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Synthesis and Reactivity of 2-(Benzothiazol-2-yl)-1-bromo-1,2-ethanedione-1-arylhydrazones

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ABSTRACT

The novel, highly versatile 2-(benzothiazol-2-yl)-1-bromo-1,2-ethanedione-1-arylhydrazones **3** *were prepared and their behavior toward some nucleophiles was investigated. Thus, reaction of* **3** *with the sodium salt of malononitrile afforded the aminopyrazolecarbonitriles* **5** *that undergo cyclocondensation with hydrazine, formic acid, and formamide to give the corresponding pyrazolo[3,4-d]pyridazine* **6**, *pyrazolo[3,4-d]pyrimidinone* **7**, *and pyrazolo[3,4-d]pyrimidine* **8** *derivatives, respectively. Similarly, reactions of* **3** *with each of acetylacetone, dibenzoylmethane, and benzoylacetonitrile afforded the corresponding pyrazole derivatives* **9**, **10**, *and* **11**, *respectively. The latter products undergo cyclocondensation with hydrazine to afford the corresponding pyrazolo[3,4-d]pyridazines* **12**, **13**, *and* **14**, *respectively.*

Benzothiazole derivatives have attracted a great deal of interest due to their biological and commercial importance. They have been found to have antiviral [1], antibacterial [2], antimicrobial [3], and fungicidal activities [4]. They are also useful as antiallergic [5], anti-inflammatory [6], and anthelmintic [7] agents, and as appetite depressants [8], intermediates for dyes [9], plant protectants [10], and photographic sensitizers [11]. In continuation of our previous studies aiming at the synthesis of functionalized heterocycles [12–15], it seemed of interest to undertake the synthesis of several heterocyclic systems containing the benzothiazole moiety that would be expected to have biological potency. We report here the synthesis of the versatile, hitherto unreported 2-(benzothiazol-2-yl)-1-bromo-1,2-ethanedione-1-arylhydrazones **3a–c** and their utility in the synthesis of several pyrazoles, pyrazolo[3,4-d]pyridazines, pyrazolo[3,4-d]pyrimidinones, and pyrazolo[3,4-d]pyrimidines incorporating the benzothiazole moiety.

Thus, coupling of the sulfonium bromide **2** with diazotized aromatic amines in ethanol buffered with sodium acetate at 0–5°C, or with N-nitrosoacetanilides in ethanol at room temperature, afforded the arylhydrazones **3a–c** (Scheme 1). All attempts to prepare **3** by direct coupling of **1** with diazotized aromatic amines or N-nitrosoacetanilides were unsuccessful. The structures of the arylhydrazones **3a–c** were established on the basis of their elemental analyses and spectral data as well as their chemical transformations depicted in Scheme 2. The ^{1}H-NMR spectra of **3a–c** displayed, in each case, an exchangeable signal around δ 8.90 due to the NH proton. Their IR spectra showed also in each case a conjugated carbonyl absorption band near 1650 cm^{-1} and a hydrazone N–H stretching near 3250 cm^{-1}.

2-Bromoacetylbenzothiazole (**1**) reacts with malononitrile in ethanolic sodium hydroxide solution to afford one isolable product that analyzed correctly for $C_{12}H_7N_3OS$. The structure of the latter product was identified as 2-(benzothiazol-2-yl)-2-oxoethylpropanedinitrile (**4**) on the basis of its IR and ^{1}H-NMR spectra. For example, its IR spectrum showed two characteristic bands at 2261 and 1693 cm^{-1} due

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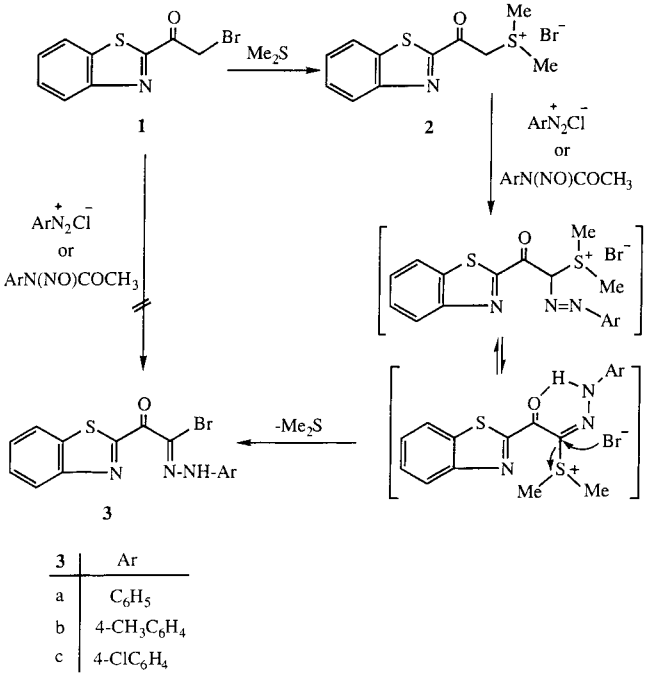
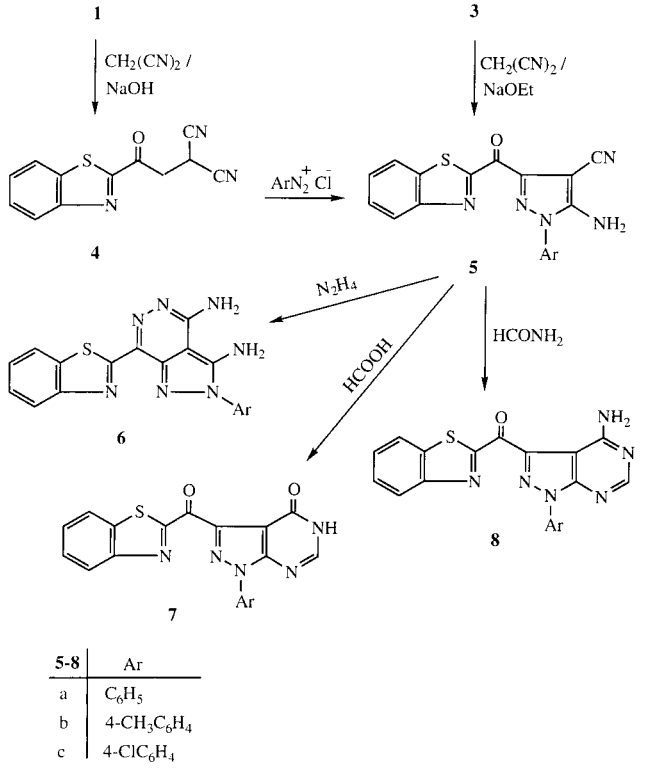


3	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4

SCHEME 1



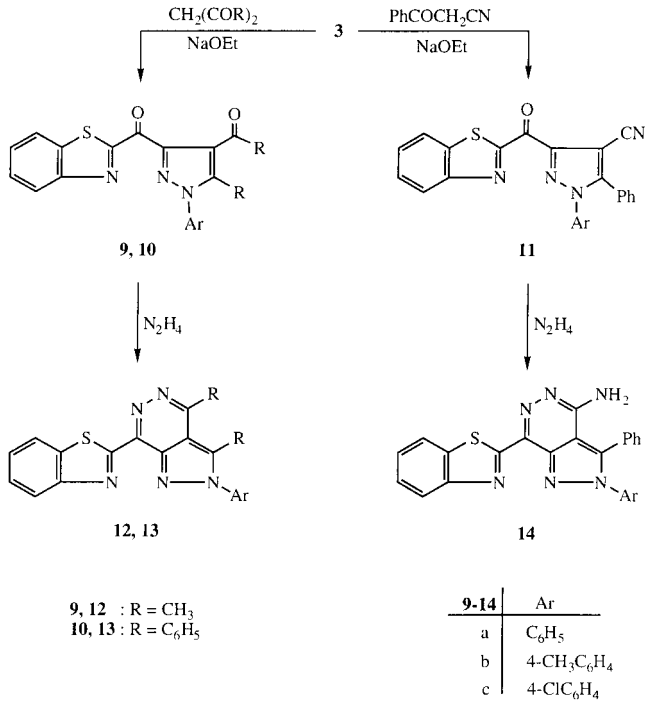
5-8	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4

SCHEME 2

to nitrile and carbonyl functions, respectively. Its ^{1}H-NMR spectrum displayed a doublet at δ 4.10 and a triplet at δ 4.43 due to methylene and methine protons, respectively.

Treatment of **4** with the diazonium salts of aniline, *p*-toluidine, and *p*-chloroaniline in ethanolic sodium acetate solution at 0–5°C furnished the corresponding pyrazolecarbonitriles **5a–c**. The structures of the latter products were established on the basis of both elemental and spectral data as well as on their alternate synthesis from **3**. Thus, when the arylhydrazones **3a–c** were treated with malononitrile in ethanolic sodium ethoxide solution at room temperature, they afforded compounds identical in all respects (mp, mixed mp, and spectra) with the products **5a–c** (Scheme 2). The IR spectra of **5a–c** revealed, in each case, two absorption bands in the region 3365–3220 cm^{-1}, one band near 2220 cm^{-1}, and one band near 1665 cm^{-1}, corresponding to amino, nitrile, and carbonyl functions, respectively. The ^{1}H-NMR spectrum of **5b**, for example, displayed a broad signal at δ 7.13 that disappeared when shaken with D_2O, assignable to NH_2 protons in addition to a singlet at δ 2.43 and a multiplet at δ 7.4–8.3 due to methyl and aromatic protons, respectively. The synthetic potential of the newly synthesized pyrazolecarbonitriles **5a–c** was achieved by their reactions with different reagents leading to several new fused-ring heterocycles. Thus, heating the pyrazolecarbonitriles **5a–c** with hydrazine hydrate, formic acid, and with formamide furnished the corresponding 5-aryl-3-(benzothiazol-2-yl)-6,7-diaminopyrazolo[3,4-d]pyridazines **6a–c**, 1-aryl-3-(benzothiazol-2-yl)carbonyl-5H-pyrazolo[3,4-d]-pyrimidin-4-ones **7a–c**, and 4-amino-1-aryl-3-(benzothiazol-2-yl)carbonylpyrazolo [3,4-d]pyrimidines **8a–c**, respectively (Scheme 2). The assignment of the latter structures was based on the elemental analyses and spectral data of the reaction products. Thus, the IR spectra of **6a–c** showed, in each case, the absence of both nitrile and carbonyl absorption bands and revealed four absorption bands in the region 3425–3175 cm^{-1} due to two amino groups. Whereas, the IR spectra of **7a–c** revealed, in each case, a broad band near 1710 cm^{-1} assignable to two overlapped carbonyl absorption bands in addition to one band in the region 3280–3185 cm^{-1} due to NH stretching. The IR spectra of **8a–c** showed, however, one band near 1650 cm^{-1} due to carbonyl absorption and two bands in the region 3300–3140 cm^{-1} due to the amino group.

The arylhydrazones **3a–c** react also with 2,4-pentanedione, 1,3-diphenyl-1,3-propanedione, and 3-oxo-3-phenylpropanenitrile in ethanolic sodium ethoxide solution, at room temperature, to afford the corresponding 3-(benzothiazol-2-yl)carbonylpy-



SCHEME 3

razoles **9a–c**, **10a–c**, and **11a–c**, respectively. The latter pyrazoles undergo cyclocondensation when heated with hydrazine hydrate to afford the corresponding 3-(benzothiazol-2-yl)carbonylpyrazolo-[3,4-d]pyridazines **12a–c**, **13a–c**, and **14a–c**, respectively (Scheme 3). The identities of the latter pyrazoles and pyrazolo[3,4-d]pyridazines structures were confirmed by elemental analyses and spectral data of the reaction products (Table 1).

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. IR spectra were measured as KBr pellets on a Pye-Unicam SP 3-300 spectrophotometer. ^{1}H-NMR spectra were recorded in deuterated chloroform or dimethylsulfoxide solution at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 2-Bromoacetylbenzothiazole (**1**) [16] and 3-oxo-3-phenylpropanenitrile [17] were prepared as described in the literature.

1-(Benzothiazol-2-yl)-1-ethanone-2-dimethylsulfonium Bromide (**2**)

2-Bromoacetylbenzothiazole (**1**) (12.8 g, 50 mmol) was refluxed with dimethyl sulfide (6 mL) in absolute methanol (75 mL) for 30 minutes. The reaction mixture was cooled, and the precipitated solid was filtered off, washed with ether, and recrystallized from ethanol to afford **2** in 80% yield (12.5 g); mp 143°C; ν_{max}/cm^{-1} (KBr) 1700 (C=O). ^{1}H-NMR spectrum was not obtained due to the insufficient solubility in the usual NMR solvents. Found: C, 41.82; H, 3.87; N, 4.31; S, 20.06%. $C_{11}H_{12}BrNOS_2$ requires C, 41.51; H, 3.80; N, 4.40; S, 20.15%.

2-(Benzothiazol-2-yl)-1-bromo-1,2-ethanedione-1-arylhydrazones ***3a–c***

Method A. General Procedure. To a cold solution of the sulfonium bromide **2** (9.54 g, 30 mmol) in ethanol (50 mL) and sodium acetate trihydrate (5 g) was added the appropriate arene diazonium chloride solution (30 mmol) over a period of 30 minutes with stirring. After the addition was complete, the reaction mixture was stirred for a further 3 hours at 0–5°C and left to stand in an ice box for 12 hours, then it was diluted with water. The solid that formed was filtered off, washed with water, and dried. Recrystallization from acetic acid yielded the corresponding arylhydrazones **3a–c** in 60–70% yield. **3a** (65%): mp 168–70°C; ν_{max}/cm^{-1} (KBr) 3260 (NH), 1658 (C=O), 1600 (C=N); δ_H ($CDCl_3$) 7.15–8.30 (9H, m), 8.89 (1H, br). Found: C, 49.83; H, 2.73; N, 11.38; S, 9.10%. $C_{15}H_{10}BrN_3OS$ requires C, 50.01; H, 2.80; N, 11.66; S, 8.90%. **3b** (66%): mp 152–153°C; ν_{max}/cm^{-1} (KBr) 3260 (NH), 1640 (C=O), 1600 (C=N); δ_H ($CDCl_3$) 2.28 (3H, s), 7.19–8.33 (8H, m), 8.92 (1H, br). Found: C, 51.46; H, 3.41; N, 11.03; S, 8.47%. $C_{16}H_{12}BrN_3OS$ requires C, 51.34; H, 3.23; N, 11.22; S, 8.56%. **3c** (70%): mp 211–213°C; ν_{max}/cm^{-1} (KBr) 3225 (NH), 1640 (C=O), 1600 (C=N); δ_H ($CDCl_3$) 7.48–8.23 (8H, m), 8.96 (1H, br). Found: C, 45.92; H, 2.40; N, 10.43; S, 8.18%. $C_{15}H_9BrClN_3OS$ requires C, 45.65; H, 2.30; N, 10.65; S, 8.12%.

Method B. General Procedure. A mixture of the sulfonium bromide **2** (9.54 g, 30 mmol) and the appropriate N-nitrosoacetanilide derivative (30 mmol) in ethanol (50 mL) was stirred at room temperature for 12 hours, then it was diluted with water. The precipitated product was collected by filtration, washed with water, and dried. Recrystallization from acetic acid afforded products identical in all respects (mp, mixed mp, and spectra) with those obtained by method A above.

2-(Benzothiazol-2-yl)-2-oxoethylpropanedinitrile (**4**)

To a stirred solution of 2-bromoacetylbenzothiazole (**1**) (5.12 g, 20 mmol) and malononitrile (1.32 g, 20

TABLE 1 IR and ^{1}H-NMR Data of Compounds **9–14**

Comp. No.	ν_{max}/cm^{-1}	δ_H
9a	1680, 1660 (2 C=O), 1610 (C=N)	2.49 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.53–8.26 (m, 9H, ArH)[a]
9b	1680, 1654 (2 C=O), 1610 (C=N)	2.34 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.46–8.28 (m, 8H, ArH)[a]
9c	1683, 1668 (2 C=O), 1610 (C=N)	2.5 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.41–8.3 (m, 8H, ArH)[a]
10a	1680, 1660 (2 C=O), 1600 (C=N)	7.42–8.31 (m, ArH)[a]
10b	1685, 1662 (2 C=O), 1596 (C=N)	2.3 (s, 3H, CH_3), 7.48–8.27 (m, 18H, ArH)[a]
10c	1678, 1660 (2 C=O), 1600 (C=N)	7.37–8.3 (m, ArH)[a]
11a	2234 (C≡N), 1667 (C=O), 1593 (C=N)	7.13–8.2 (m, ArH)[a]
11b	2220 (C≡N), 1665 (C=O), 1595 (C=N)	2.25 (s, 3H, CH_3), 7.04–8.2 (m, 13H, ArH)[a]
11c	2231 (C≡N), 1665 (C=O), 1590 (C=N)	7.2–8.22 (m, ArH)[a]
12a	1600 (C=N)	2.85 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 7.43–8.27 (m, 9H, ArH)[a]
12b	1600 (C=N)	2.31 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 7.5–8.27 (m, 8H, ArH)[a]
12c	1615 (C=N)	—
13a	1600 (C=N)	7.36–8.3 (m, ArH)[a]
13b	1600 (C=N)	2.30 (s, 3H, CH_3), 7.28–8.3 (m, 18H, ArH)[a]
13c	1600 (C=N)	—
14a	3287, 3092 (NH_2), 1635 (C=N)	7.2–8.25 (m, 14H, ArH), 9.12 (br, 2H, NH_2)[b]
14b	3305, 3090 (NH_2), 1637 (C=N)	2.3 (s, 3H, CH_3), 7.11–8.22 (m, 13H, ArH), 9.08 (br, 2H, NH_2)[b]
14c	3289, 3102 (NH_2), 1634 (C=N)	—

[a]In $CDCl_3$.
[b]In DMSO-d_6.

mmol) in ethanol (20 mL) was added sodium hydroxide solution (0.7 g, in water 5 mL) dropwise over a period of 30 minutes. After complete addition, the mixture was diluted with water. The solid that precipitated was filtered off, washed with water, dried, and finally recrystallized from ethanol to give 3.0 g (63% yield) of **4**, mp 155–157°C; ν_{max}/cm^{-1} (KBr) 2261 (C≡N), 1693 (C=O); δ_H ($CDCl_3$) 4.1 (2H, d, J = 6.6 Hz), 4.43 (1H, t, J = 6.6 Hz), 7.57–8.24 (4H, m). Found: C, 59.92; H, 2.98; N, 17.31; S, 13.15%. $C_{12}H_7N_3OS$ requires C, 59.75; H, 2.92; N, 17.42; S, 13.29%.

5-Amino-1-aryl-3-(benzothiazol-2-yl)carbonylpyrazole-5-carbonitriles **5a–c**

Route A. General Procedure. To a cold solution of **4** (2.41 g, 10 mmol) and sodium acetate trihydrate (3 g) in ethanol (30 mL) was added the appropriate arene diazonium chloride solution (10 mmol) over a period of 30 minutes. After having been stirred for a further 3 hours at 0–5°C, the reaction mixture was left to stand in an ice box for 12 hours. The solid that precipitated was filtered off, washed with water, and dried. Recrystallization from dimethylformamide afforded **5a–c** in 60–68% yield. **5a** (75%): mp 268–270°C; ν_{max}/cm^{-1} (KBr) 3325, 3260 (NH_2), 2220 (C≡N), 1665 (C=O), 1620 (C=N). Found: C, 62.32; H, 3.30; N, 20.06; S, 9.17%. $C_{18}H_{11}N_5OS$ requires C, 62.59; H, 3.21; N, 20.28; S, 9.62%. **5b** (73%): mp 276–278°C; ν_{max}/cm^{-1} (KBr) 3312, 3226 (NH_2), 2225 (C≡N), 1665 (C=O), 1629 (C=N); δ_H (DMSO-d_6) 2.43 (3H, s), 7.13 (2H, br), 7.42–8.3 (8H, m). Found: C, 63.72; H, 3.71; N, 19.26; S, 8.99%. $C_{19}H_{13}N_5OS$ requires C, 63.49; H, 3.64; N, 19.48; S, 8.92%. **5c** (93%): mp 290–292°C; ν_{max}/cm^{-1} (KBr) 3365, 3220 (NH_2), 2222 (C≡N), 1668 (C=O), 1620 (C=N). Found: C, 56.91; H, 2.80; N, 18.63; S, 8.33%. $C_{18}H_{10}ClN_5OS$ requires C, 56.93; H, 2.65; N, 18.44; S, 8.42%.

Route B. General Procedure. To an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute ethanol (20 mL)] was added malononitrile (132 mg, 2 mmol) with stirring. To the resulting solution, each appropriate arylhydrazone **3a–c** (2 mmol) was added portionwise at room temperature. The reaction mixture was stirred for 12 hours during which the hydrazonoyl bromide **3** dissolved and a solid product precipitated. The latter products were filtered off, washed with water, dried, and finally recrystallized from dimethylformamide to afford 73–93% yield of compounds identical in all respects (mp, mixed mp, and spectra) with those obtained by route A above.

Reaction of **5a–c** *with Hydrazine Hydrate*

General Procedure. A mixture of the appropriate pyrazole **5a–c** (5 mmol) and hydrazine hydrate

TABLE 2 Physical Data of the Pyrazoles **9**, **10**, and **11** and the Pyrazolo[3,4-d]Pyridazines **12**, **13**, and **14**

Comp. No.	Mp (°C)	Yield (%)	Molecular Formula	Anal. Calcd/(Found) C%	H%	N%	S%
9a	110–112[a]	68	$C_{20}H_{15}N_3O_2S$	66.46 (66.28)	4.18 (4.20)	11.62 (11.43)	8.87 (8.95)
9b	98–100[a]	68	$C_{21}H_{17}N_3O_2S$	67.18 (66.80)	4.56 (4.24)	11.19 (11.32)	8.54 (8.30)
9c	160–161[a]	85	$C_{20}H_{14}ClN_3O_2S$	60.68 (60.45)	3.56 (3.33)	10.61 (10.38)	8.10 (8.13)
10a	162–164[a]	97	$C_{30}H_{19}N_3O_2S$	74.21 (74.00)	3.94 (3.86)	8.65 (8.42)	6.59 (6.50)
10b	159–161[a]	95	$C_{31}H_{21}N_3O_2S$	74.53 (74.28)	4.23 (4.35)	8.41 (8.19)	6.42 (6.50)
10c	171–173[a]	98	$C_{30}H_{18}ClN_3O_2S$	69.30 (69.27)	3.48 (3.60)	8.08 (7.91)	6.17 (6.12)
11a	212–214[b]	65	$C_{24}H_{14}N_4OS$	70.92 (71.20)	3.47 (3.30)	13.78 (13.52)	7.88 (7.95)
11b	213–215[b]	60	$C_{25}H_{16}N_4OS$	71.40 (71.32)	3.83 (3.90)	13.32 (13.15)	7.62 (7.45)
11c	210–212[b]	78	$C_{24}H_{13}ClN_4OS$	65.38 (65.66)	2.97 (3.11)	12.71 (12.48)	7.25 (7.40)
12a	304–305[b]	85	$C_{20}H_{15}N_5S$	67.20 (67.37)	4.23 (4.25)	19.59 (19.25)	8.96 (8.77)
12b	313–315[b]	87	$C_{21}H_{17}N_5S$	67.89 (68.00)	4.61 (4.51)	18.85 (18.71)	8.63 (8.7)
12c	315–317[b]	90	$C_{20}H_{14}ClN_5S$	61.29 (61.21)	3.60 (3.80)	17.87 (17.63)	8.18 (8.10)
13a	285–287[b]	75	$C_{30}H_{19}N_5S$	74.83 (75.10)	3.98 (4.10)	14.54 (14.32)	6.64 (6.49)
13b	298–299[b]	68	$C_{31}H_{21}N_5S$	75.13 (75.20)	4.27 (4.30)	14.13 (14.23)	6.45 (6.38)
13c	281–283[b]	68	$C_{30}H_{18}ClN_5S$	69.83 (69.64)	3.51 (3.60)	13.57 (13.80)	6.20 (6.22)
14a	312–314[b]	60	$C_{24}H_{16}N_6S$	68.55 (68.70)	3.83 (3.92)	19.98 (19.71)	7.62 (7.68)
14b	319–321[b]	55	$C_{25}H_{18}N_6S$	69.11 (68.94)	4.17 (4.00)	19.34 (19.63)	7.37 (7.16)
14c	320–322[b]	57	$C_{24}H_{15}ClN_6S$	63.36 (63.15)	3.32 (3.30)	18.47 (18.12)	7.03 (6.78)

[a]Crystallization solvent is ethanol.
[b]Crystallization solvent is dimethylformamide.

(1 mL, 80%) in ethanol (20 mL) was refluxed for 5 hours and then cooled. The precipitated product was collected by filtration, washed with ethanol, and dried. Recrystallization from dimethylformamide afforded the pyrazolo[3,4-d]pyridazine derivatives **6a–c** in 55–60% yield. These products were insoluble in the usual NMR solvents. **6a** (59%): mp >350°C; ν_{max}/cm^{-1} (KBr) 3415, 3344, 3242, 3205 (2 NH_2), 1643, 1621 (2 C=N); *m/z* 359 (M^+). Found: C, 60.23; H, 3.47; N, 26.98; S, 8.94%. $C_{18}H_{13}N_7S$ requires C, 60.15; H, 3.64; N, 27.28; S, 8.92%. **6b** (55%): mp 334–336°C; ν_{max}/cm^{-1} (KBr) 3405, 3312, 3226, 3175 (2 NH_2), 1636, 1621 (2 C=N). Found: C, 59.94; H, 4.13; N, 26.17; S, 8.60%. $C_{19}H_{15}N_7S$ requires C, 61.10; H, 4.05; N, 26.25; S, 8.58%. **6c** (60%): mp >350°C; ν_{max}/cm^{-1} (KBr) 3423, 3355, 3320, 3178 (2 NH_2), 1649, 1618 (2 C=N). Found: C, 54.69; H, 3.16; N, 24.73; S, 8.13%. $C_{18}H_{12}ClN_7S$ requires C, 54.89; H, 3.07; N, 24.89; S, 8.12%.

Reaction of **5a–c** *with Formic Acid*

General Procedure. A solution of the appropriate pyrazole **5a–c** (5 mmol) in formic acid (20 mL, 85%) was refluxed for 8 hours. The reaction mixture was then cooled and treated with ammonia solution (20%). The precipitated product was filtered off, washed with water, and dried. Recrystallization from dimethylformamide afforded each of the pyrazolo[3,4-d]pyrimidinones **7a–c** in 80–85% yield. **7a**

(81%): mp 274–276°C; ν_{max}/cm^{-1} (KBr) 3230 (NH), 1710 (br 2 overlapped C=O), 1595 (C=N). Found: C, 61.37; H, 3.10; N, 18.53; S, 8.60%. $C_{19}H_{11}N_5O_2S$ requires C, 61.11; H, 2.97; N, 18.76; S, 8.58%. **7b** (80%): mp 308–310°C; ν_{max}/cm^{-1} (KBr) 3185 (NH), 1708 (br 2 overlapped C=O), 1600 (C=N); δ_H (DMSO-d_6) 2.56 (3H, s), 7.56–8.49 (10H, m). Found: C, 61.77; H, 3.42; N, 14.63; S, 8.13%. $C_{20}H_{13}N_5O_2S$ requires C, 62.00; H, 3.38; N, 14.46; S, 8.27%. **7c** (85%): mp 321–323°C; ν_{max}/cm^{-1} (KBr) 3280 (NH), 1680 (br 2 overlapped C=O), 1592 (C=N); *m/z* 409 ($M^+ + 2$), 408 ($M^+ + 1$), 407 (M^+). Found: C, 55.84; H, 2.38; N, 17.31; S, 7.90%. $C_{19}H_{10}ClN_5O_2S$ requires C, 55.95; H, 2.47; N, 17.17; S, 7.86%.

Reaction of **5a–c** *with Formamide*

General Procedure. A mixture of the appropriate pyrazole **5a–c** (5 mmol), formamide (10 mL), formic acid (5 mL), and dimethylformamide (5 mL) was refluxed for 8 hours and then cooled. The precipitated solid was filtered off, washed with water, and dried. Recrystallization from dioxane afforded each of the pyrazolo[3,4-d]pyrimidines **8a–c** in 76–85% yield. **8a** (82%): mp 190–192°C; ν_{max}/cm^{-1} (KBr) 3286, 3168 (NH_2), 1654 (C=O), 1600 (C=N); δ_H ($CDCl_3$) 7.2–8.76 (10H, m), 10.42 (2H, br). Found: C, 61.14; H, 3.30; N, 22.29; S, 8.67%. $C_{19}H_{12}N_6OS$ requires C, 61.27; H, 3.25; N, 22.56; S, 8.61%. **8b** (76%): mp 216–218°C; ν_{max}/cm^{-1} (KBr) 3256, 3143 (NH_2), 1656 (C=O), 1600 (C=N); δ_H ($CDCl_3$) 2.48 (3H, s), 7.26–8.84 (9H, m), 10.6 (2H, br). Found: C, 62.30; H, 3.77; N, 21.68; S, 8.22%. $C_{20}H_{14}N_6OS$ requires C, 62.16; H, 3.65; N, 21.75; S, 8.29%. **8c** (85%): mp 233–235°C; ν_{max}/cm^{-1} (KBr) 3297, 3156 (NH_2), 1655 (C=O), 1597 (C=N). Found: C, 55.83; H, 2.66; N, 20.48; S, 7.73%. $C_{19}H_{11}ClN_6OS$ requires C, 56.08; H, 2.72; N, 20.65; S, 7.88%.

Reaction of arylhydrazones 3a–c with Active Methylene Compounds

General Procedure. The appropriate active methylene compound (2,4-pentanedione, 1,3-diphenyl-1,3-propanedione, or 3-oxo-3-phenylpropanenitrile) (10 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and absolute ethanol (20 mL)] with stirring. After each mixture had been stirred for 15 minutes, the appropriate arylhydrazone **3a–c** (10 mmol) was added portionwise to the resulting solution. The reaction mixture was stirred for a further 12 hours at room temperature. The solid that formed was filtered off, washed with water, and dried. Recrystallization from the proper solvent afforded the pyrazole derivatives **9**, **10**, and **11**, respectively, in 68–98% yield. The synthesized pyrazoles together with their physical constants are listed in Table 2.

Reaction of pyrazoles 9, 10 and 11 with hydrazine hydrate

General Procedure. A mixture of the appropriate pyrazole derivative **9**, **10**, or **11** (2 mmol) and hydrazine hydrate (0.5 mL, 80%) in ethanol (20 mL) was refluxed for 1 hour and then cooled. The solid product that formed was collected by filtration, washed with water, dried, and finally recrystallized from dimethylformamide to afford the pyrazolo[3,4-d]pyridazines **12a–c**, **13a–c**, and **14a–c**, respectively, in 55–98% yield. The compounds synthesized together with their physical data are listed in Table 2.

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