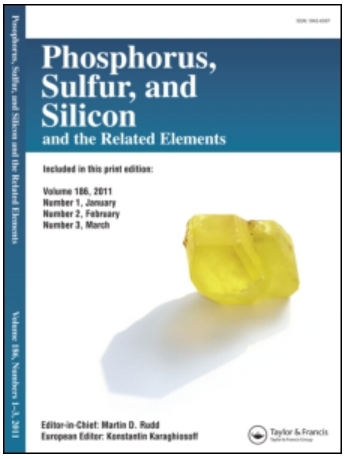


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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

Online publication date: 27 October 2010

To cite this Article Latif, Fawi M. Abd El , Rady, Eman A. Ei and Khalil, Mohamed A.(2002) 'Reactions of 2-Cyano-2-nitrosomethylbenzthiazole: One-Pot Synthesis of New Polyfunctional Pyrazine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 10, 2497 — 2505
To link to this Article: DOI: 10.1080/10426500214131
URL: http://dx.doi.org/10.1080/10426500214131

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:2497–2505

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290110658

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

(Accepted December 31, 2001)

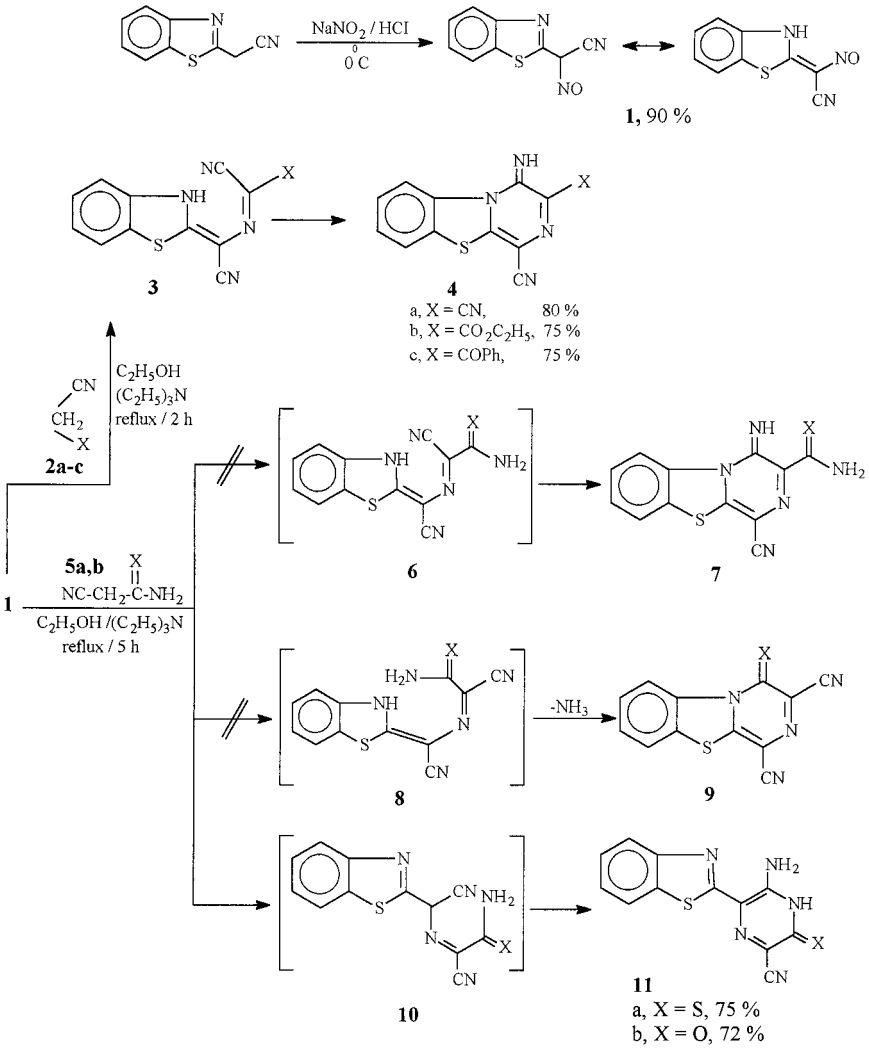
2-Cyano-2-nitrosomethylbenzthiazole reacts with some active methylene and nucleophile derivatives to yield new fused and isolated polyfunctional pyrazine, -[1,2,4]triazine, -[1,4,5]benzoxadiazepin, -[1,4,5]benzothiadiazepine, [1,4,5]benzotriazepine, -triazole and -triazolo-[3,2-c]triazine derivatives 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

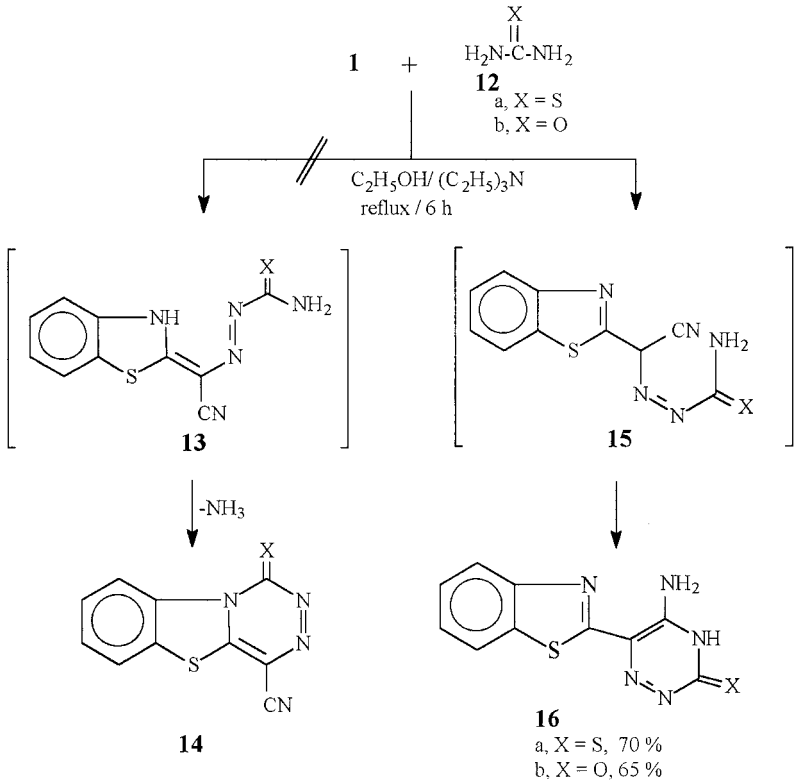


SCHEME 1

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

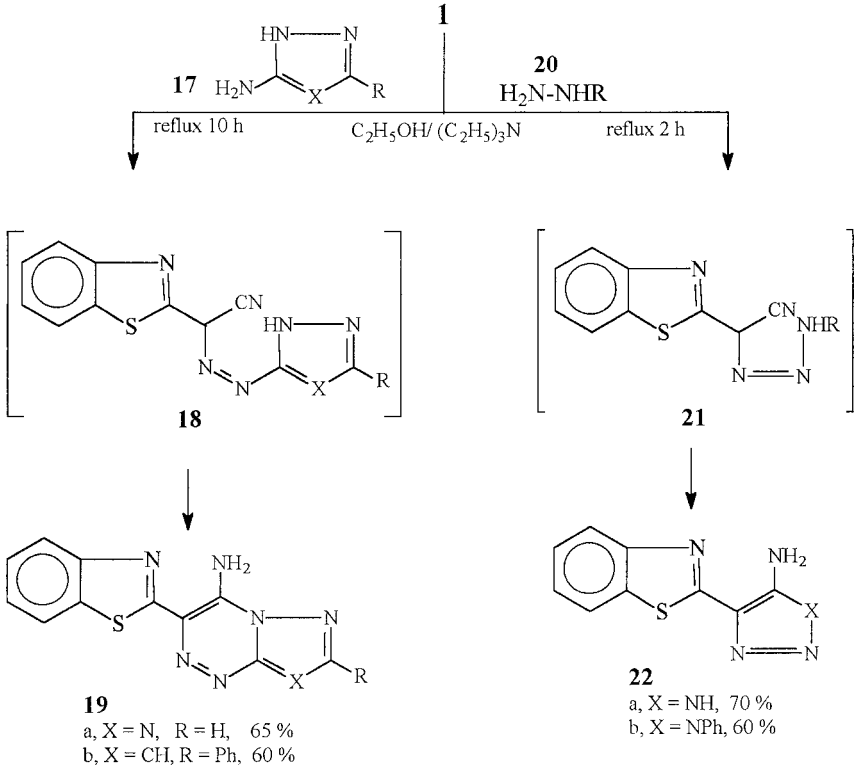
(M^+, 15). Several isomeric structures (**7–11**) seemed possible for this product (Scheme 1). Structure **11** was preferred over structure **9** based on mass and IR spectra, structure **9**, however assumed to be formed by elimination of amoina from its precursor **8**. On the other hand, IR spectrum 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

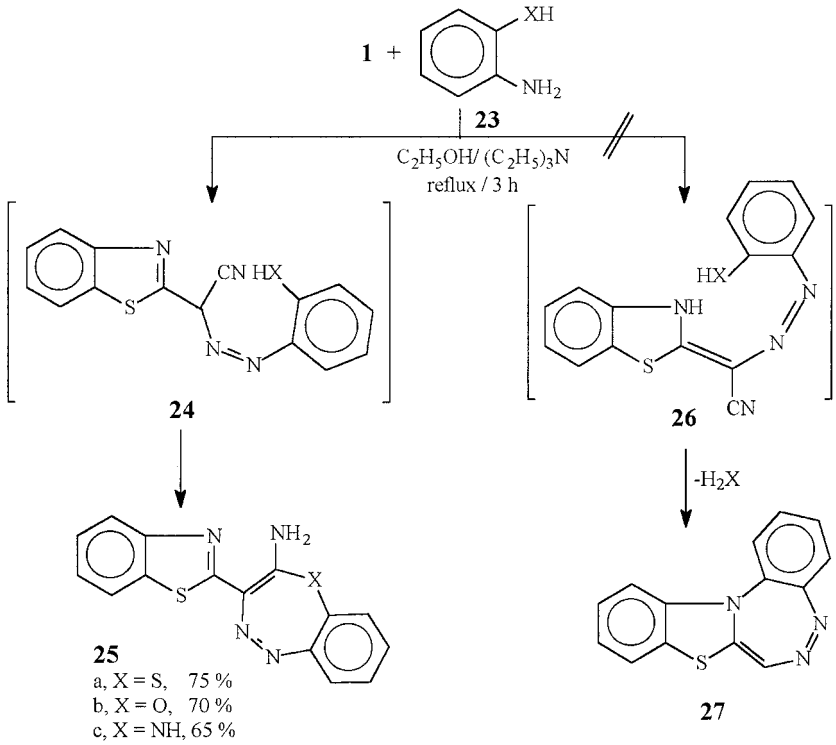


SCHEME 2

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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