

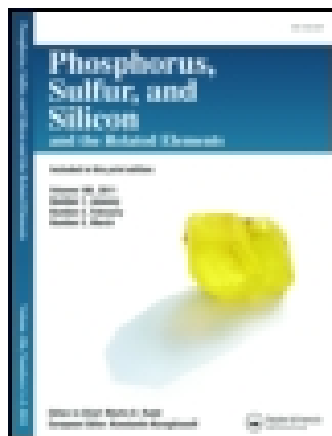
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REVISED SYNTHESIS OF SOME NEW DERIVATIVES OF BIOLOGICAL INTEREST 2-HETEROCYCLIC BENZOTHAZOLYL DERIVATIVES OF BIOLOGICAL INTEREST

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REVISED SYNTHESIS OF SOME NEW 2-HETEROCYCLIC BENZOTHAZOLYL DERIVATIVES OF BIOLOGICAL INTEREST

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Substituted benzothiazole at position 2 by a heterocyclic ring has been prepared by the action of bifunctional compounds on the active intermediate α -2-benzothiazolyl- β -arylaminoacrylonitrile (III). Compound III was obtained by refluxing α -2-benzothiazolyl- β , β -dimethylthioacrylonitrile (II) with aromatic amines in ethanol for a long time. Refluxing equimolar amounts of III and hydrazine, hydroxylamine, guanidine ethylenediamine and ethanolamine in presence of DMF yielded the corresponding 2-pyrazolo, isoxazolo, pyrimidino, 1,4-diazepino and 1,4-oxazepinobenzothiazole (V-IX), respectively. The structures of all newly prepared compounds have been confirmed by analytical and spectral data.

The biological importance of benzothiazole derivatives has resulted in much interest in their synthesis and chemistry^[1,2]. For the past decade the authors have been exploring the synthetic potential, scope, and limitations of activated nitriles in heterocyclic synthesis^[3-5]. Several new approaches for the synthesis of five members, six members and their fused heterocyclic derivatives have been developed during this work^[6,7].

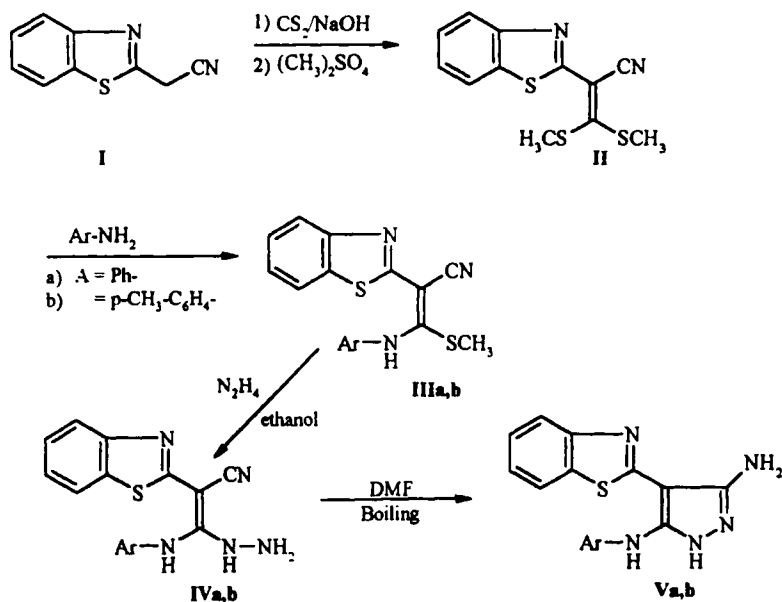
As a part of this investigation the reactions of α β -unsaturated nitriles (IIIa,b) and certain activated bifunctional reagents have been investigated. Reactions of this type have not been reported previously, but were found to give products in excellent yields under very mild conditions. Moreover, the resulting benzothiazole derivatives have latent functional substituents

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which have potential for further chemical transformations and new routes for the preparation of substituted benzothiazole derivatives with possible biological activity.

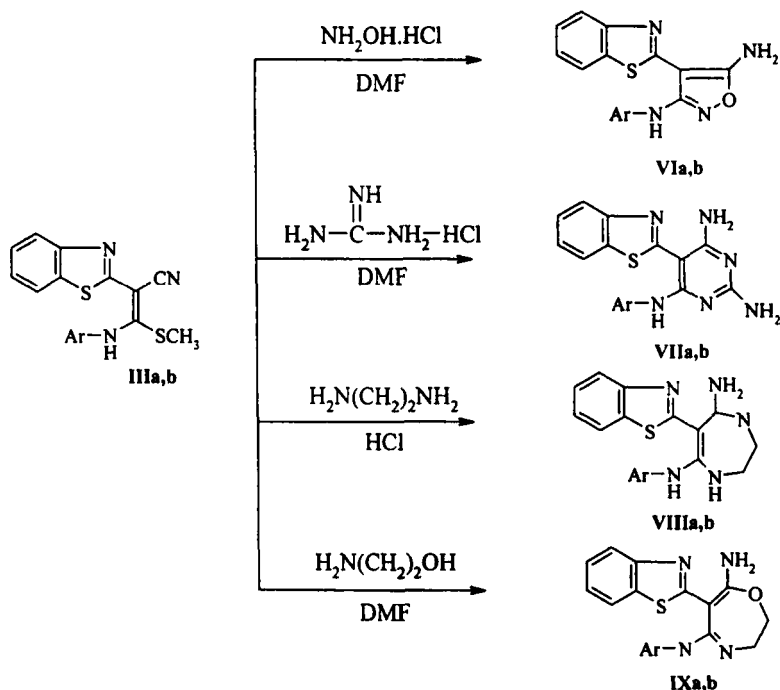
Thus, it has been found that 2-cyanomethyl benzothiazole (I) underwent reaction with carbon disulphide in the presence of sodium hydride in dimethyl sulfoxide and methylation to give 2-[2-benzothiazolyl]-3,3-bis(methylthio) acrylonitriles (II). Structure II is suggested for the reaction product on the basis of elemental analyses, spectral evidence, and chemical behaviour. The infrared spectrum of II showed absorption at 2220 cm^{-1} (CN), and the ^1H NMR spectrum revealed singlets at δ 2.5, 2.6 assigned to the thiomethyl protons and a multiplet at 7.1–8.3 assigned to aromatic protons. Compound II reacted with different aromatic amines in boiling ethanol to give 2-[2-benzothiazolyl]-3-methylthio-3-arylaminacrylonitrile (IIIa,b). The ^1H NMR spectra of IIIa,b contain a singlet at δ 2.4 assignable to thiomethyl protons, a multiplet corresponding to the aromatic protons at δ 7–8.3, and a signal bands at 2208 (CN), 1550–1590 [$\text{N}-\text{C}(\text{SCH}_3)=\text{C}$] and 3250 cm^{-1} (NH). Treatment of the key intermediate IIIa,b with hydrazine hydrate in DMF gave a single product which analyzed correctly for $\text{C}_{16}\text{H}_{13}\text{N}_5\text{S}$ (Va) and $\text{C}_{17}\text{H}_{15}\text{N}_5\text{S}$ (Vb).

The structure of V was inferred from its spectral data. Thus, the infrared spectrum of (Vb) showed a band at 3189, 3229 and 3419 cm^{-1} , corresponding to the NH and NH_2 groups, respectively, and was avoid a band due to the cyano group. The ^1H NMR spectra revealed a singlet at 2.3, assigned for the methyl protons, a broad band located at δ 6.48, assignable to amino group, and a multiplet at δ 7–8.2, assigned for aromatic protons. The NH proton appeared at δ 10, 12 ppm. The formation of Va,b is assumed to proceed via the replacement of the SCH_3 group by the hydrazine moiety to give the intermediates IVa,b which then cyclized via the cyano group to afford the final isolable products Va,b. In fact, the structures of Va,b was further confirmed by alternative syntheses. Thus, it has been found treatment of IIIa with hydrazine hydrate for a long time in boiling ethanol produced the intermediate IVa. Refluxing IVa in DMF lead to the formation of a product identical in all respects (mp, mixed mp, IR, ^1H NMR) with Va. Structure IVa is suggested for the reaction product on the basis of both elemental and spectral analysis. The infrared spectrum of compound IVa showed absorption at 2216 (CN), 3347 (NH), 3418, and 3581 cm^{-1} (NH_2) groups, and the ^1H NMR spectrum revealed a broad signal at δ 6.4 assigned for NH_2 protons, a multiplet at δ 7.2–7.8 for aromatic protons, and a singlet at δ 10.7 for NH proton.



Similar to the behaviour of IIIa,b towards hydrazine hydrate, IIIa,b also reacted with hydroxyl amine in DMF giving the aminoisoxazole VIa,b. The structure of VIa,b were supported by spectral data. The IR spectrum the product revealed the absence of a CN absorption, and the ^1H NMR spectrum revealed at broad signal at δ 6.9 for the amino protons, indicating that the cyano group was involved in the cyclization via an intermediate similar to compound IV. In a similar way, it has been found that, compounds IIIa,b reacted with guanidine hydrochloride in DMF to give the pyrimidine derivatives VIIa,b in satisfactory yield. Elemental and spectral data were in agreement with structure VII (cf. Table I). In addition to that above, compound IIIa,b reacted with the bifunctional ethylenediamine and ethanolamine in DMF giving the corresponding diazepines VIIa,b and oxazepines IXa,b derivatives, respectively, in good yields. Both structures VIIIa,b and IXa,b were established on the basis of both elemental and spectral data. In general, the ^1H NMR of both compounds VIIIa,b and IXa,b revealed two triplets assigned to $\text{CH}_2\text{-CH}_2$ protons, broad signals at δ 3.6–3.7, assignable the NH_2 protons a multiplet at δ 7.2–8.5 assigned to the aromatic protons, and a singlet at δ 12.1 for the NH proton.

These results indicate that the reaction of α,β -unsaturated nitriles and bifunctional reagents provides an excellent route for the synthesis of several, otherwise not easily accessible, 2-substituted benzothiazoles. The compounds synthesized will be subjected to biological testing.



EXPERIMENTAL

- Melting points were uncorrected. Infrared spectrum were recorded on Pye-Unicam SP 1100 Spectrophotometer using KBr Wafer technique.
- ^1H NMR of the prepared compound were determined on a 200 MHz, Varian-Gemini, Faculty of Science, Cairo University.
- Mass spectra was tested on GC-MSQP-1000 Ex. Shimadzye (Japan), Faculty of Science, Cairo Univiersity.

TABLE I Characterization data of compounds (II-IX)

Compd. No.	M.p. °C	Yield %	Mol. Formula	Microanalysis and Calc. Found				Characterization
				C	H	N	S	
II	120 ⁸	60	C ₁₂ H ₁₀ N ₂ S ₃ (278.42)	51.77	3.62	10.06	34.55	IR: 2220 cm ⁻¹ ; (CN), ¹ H NMR: (CDCl ₃), δ 2.5 (s, 3H, SCH ₃), 2.6 (s, 3H, SCH ₃), 7.1–8.3 (m, 4H, Ar)
IIIa	175 ⁸	82	C ₁₇ H ₁₃ N ₃ S ₂ (323.44)	63.13	4.05	12.99	19.83	IR: IIIa,b 2208 cm ⁻¹ ; (CN), 3250 cm ⁻¹ (NH)
IIIb	148 ⁸	80	C ₁₈ H ₁₅ N ₃ S ₂ (337.47)	64.06	4.48	12.45	19.00	¹ H NMR: (CDCl ₃) IIIa 2.4 (s, 3H, SCH ₃); 7–8.3 (m, 4H, Ar), 10.1 (s, H NMR, NH exchangeable with D ₂ O)
IVa	197	55	C ₁₆ H ₁₃ N ₃ S (307.38)	62.52	4.26	22.78	10.43	IR: 2216, 3347, 3418, 3581 cm ⁻¹ ; CN, NH, NH ₂ respectively
Va	> 300	74	C ₁₆ H ₁₃ N ₃ S (307.38)	62.52	4.26	22.78	10.43	MS: (m/z) 307 (M ⁺), 291, 199
Vb	> 300	70	C ₁₇ H ₁₅ N ₃ S (321.41)	63.93	4.10	21.98	10.04	IR: 3226, 3417, cm ⁻¹ (NH ₂) 1620 cm ⁻¹ (C=N)
Vla	167	81	C ₁₆ H ₁₂ N ₄ S (292.37)	65.06	4.09	18.97	10.83	MS: (m/z) 307 (M ⁺), 290, 248, 232, 217.
Vlb	185	84	C ₁₇ H ₁₄ N ₃ S (307.38)	66.42	4.92	18.23	10.43	IR: 3229, 3419, cm ⁻¹ (NH ₂) 1620 cm ⁻¹ (C=N)
VIIa	226	72	C ₁₇ H ₁₄ N ₆ S (334.41)	61.09	4.22	25.13	9.59	IR: 3280, 3423, cm ⁻¹ (NH ₂) 1624 cm ⁻¹ (C=N)
				61.16	4.15	25.00	9.67	MS: (m/z) 308 (M ⁺), 292, 291, 267, 161 146.
								IR: 3275, 3420, cm ⁻¹ (NH ₂) 1620 cm ⁻¹ (C=N)
								IR: 3250, 3418, cm ⁻¹ (NH ₂) 1624 cm ⁻¹ (C=N)

Compd. No.	M.p. °C	Yield %	Mol. Formula	Microanalysis and Calc. Found				Characterization
				C	H	N	S	
VIIIb	182	69	C ₁₈ H ₁₆ N ₆ S (348.43)	62.05 62.18	4.63 4.72	24.12 24.22	9.20 9.02	IR: 3225, 3416, cm ⁻¹ (NH ₂) 1632 cm ⁻¹ (C=N) ¹ H NMR (DMSO-d ₆) δ 2.23 (s, 3H, CH ₃), 5.1 (b, 2H, NH ₂), 7.2–8 (m, 8H aromatic protons). MS: (m/z) 348 (M ⁺) 316, 305, 302, 290, 216
VIIIa	147	58	C ₁₈ H ₁₇ N ₅ S (335.44)	64.45 64.38	5.11 5.02	20.88 20.69	9.56 9.48	IR: 3317 cm ⁻¹ (NH) 1626 cm ⁻¹ (C=N) ¹ H NMR; (DMSO-d ₆) δ 2.14 (t, 2H, CH ₂), 2.8 (t, 2H, CH ₂), 3.6 (b, 2H, NH ₂), 7–8.5 (m, 9H, aromatic protons).
VIIIb	207	62	C ₁₉ H ₁₉ N ₅ S (349.46)	65.30 65.18	5.48 5.38	20.04 20.00	9.18 9.05	IR: 3319 cm ⁻¹ (NH) 1629 cm ⁻¹ (C=N)
IXa	219	60	C ₁₈ H ₁₆ N ₄ OS (336.42)	64.26 63.98	4.79 4.62	16.65 16.61	9.53 9.41	IR: 3340 (NH), ¹ H NMR; (DMSO-d ₆) δ 2.4 (t, 2H, CH ₂), 3.3 (t, 2H, CH ₂), 3.7 (b, 2H, NH ₂), 7–8.5 (m, 9H aromatic protons).
IXb	202	63	C ₁₉ H ₁₈ N ₄ OS (350.45)	65.12 64.99	5.18 5.22	15.99 15.81	9.15 9.02	IR: 3338 (NH), 3466, 3512, (C=N)

2-[Benzthiazolyl-(2)]-3,3-bis(methoylthio)acrylonitrile (II)

A mixture of 2-cyanomethylbenzothiazole (I) (0.05 mol) in 100 ml of DMSO with sodium hydride (0.05 mol) was stirred under a nitrogen atmosphere. A solution of methyl iodide (0.12 mol) was added to the red reaction mixture which was allowed to stand at 8–10°C for 3 h. The reaction mixture was poured into ice (700 g) to give II. The obtainable solid product was filtered and recrystallized from ethanol (cf. *Table I*).

2-[2-Benzothiazolyl]-3-methylthio-3-arylaminoacrylonitrile (IIIa,b)

A mixture of II (0.05 mol) and aromatic amines (0.05 mol) in 30 ml of ethanol was refluxed for 8 hrs. The reaction mixture was then cooled, and the solid product was filtered off and recrystallized from ethanol to give IIIa,b (cf. *Table I*).

3-Phenylamino-3-hydrazino-2-[2-benzothiazolyl]acrylonitrile IVa,b

A mixture of IIIa (0.05 mol) or IIIb and hydrazine hydrate (0.05 mol) in ethanol was refluxed for 4 hrs. The reaction mixture was then cooled and the solid product was filtered off and recrystallized from ethanol to give compound IVa,b (cf. *Table I*).

General procedure for the synthesis of compounds (V-IX)

A mixture of III (0.05 mol), hydrazine hydrate (0.05 mol) and/or ethanolamine, guanidine, ethylenediamine, or hydroxyl amine was refluxed for 18 hrs. The reaction mixture then poured onto ice water (200 ml). The solid product was filtered off and recrystallized from ethanol: DMF (1:1) to give the corresponding derivatives, Va,b-IXa,b respectively. (cf. *Table I*).

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