ppm: δ 6.44 (d, $J = 15.8$, 1H, =CH), 7.29 (t, $J = 7.5$, 1H, benzofuran), 7.36 (s, 1H, 3–H benzofuran), 7.42 (t, $J = 7.1$, 1H, benzofuran), 7.60 (d, $J = 15.8$, 1H, CH=), 7.62 (d, $J = 7.5$, 1H, benzofuran), 7.71 (d, $J = 7.5$, 1H, benzofuran).^{13}C NMR ppm: δ 111.3 (C-3), 111.6 (C-7), 119.5 (C-4), 122.1 (C-5), 123.5 (C-6), 126.6 (C-3a), 128.0

(C=C), 130.9(C=C), 152.0 (C-2), 154.5 (C-7a), 167.0 (C=0). MS m/z: 188 (M^+). Anal. requires for $C_{11}H_8O_3$ (188.18) calcd./found: C, 70.21/70.30; H, 4.29/4.22.

(2*E*)-3-(1-Benzofuran-2-yl)-2-propenoyl Chloride 4b

A mixture of acid **6** (18.8 g, 0.1 mol) and thionyl chloride (17.8 g, 0.15 mol) in benzene was refluxed for 3 h; the product was distilled in vacuo. Yield 56%.

General Procedure for the Synthesis of Compounds (9a–i)

A mixture of 4-amino-5-R-1,2,4-triazole-3-thione **8** (5.0 mmol) and acid **4a** or acid chloride **4b** (5.5 mmol) in $POCl_3$ (20 ml) was refluxed for 1 h. The reaction mixture was gradually poured onto crushed ice with stirring. Some solid K_2CO_3 was added to the mixture with stirring, and then an appropriate amount of solid KOH was added to pH 8. The solid which separated after standing overnight was filtered, washed with cold water, dried, and recrystallized from DMF. The physical and spectral properties the compounds (**9 a–i**) are given below.

6-[(E)-2-(1-benzofuran-2-yl)ethenyl]-3-methyl[1,2,4]triazolo-[3,4-b] [1,3,4]thiadiazole (9a)

This compound was isolated as a reddish brown powdered solid, m.p. 257–258°C (ethanol–DMF) in 76% yield. ^1H NMR ppm: δ 2.66 (s, 3H, CH_3), 7.22–7.29 (m, 2H, benzofuran), 7.33 (d, J =16.6, 1H, CH=), 7.38 (pseudo t, 1H, benzofuran), 7.53 (d, J =7.8, 1H, benzofuran), 7.65 (d, J =16.6, 1H, =CH), 7.66 (d, J =7.8, 1H, benzofuran). MS m/z: 282 (M^+). Anal. requires for $C_{14}H_{10}N_4OS$ (282.32) calcd./found: C, 59.56/59.39; H, 3.57/3.46; N, 19.85/19.91; S, 11.36/11.31.

6-[(E)-2-(1-benzofuran-2-yl)ethenyl]-3-propyl[1,2,4]triazolo-[3,4-b] [1,3,4]thiadiazole (9b)

This compound was isolated as brown needles, m.p. 199–199°C (ethanol–DMF) in 71% yield. ^1H NMR ppm: δ 1.04 (t, J = 6.8, 3H, CH_3), 1.87 (6 lines, 2H, CH_2), 2.99 (t, J = 7.8, 2H, CH_2), 7.26 (t, J = 7.8, 1H, benzofuran), 7.27 (s, 1H, 3–H benzofuran), 7.34 (d, J = 16.1, 1H, CH=), 7.38 (pseudo t, 1H, benzofuran), 7.52 (d, J = 8.8, 1H, benzofuran), 7.64 (d, J = 16.1, 1H, CH=), 7.67 (d, J = 7.8, 1H, benzofuran). MS m/z: 310 (M^+). Anal. requires for $C_{16}H_{14}N_4OS$ (310.38) calcd./found: C, 61.92/61.82; H, 4.55/4.38; N, 4.55/4.76; S, 10.33/10.36.

*6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl]-3-benzyl[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazole (9c)*

This compound was isolated as a light yellow solid, m.p. 221–222°C (ethanol–DMF) in 81% yield. ^{1}H NMR ppm: δ 4.39 (s, 2H, CH_2), 7.21–7.41 (m, 9H, aromatic + CH=), 7.51 (d,$J =$ 8.8, 1H, benzofuran), 7.64 (d,$J =$ 16.6, 1H, =CH), 7.66 (d,$J =$ 7.8, 1H, benzofuran). MS m/z: 358 (M^+). Anal. requires for $C_{20}H_{14}N_4OS$ (358.42) calcd./found: C, 67.02/66.72; H, 3.94/3.89; N, 15.63/15.57; S, 8.95/8.81.

*6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl]-3-(3-methylphenyl)[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole (9d)*

This compound was isolated as a light yellow powdered solid, m.p. 215–216°C (ethanol–DMF) in 84% yield. ^{1}H NMR ppm: δ 2.54 (s, 3H, CH_3), 7.21–7.54 (m, 7H, aromatic + CH=), 7.68 (d,$J =$ 7.8, 1H, benzofuran), 7.75 (d,$J =$ 16.6, 1H, =CH), 8.08 (br. s, 2H, C_6H_4). MS m/z: 358 (M^+). Anal. requires for $C_{20}H_{14}N_4OS$ (358.42) calcd./found: C, 67.02/66.67; H, 3.94/3.91; N, 15.63/15.74; S, 8.95/8.85.

*6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl]-3-(4-methylphenyl)[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazole (9e)*

This compound was isolated as a white powdered solid, m.p. 191–193°C (ethanol-DMF) in 87% yield. ^{1}H NMR ppm: δ 2.39 (s, 3H, CH_3), 7.29 (pseudo t, 1H, benzofuran), 7.36–7.48 (m, 5H, aromatic), 7.62 (d, $J =$ 8.6, 1H, benzofuran), 7.73 (d, $J =$ 8.6, 1H, benzofuran), 7.78 (d, $J =$ 15.6, 1H, CH=), 8.14 (d, $J =$ 8.6, 2H, C_6H_4). MS m/z: 358 (M^+). Anal. requires for $C_{20}H_{14}N_4OS$ (358.42) calcd./found: C, 67.02/67.10; H, 3.94/3.88; N, 15.63/15.55; S, 8.95/9.04.

*6-[(*E*)-2-(1-benzofuran-2-yl)ethenyl]-3-(4-bromophenyl)[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazole (9f)*

This compound was isolated as a light yellow powdered solid, m.p. 224–226°C (ethanol–DMF) in 81% yield. ^{1}H NMR ppm: 7.27 (pseudo t, 1H, benzofuran), 7.31 (s, 1H, 3–H benzofuran), 7.40 (pseudo t, 1H, benzofuran), 7.47 (d, $J =$ 15.6, 1H, CH=), 7.53 (d,$J =$ 7.8, 1H, benzofuran), 7.68 (d, $J =$ 7.8, 1H, benzofuran), 7.74 (d, $J =$ 8.8, 2H, C_6H_4) 7.79 (d, $J =$ 15.6, 1H, =CH), 8.22 (d, $J =$ 8.8, 2H, C_6H_4). MS m/z: 423 (M^+). Anal. requires for $C_{19}H_{11}BrN_4OS$ (423.29) calcd./found: C, 53.91/54.02; H, 2.62/2.69; N, 13.24/13.30; S, 7.58/7.47.

6-[(E)-2-(1-benzofuran-2-yl)ethenyl]-3-(2-methyl-3-furyl)[1,2,4]-triazolo-[3,4-b][1,3,4]thiadiazole (9g)

This compound was isolated as brown needles, m.p. 204–205°C (ethanol–DMF) in 64% yield. ^{1}H NMR ppm: δ 2.70 (s, 3H, CH_3), 7.08 (br. s, 1H, 4–H furan), 7.26 (pseudo t, 1H, benzofuran), 7.28 (s, 1H, 3–H benzofuran), 7.38 (pseudo t, 1H, benzofuran), 7.40 (d, $J = 15.6$, 1H, CH=), 7.52 (d, $J = 7.8$, 1H, benzofuran), 7.61 (br. s, 1H, 5–H furan), 7.67 (d, $J = 7.8$, 1H, benzofuran), 7.70 (d, $J = 15.6$, 1H, =CH). MS m/z: 348 (M^+). Anal. requires for $C_{18}H_{12}N_4O_2S$ (348.38) calcd./found: C, 62.06/61.97; H, 3.47/3.36; N, 16.08/15.95; S, 9.20/9.29.

6-[(E)-2-(1-benzofuran-2-yl)ethenyl]-3-(2-furyl)[1,2,4]-triazolo-[3,4-b][1,3,4]thiadiazole (9h)

This compound was isolated as a yellow-powdered solid, m.p. 256–257°C (ethanol–DMF) in 57% yield. ^{1}H NMR ppm: 6.73 (br. s, 1H, 4-H furan), 7.23–7.32 (m, 3H, aromatic), 7.38 (pseudo t, 1H, benzofuran), 7.43 (d, $J = 16.1$, 1H, CH=), 7.53 (d, $J = 7.8$, 1H, benzofuran), 7.68 (d, $J = 7.8$, 1H, benzofuran), 7.76 (d, $J = 16.1$, 1H, =CH), 7.90 (br. s, 1H, 5–H furan). MS m/z: 334 (M^+). Anal. requires for $C_{17}H_{10}N_4O_2S$ (334.35) calcd./found: C, 61.07/60.90; H, 3.01/3.11; N, 16.76/16.95; S, 9.59/9.63.

6-[(E)-2-(1-benzofuran-2-yl)ethenyl]-3-(3-methyl-2-furyl)[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole (9i)

This compound was isolated as a reddish brown powdered solid, m.p. 222–223°C (ethanol–DMF). ^{1}H NMR ppm: δ 2.40 (s, 3H, CH_3), 6.57 (br. s, 1H, 4–H furan), 7.26 (t, $J = 7.8$, 1H, benzofuran), 7.29 (s, 1H, 3–H benzofuran), 7.39 (t, $J = 7.8$, 1H, benzofuran), 7.42 (d, $J = 16.1$, 1H, CH=), 7.52 (d, $J = 7.8$, 1H, benzofuran), 7.66 (d, $J = 7.8$, 1H, benzofuran), 7.70 (d, $J = 16.1$, 1H, =CH), 7.76 (br. s, 1H, 5–H furan). MS m/z: 348 (M^+). Anal. requires for $C_{18}H_{12}N_4O_2S$ (348.38) calcd./found: C, 62.06/61.83; H, 3.47/3.44; N, 16.08/15.96; S, 9.20/9.16.

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