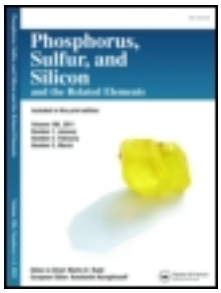

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Reactions of 2-Cyano-2-nitrosomethylbenzthiazole: One-Pot Synthesis of New Polyfunctional Pyrazine Derivatives

Fawi M. Abd El Latif [a] , Eman A. Ei Rady [a] & Mohamed A. Khalil [a]

[a] Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

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REACTIONS OF 2-CYANO-2-NITROSOMETHYLBENZTHIAZOLE: ONE-POT SYNTHESIS OF NEW POLYFUNCTIONAL PYRAZINE DERIVATIVES

Fawi M. Abd El Latif, Eman A. Ei Rady, and Mohamed A. Khalil
Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

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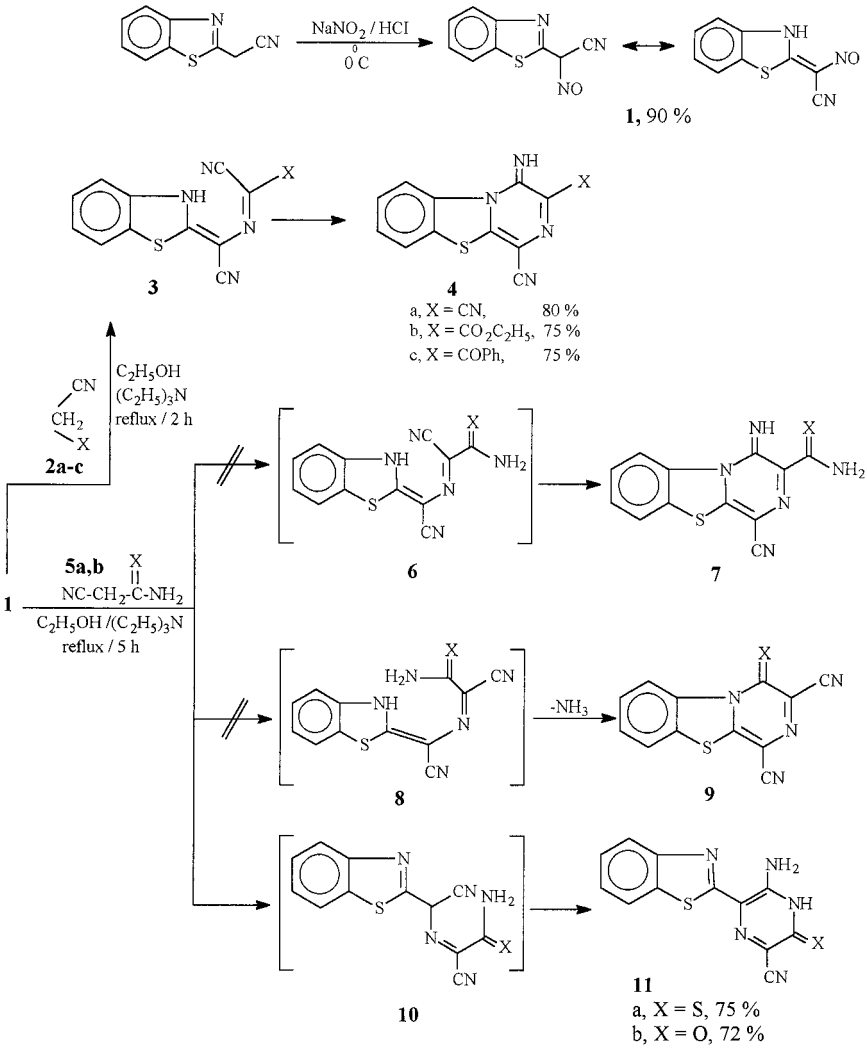
2-Cyano-2-nitrosomethylbenzthiazole reacts with some active methylene and nucleophile derivatives to yield new fused and isolated polyfunctional pyrazine, -[1,2,4]triazine, -[1,4,5]benzoxadiazepin, -[1,4,5]benzothiadiazepine, [1,4,5]benzotriazepine, -triazole and -triazolo-[3,2-c]triazine derivatives in one-pot reaction. The structures were based on IR, MS, and ^1H NMR spectra and elemental data.

Keywords: -[1,4,5]Benzothiadiazepine; 2-cyano-2-nitrosomethylbenzothiazole; benzothia[2,3-a]pyrazine

Azolylacetonitriles are readily obtainable compounds that have been extensively utilized as intermediates in heterocyclic synthesis.[1–4] In connection with our interest in the synthesis of condensed azines,[5–10] we report herein a new and simple route for the synthesis of benzthiazole derivatives of polyfunctional pyrazine and other azine compounds that may have pharmaceutical effects.

Thus, nitrozation of 2-cyanomethylbenzthiazole by sodium nitrite in ethanolic hydrochloric acid mixture yielded the 2-cyano-2-nitrosomethylbenzthiazole **1** in quantitative yield. The MS of **1** showed *m/z* at 203 (M^+, 70), 173 (M—NO, 100), 145 (173-N_2, 71). The nitroso compound **1** reacts readily with malononitrile **2a**, ethyl cyanoacetate **2b** and benzoylacetonitrile **2c** in boiled ethanol containing triethylamine to yield the corresponding benzothiazolo[2,3-**a**]pyrazine derivatives **4a–c** in 75–80% yields. The formation of **4** was assumed to proceed via

Address correspondence to Fawi M. Abd Latif, Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt. E-mail: Latif72001@yahoo.com

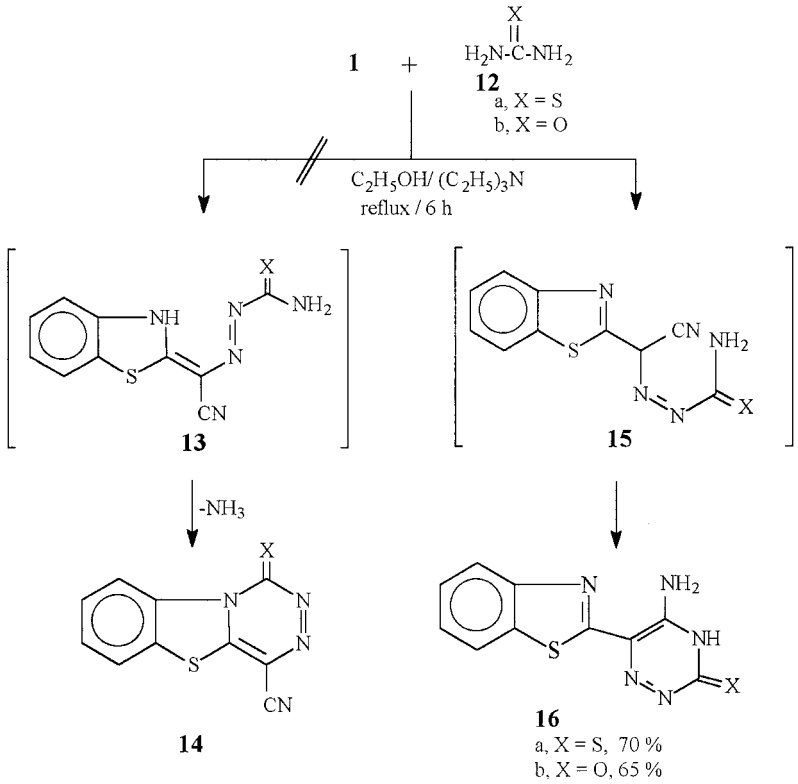


SCHEME 1

the intermediate **3**, which cyclizes to **4**, (c. f. Scheme 1). The IR spectrum of **4b** showed bands at ν 3125, 2215, 1720 cm^{-1} due to NH, CN, and CO groups. The MS of **4b** showed *m/z* at 298 (M^+, 10) and the ^1H NMR spectrum (DMSO) of **4b** showed triplet and quartet at δ 1.2 and 4.2 ppm assignable to the protons of the ester, and at 7.1–7.9 due to NH and aromatic protons. However, the nitroso compound **1** reacts directly with cyanoacetamide **5a** in ethanol containing triethylamine at reflux temperature to yield a product its mass spectrum showed *m/z* = 269

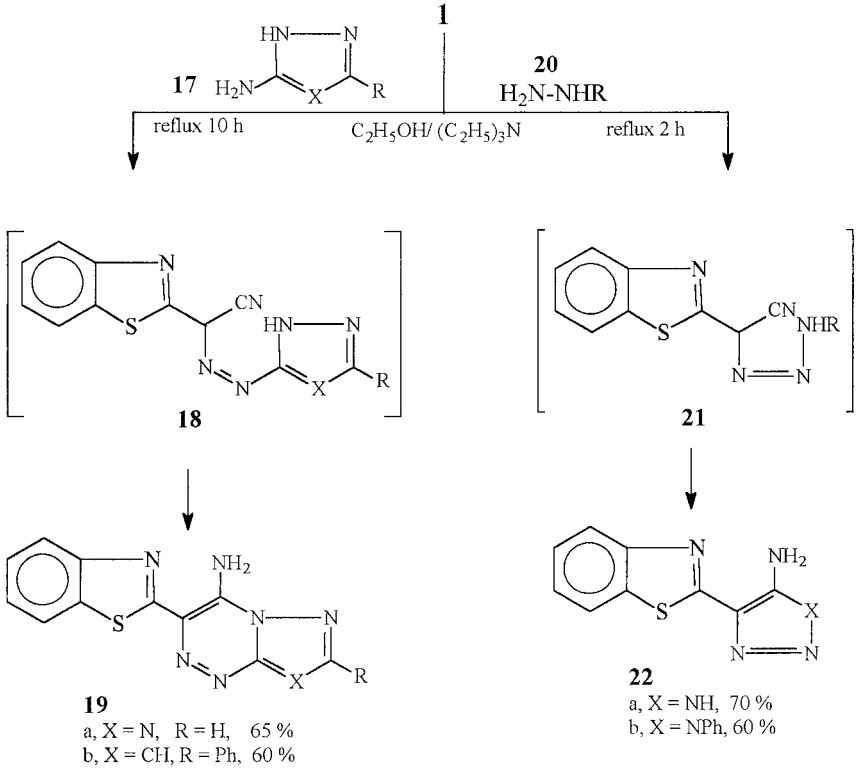
(M^+, 15). Several isomeric structures (**7–11**) seemed possible for this product (Scheme 1). Structure **11** was preferred over structure **9** based on mass and IR spectra, structure **9**, however assumed to be formed by elimination of amoina from its precursor **8**. On the other hand, IR spectrum of **11a** revealed characteristic absorption bands at ν 3345, 3218, 2215, and 1690 cm^{-1} assigned for NH_2, NH, CN, and C=O groups, respectively. If the product was **7**, lower absorption frequencies for amidic C=O should observed, and an expected hydrogen bond would revealed a broad NH absorption band. The ^1H NMR (DMSO) of **11a** revealed signals at δ 7.1–7.8 assigned to aromatic, NH and at 8.2 ppm due to NH_2 protons. In analogy, compound **1** reacts with **5b** to give **11b**.

The reactivity of the nitroso function in **1** was also explored via its reaction with some laboratory available nucleophiles reagents. Thus, the reaction with thiourea **12a** and urea **12b** yielded the substituted [1,2,4]triazines **16a**,**b**. Again, two theoretical possible structures **14** and **16** can be considered (c.f. Scheme 2). Structure **16** was suggested for

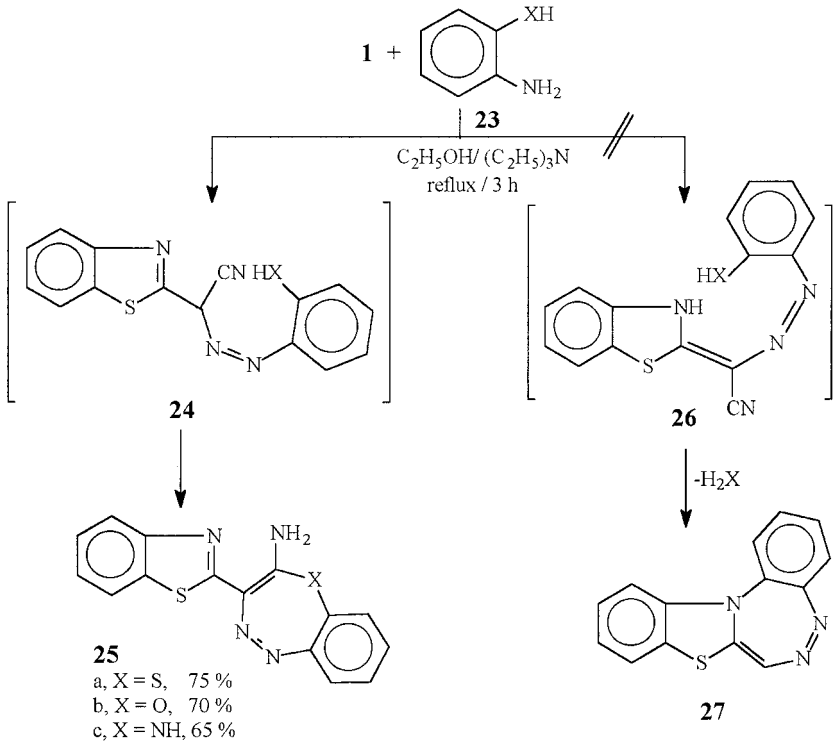


SCHEME 2

this product based on the MS of **16a** which showed *m/z* at 263 (M + 2, 15), 245 (M–NH_2, 14), 229 (M–S, 11), 213 (M–S–NH_2, 15), 203 (34), and 173 (53%). The IR spectrum of **16a** revealed bands at ν 3325, 3215 cm^{-1} (NH_2, NH) and IR spectrum of **16b** showed characteristic absorption bands at ν 3325, 3215, and 1685 cm^{-1} for NH_2, NH, and CO groups. However, the nitroso compound **1** reacted with **17a**,**b** to afford substituted triazolo[3,2-c][1,2,4]triazine **19a** and pyrazolo[3,2-c][1,2,4]triazine **19b** via condensation intermediate **18**, which then cyclizes to **19**. The ^1H NMR (DMSO) spectrum of **19a** revealed signals at δ 7.1–7.9 and 8.1 ppm due to the aromatic and NH_2 protons. Similarly, the nitroso compound **1** reacts with hydrazine hydrate **20a**, phenylhydrazine **20b** to give 5-amino-4-(benzthiazole-2-yl)-1,2,3-triazole **22a**,**b** (c.f. Scheme 3). The IR spectrum of **22a** showed bands at ν 3345 and 3125 cm^{-1} assignable to NH_2 and NH groups, with the disappearance of the characteristic absorption due to cyano function. The MS of **22a** showed *m/z* at 219 (M + 2, 3), 217 (M^+, 5), 203 (M–N, 8), 177 (M–N–CN, 7), 173 (M–N_2–NH_2), and 146 (M–N_2–NH_2–HCN, 13%).



SCHEME 3



SCHEME 4

Finally, *o*-aminothiophenol **23a**, *o*-aminophenol **23b** and *o*-phenylenediamine **23c** reacted easily with compound **1** in refluxing ethanol containing triethylamine to yield the new 2-amino-3-(benzthiazole-2-yl)-[1,4,5]thiadiazepine **25a**, -[1,4,5]-oxadiazepine **25b** and -[1,4,5]-triazepine **25c** in 65–75 % yields. The fused tetracyclic structure **27** was ruled out based on the IR, ^{1}H NMR, MS and elemental analysis (Scheme 4). The IR spectra of **25** revealed bands at ν 3325–3245 cm^{-1} attributed to the NH_2 group. The MS of **25a** showed *m/z* at 311 (M + 1, 93), 294 (M—NH_2, 5), 282 (M—N_2, 82), 268 (M—N_2—N, 22), 248 (M—N—NH_2—S, 76), and 173 (100%). The MS of **25c** showed *m/z* at 294 (M + 1, 40), 264 (M—H—N_2, 30), 248 (M—N_2—H—NH_2, 5), and 173 (65%).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded (KBR, ν = cm^{-1}) on a Shimadzu 408 and a Pye Unicam Spectrophotometer. ^{1}H NMR spectra (DMSO-d_6 δ = ppm) were recorded on a Varian EM

TABLE I The Physical, Analytical, and Spectral Data

Comp. no.	Mp(°C) solvent	Yield %	M. formula (M. Wt.)	Analysis % calcd./found				Spectral data	
				C	H	N	S	^{1}H NMR δ ppm	MS [M^+] m/z (%)
1	199–200 EtOH	90	$C_9H_5N_3OS$ (203.13)	53.22 53.04	2.48 2.37	20.69 20.52	15.78 15.62	3.5 (s, 1H, CH), 7.1–7.8 (m, 4H, Ar—H).	203 (M^+, 93)
4a	203–205 EtOH	80	$C_{12}H_5N_5S$ (251.27)	57.36 57.19	2.01 1.88	27.87 27.72	12.76 12.64	7.1–7.8 (m, 5H, Ar—H + NH).	251 (M^+, 65)
4b	135–137 MeOH	75	$C_{14}H_{10}N_4O_2S$ (298.32)	56.37 56.21	3.38 3.23	18.78 18.65	10.75 10.61	1.2 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.1–7.9 (m, 5H, Ar—H + NH).	298 (M^+, 10)
11a	150–152 MeOH	72	$C_{12}H_7N_5OS$ (269.28)	53.52 53.37	2.62 2.48	26.01 26.13	11.91 11.78	7.1–7.8 (m, 5H, Ar—H + NH), 8.2 (s, 2H, NH_2).	269 (M^+, 15)
11b	170–172 EtOH	75	$C_{12}H_7N_5S_2$ (285.34)	50.51 50.34	2.47 2.31	24.54 24.40	22.47 22.32	7.1–7.8 (m, 5H, Ar—H + NH), 8.1 (s, 2H, NH_2).	285 (M^+, 40)
16a	203–232 EtOH	70	$C_{10}H_7N_5S_2$ (261.32)	45.96 45.82	2.70 2.57	26.80 26.68	24.54 24.41	5.6 (br, 2H, NH_2), 7.3–7.7 (m, 5H, Ar—H + NH).	263 (M + 2, 15)
16b	165–167 MeOH	65	$C_{10}H_7N_5OS$ (245.26)	48.97 48.84	2.88 2.75	28.55 28.41	13.07 13.19	5.3 (br, 2H, NH_2), 7.1–7.8 (m, 5H, Ar—H + NH).	245 (M^+, 20)
19a	170–172 MeOH	65	$C_{11}H_7N_7S$ (269.29)	49.06 48.96	2.62 2.50	36.41 36.38	11.91 11.77	7.1–7.9 (m, 5H, Ar—H + CH-triazole), 8.1 (s, 2H, NH_2).	269 (M^+, 35)
19b	155–157 MeOH	60	$C_{18}H_{12}N_6S$ (344.40)	62.78 62.65	3.51 3.37	24.40 24.27	09.31 09.18	7.1–7.8 (m, 10H, Ar—H), 8.2 (s, 2H, NH_2).	344 (M^+, 15)
22a	99–100 EtOH	70	$C_9H_7N_5S$ (217.25)	49.76 49.62	3.25 3.14	32.24 32.11	14.76 14.63	5.2 (s, 2H, NH_2), 7.4–7.9 (m, 4H, Ar—H) 8.4 (s, 1H, NH).	219 (M +, 2,3)
22b	185–187 EtOH	60	$C_{15}H_{11}N_5S$ (293.35)	61.42 61.31	3.78 3.64	23.87 23.73	10.93 10.81	5.4 (s, 2H, NH_2), 7.1–7.9 (m, 10H, Ar—H).	293 (M^+, 12)
25a	175–178 DMF	75	$C_{15}H_{10}N_4S_2$ (310.40)	58.04 57.89	3.25 3.12	18.05 18.18	20.66 20.53	7.3–7.9 (m, 8H, Ar—H), 8.1 (br, 2H, NH_2).	311 (M + 2, 93)
25b	130–132 MeOH	70	$C_{15}H_{10}N_4OS$ (294.33)	61.21 61.05	6.42 3.30	19.04 18.88	10.89 10.74	7.2–7.9 (m, 8H, Ar—H), 8.2 (br, 2H, NH_2).	294 (M^+, 35)
25c	160–162 MeOH	65	$C_{15}H_{11}N_5S$ (293.35)	61.44 61.33	3.78 3.64	23.78 23.74	10.93 10.81	7.1–7.9 (m, 9H, Ar—H + NH), 8.1 (br, 2H, NH_2).	294 (M + 1, 40)

390 90 MHz spectrometer. TMS was used as internal reference. Mass spectra were recorded on a mass spectrometer MS 9 (AET) EI Mode. Elemental analysis were carried out at Microanalytical Center, Cairo University, Egypt.

2-Cyanomethylbenzthiazole was prepared according to the procedure described in literature.[11]

2-Cyano-2-nitrosomethylbenzothiazole (1)

2-Cyanomethylbenzothiazole (1.7 g, 0.01 mol) was dissolved in a mixture of 10 ml of hydrochloric acid and 30 ml of ethanol, then cooled in an ice bath at 0°C. A cold solution of sodium nitrite (2.07 g, 0.03 mol) was added dropwise throughout a period of 30 min. The reaction mixture was allowed to stand for 24 h in a refrigerator; the solid product so formed was filtered, washed with water, dried, and recrystallized from ethanol to give pale yellow (Table I).

General Procedure for the Synthesis of 2.10-Dicyano-3-imino-benzthiazolo[2,3-a]pyrazine (4a) and its Derivative (4b)

A mixture of **1** (0.5 g, 0.01 mol), malononitrile **2a** (0.16 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 30 ml of absolute ethanol for 2 h. The colorless crystalls (**4a**) which deposit during the reaction are isolated by vacuum filtration, washed with methanol, and recrystallized from ethanol. The nitroso compound **1** reacted analogously with ethyl cyanoacetate **2b** (0.28 g, 0.01 mol) to give **4b**. The spectral, physical, and elemental analytical data are listed in Table I.

General Procedure for the Synthesis of 2-Amino-3-(benzthiazole-2-yl)-5-cyano-1,6-dihydropyrazin-6-one (11a) and its 6-Thione Isomer (11b)

A mixture of **1** (0.5 g, 0.01 mol), cyanooacetamide **2a** (0.2 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 40 ml of absolute ethanol for 5 h. The solution was concentrated under reduce pressure. The residue was treated with methanol and the crude product **11a** was filtered, washed with methanol, and recrystallized from ethanol. Similarly, the nitroso **1** was reacted with cyanothioacetamide **5b** (0.25 g, 0.01 mol) under the same reaction conditions to give the corresponding pyrazine-6-thione **11b**. The spectral, physical, and elemental analytical data are listed in Table I.

General Procedure for the Synthesis of 2-Amino-3-(benzthiazole-2-yl)-1,6-dihydropyrazine-6-thione (16a) and its Derivative (16b)

A mixture of **1** (0.5 g, 0.01 mol), thiourea **12a** (0.19 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 30 ml of absolute ethanol for 6 h. The solution was concentrated under reduce pressure and the solid product **16a** so formed was filtered, washed with ethanol, and recrystallized from ethanol. The nitroso compound **1** reacted analogously with urea **12b** (0.14 g, 0.01 mol) to give **16b** (Table I).

General Procedure for the Synthesis of 5-Amino-6-(benzthiazole-2-yl)[1,2,4]triazolo[3,2-c][1,2,4]triazine (19a) and 7-Phenylpyrazolo[3,2-c][1,2,4]triazine (19b)

A mixture of **1** (0.5 g, 0.01 mol), 5-amino-1*H*-1,2,4-triazole **17a** (0.20 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 30 ml of absolute ethanol for 10 h. The solution was concentrated under reduce pressure and the solid product **19a** so formed was filtered, washed, with ethanol and recrystallized from methanol. The nitroso compound **1** reacted analogously with 5-amino-3-phenyl-1*H*-pyrazole **17b** (0.39 g, 0.01 mol) to give the corresponding title compounds **19b**. The spectral, physical, and elemental analytical data are listed in Table I.

General Procedure for the Synthesis of 5-Amino-4-(benzthiazole-2-yl)1,2,3-triazole (22a) and its Derivative (22b)

A mixture of **1** (0.5 g, 0.01 mol), hydrazine hydrate **20a** (0.12 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 30 ml of absolute ethanol for 2 h. The colorless crystals formed during the reaction were filtered, washed with methanol, and recrystallized from ethanol. The nitroso compound **1** reacted analogously with phenylhydrazine **20b** (0.27 g, 0.01 mol) to give the corresponding title compound **22b**. The spectral, physical, and elemental analytical data are listed in Table I.

General Procedure for the Synthesis of 2-Amino-3-(benzthiazole-2-yl)[1,4,5]benzothiadiazepine (25a), -[1,4,5]Benzoxadiazepine (25b) and -[1,4,5]Benzotriazepine (25c)

A mixture of **1** (0.5 g, 0.01 mol), *o*-aminothiophenol **23a** (0.30 g, 0.01 mol), and 0.1 ml of triethylamine was refluxed in 30 ml of absolute

ethanol for 3 h. The green crystalls separated during reflux were collected by vacuum filtration, washed with methanol, and recrystallized from DMF. The nitroso compound **1** reacted analogously with *o*-aminophenol **23b** (0.27 g, 0.01 mol) and *o*-phenylenediamine **23c** (0.27 g, 0.01 mol) to give the title compounds **25b**,**c**. The spectral, physical, and elemental analytical data are listed in Table I.

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