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# Synthesis of 4-Amino-3-cyano-2-methylsulfanyl-1*H*-[1,5]benzodiazepine, Benzo[1,3]azole, and Pyrazolobenzo[1,3]azole Derivatives via a New Utility of Bis(methylsulfanyl)methylene Derivatives

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ABSTRACT: *Novel polysubstituted 1,5-benzodiazepine* **5**, *2,2-bis(methylthio)benzoxazoles* **8a–d**, *2,2-bis-(acetyl)benzoxazole* **8e**, *2-(3-methyl-1-phenylpyrazolo-4-yl)benzoazole derivatives* **16a–c**, *as well as the previously reported 2-di[cyano(acetyl)-methylene]benzothiazoles* **7a,b** *have been obtained via a new utility of ketene dithioacetals* **1a,b** *and* **12** *with aniline derivatives* **2**. *Rationales for the reactions pathways are presented.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:407–412, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20031

## *INTRODUCTION*

The ketene dithioacetals **1** were successfully used in heterocyclic synthesis [1–7]. To the best of our knowledge, the ketene dithioacetal **1** was not used to prepare seven-membered ring systems so far; however, some other related derivatives were used [8,9]. The remarkable biological and pharmaceutical properties of 1,5-benzodiazepine derivatives [10–13] are behind our interest [14–18] to prepare such seven-membered ring systems.

Dedicated to Professor Dr. Dietrich Dôpp on the occasion of his 65th birthday.

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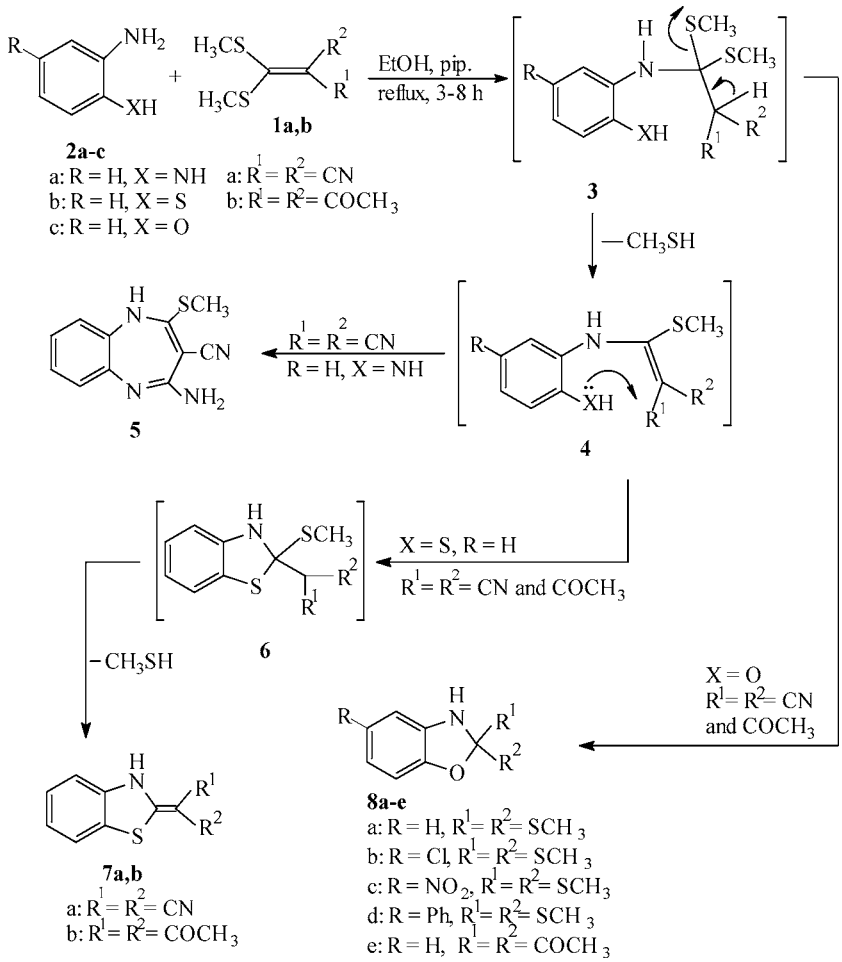
## *RESULTS AND DISCUSSION*

The bis(methylsulfanyl)methylene malononitrile **1a** reacted with 1,2-phenylenediamine **2a** in ethanol solution containing catalytic amount of piperidine at reflux temperature to yield the corresponding 4-amino-3-cyano-2-methylsulfanyl-1*H*-[1,5]benzodiazepine **5**. The structure assignment of product **5** is based on spectral and elemental analysis. The MS (70 eV) spectrum of compound **5** showed molecular ion corresponding to the formula $C_{11}H_{10}N_4S$ (231, M + 1, 35%), 182 (M-$CH_3SH$, 30), 154 (182-HCN, 9), 127 (154-$N_2$, 22), 102 (127-CH=CH, 20), 98 (100). The IR spectrum revealed absorption bands at $\nu$ 3100, 3121, 3250, and 2215 assigned for imino, amino, and cyano function groups, respectively. The $^1$H NMR spectrum of **5** showed two singlets at $\delta$ 3.4 ppm assigned for thiomethyl protons and a downfield absorption at $\delta$ 12.9 ppm assigned for amine protons, respectively. The $^{13}$C NMR spectrum of **5** showed signals at $\delta$ 56.5 assignable for one carbon of thiomethyl ($SCH_3$) and at $\delta$ 118.2 also assigned for only one cyano carbon (CN), 110.2 (C-3), 140.4 (C-4), 145.5 (C-2), in addition to the aryl carbons. A rationale for formation of the product **5** is presented in Scheme 1.

It assumes that the amine function of **2a** attacks exclusively the activated double bond of the ketene dithioacetal **1a** at the more electrophilic carbon bearing the two thiomethyl groups to give the adduct

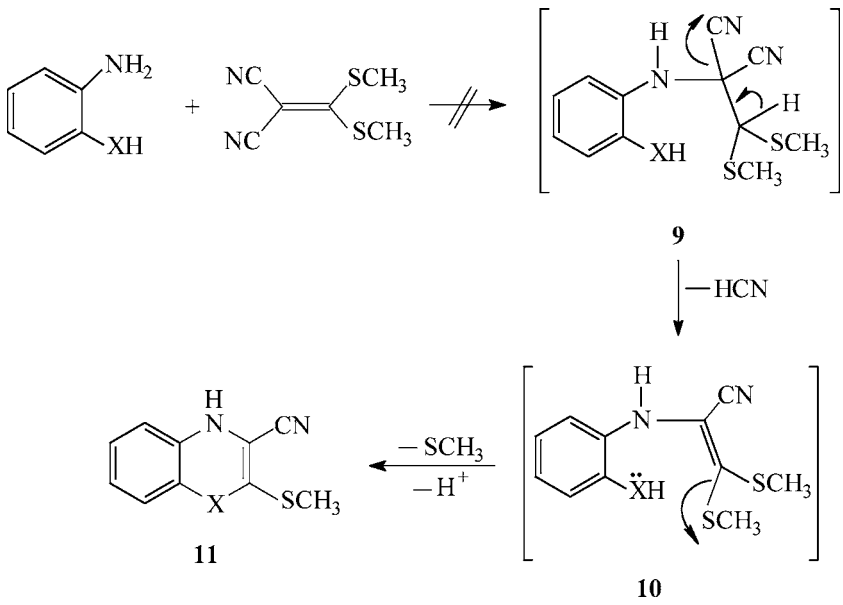



**SCHEME 1**

**3**. Elimination of one molecule of thiomethyl alcohol from **3** affords the intermediate **4**, which may also be obtained directly from losing thiomethyl alcohol from **1** and **2**. Cyclization of **4** via a nucleophilic attack by the lone pair electrons of the second amine group into the cyano function finally yielded the 1,5-benzodiazepine compound **5** (Scheme 1). The reaction of **1a** with **2b** and **2c** failed to produce any of the desired benzothiazepine or benzoxazepine derivatives. Hypothetically, the amine function might attack $C(CN)_2$) carbon; this would lead to elimination of HCN and $CH_3SH$, respectively, to afford benzopyrazine **11** via the plausible intermediate **10**. Formation of **11** is ruled out on the basis of the spectroscopic and elemental data obtained (Scheme 2).

On the other hand, reaction of 2-aminothiophenol **2b** with the ketene dithioacetals **1a,b** under the same reaction conditions yielded the previously reported benzothiazole derivatives **7a,b** via the intermediate **6**. The structure of compounds **7a,b** based on spectral and elemental analysis and compared with the data was reported [5]. The MS of compound **7a** gave a correct molecular ion at *m/z* 199 ($M^+$, 100%) as base peak. The IR spectrum showed characteristic bands at 3170 and 2212, 2210 assigned for imino and nitrile functions, respectively. The $^1$H NMR spectrum showed absorption at $\delta$ 7.1–7.9 ppm attributed for aromatic protons and at 9.2 assigned for NH proton only, with the lack of any absorption due to thiomethyl protons. $^{13}$C NMR spectrum of **7a** shows signals at $\delta$ 117.5, 118.4 (CN), 145.2 (C-2a), and 152.2 (C-2), in addition to aryl carbons.

Contrarily, 2-aminophenol **2c** reacts with ketene dithioacetals **1a,b** in a different mode, as is shown in Scheme 1. Elimination of one molecule of malononitrile from the adduct **3** affords 2,2-bis[methylthio(acetyl)]-2,3-dihydrobenzoxazole **8a–e**. The MS of **8a** showed exact molecular ion at *m/z* 213 ($M^+$, 15) corresponding for $C_9H_{11}NOS_2$. The IR spectrum showed no absorption due to cyano function. The $^1$H NMR spectrum showed one singlet at $\delta$ 3.4 ppm integrated



SCHEME 2

for six protons of two $SCH_3$. The $^{13}C$ NMR spectrum of **8a** showed signals at 45.5 and 56.7 ppm assigned for C-2 and 2(S**C**$H_3$). These spectral data prompted us to propose that the reaction may proceeds via the key intermediate **3**, which transformed via a five-endo-trig pathway with the elimination of one molecule of malononitrile to yield the benzoxazole derivatives **8** (Scheme 1).

On the other hand, 3-methyl-1-phenylpyrazole-4-methylenedithioacetal-5-one **12** was reacted with aniline derivatives **2a–c** in ethanol containing piperidine at reflux temperature to afford 2-(1-methyl-1-phenylpyrazole-5-one-4-yl)benzazole derivatives **16a–c** in moderated yields. The mass spectrum of **16b** showed *m/z* at 307 ($M^+$, 100), 174 (37), 133 (13), 105 (13), 103 (3), and 77 (15). The IR spectrum revealed absorption bands at $\nu$ 3215 and 1675 and 1628 $cm^{-1}$ assigned for NH, C=O and C=C groups, respectively. The $^1H$ NMR spectrum of **16b** showed signals at $\delta$ 2.1, 7.2–7.9, and 9.2 ppm attributed for methyl, aromatic, and NH protons, respectively. The $^{13}C$ NMR of **16b** showed characteristic signals at 172.5 and 185.2 ppm assigned for carbonyl and C-2 of thiazole ring, respectively. Formation of **16** may be proceeded as described in Scheme 3. Elimination of one molecule of thiomethyl alcohol from the adduct **13** afforded the intermediate **14**, which transformed to the intermediate **15**. The latter loses another molecule of thiomethyl alcohol to finally yield the product **16**. Formation of the expected 1,5-benzodiazepine derivatives **17** was ruled out.

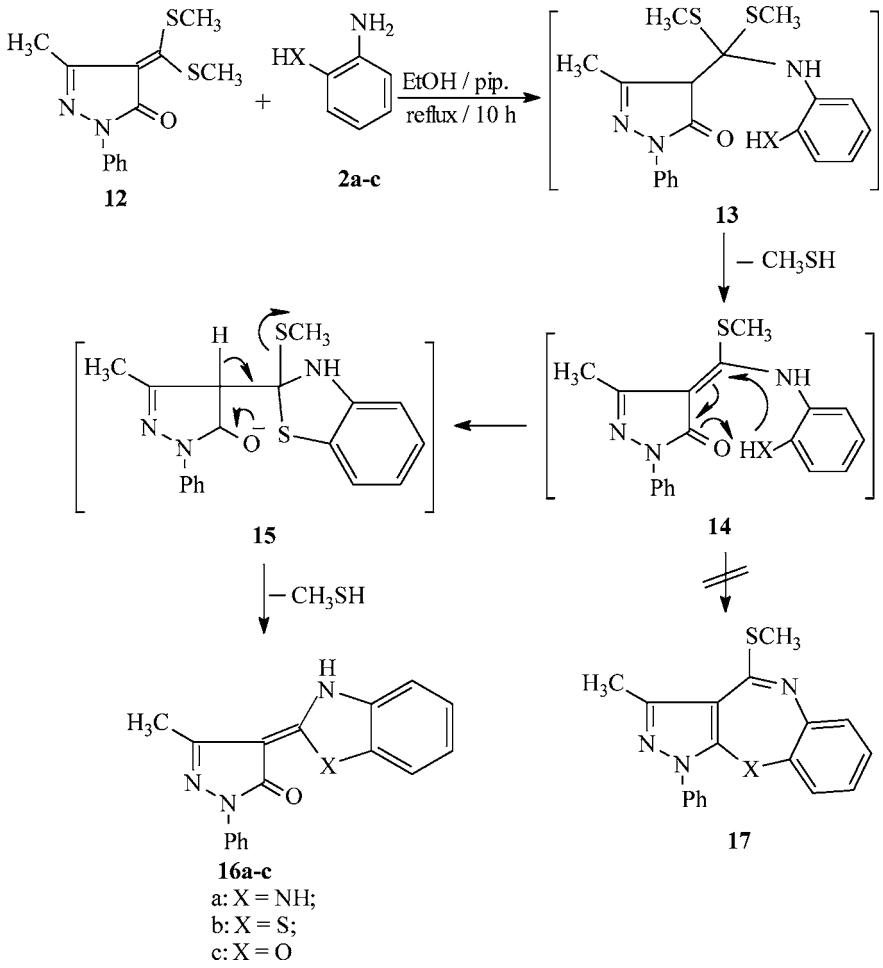
## *EXPERIMENTAL*

Melting points have been determined on a Gallen–Kamp melting point apparatus and are uncorrected. The IR spectra (potassium bromide, $\nu$ in $cm^{-1}$) were recorded on a Pye-Unicam SP-1100 spectrophotometer. $^1H$ NMR spectra (deuterochloroform and deuterodimethyl sulfoxide, $\delta$ in ppm) were run on a Varian EM-390 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded (70 eV) on a Varian MAT 311 A spectrometer, and the elemental analyses were determined at the Microanalytical Center, Cairo University, Egypt.

### *4-Amino-3-cyano-2-methylsulfanyl-1H-[1,5]benzodiazepine* **5**

A solution of **1** (1.7 g, 10 mmol), 1,2-phenylenediamine**2a** (1.0 gm, 10 mmol), and 0.1 mL of piperidine in 30 mL of dry ethanol was warmed to reflux for 3 h and concentrated under vacuum. The solid compound formed after two hours of reflux was collected by filtration, washed with 5 mL of methanol, and crystallized from dimethylformamide to give **5**.

This compound was isolated (1.4 g, 63%), mp >300°C. IR: $\nu$ 3100 (NH), 3121–3250 ($NH_2$), 2215 (CN). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.4 (s, 3H, $SCH_3$), 12.9 (s, 2H, $NH_2$), 7.1–7.9 (m, 5H, Ar—H, NH). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 56.5 (S**C**$H_3$), 110.2 (C-3), 118.2 (CN), 123.5, 124.3, 127.2, 128.3 (aryl-C), 140.4 (C-4), 145.5 (C-2). MS *m/z* (%): 231 (M + 1, 35), 182 (30), 154 (9), 127 (22), 102 (20), 98 (100). Anal calcd for $C_{11}H_{10}N_4S$




**SCHEME 3**

(230.29): C, 57.37; H, 4.38; N, 24.33; S, 13.92. Found: C, 57.19; H, 4.21; N, 24.14; S, 13.80.

### *2-Di(cyanomethylenyl)-2,3-dihydrobenzothiazole* **7a**

To 30 mL of ethanol, 1.7 g (10 mmol) of **1**, 2-aminothiolphenol **2b** (1.2 g, 10 mmol), and 0.1 mL of piperidine was refluxed for 5 h. The solid compound formed on heating was collected by filtration, washed with 5 mL of methanol, and crystallized from a mixture of equal volumes of dimethylformamide and ethanol. This compound was isolated (1.0 mg, 52%), mp 292°C (lit. 290°C). IR: $\nu$ 3170 (NH), 2212, 2210 (CN). $^1$H NMR: (DMSO-$d_6$): $\delta$ 7.1–7.9 (m, 4H, Ar—H), 9.2 (s, 1H, NH). $^{13}$C NMR: $\delta$ 117.5, 118.4 (CN), 121.2, 123.5, 126.7, 128.5 (aryl-C), 145.2 (C-2a), 152.2 (C-2). MS: $m/z$ = 199 ($M^+$, 100%), 172 (25), 146 (19), 109 (6), 77 (5). Anal calcd for $C_{10}H_5N_3S$ (199.23): C, 60.29; H, 2.53; N, 21.09; S, 16.09. Found: C, 60.10; H, 2.42; N, 20.88; S, 15.98.

### *2-Di(acetylmethylenyl)-2,3-dihydrobenzothiazole* **7b**

This was crystallized from ethanol in 60% yield, mp 160–161°C (lit. 158.5–159.5°C). IR: $\nu$ 3145 (NH), 1610 (C=O). $^1$H NMR ($CDCl_3$): $\delta$ 2.4 (s, 6H, $2CH_3$), 7.2–7.8 (m, 4H, Ar—H), 14.9 (s, 1H, NH). MS: $m/z$ = 233 ($M^+$, 100%). Anal calcd for $C_{12}H_{11}NO_2S$ (233.29): C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.50; H, 4.63; N, 5.87; S, 13.55.

### *General Procedure for 2,2-Bis[methylsulfanyl-(acetyl)]-2,3-dihydrobenzoxazoles* **8a–e**

A mixture of **1**a (1.7 g, 10 mmol), 2-aminophenol **2c** (1.2 g, 1 mmol), and 0.1 mL of piperidine in 30 mL of dry ethanol was refluxed for five hours and then concentrated under vacuum till dryness. The solid formed was triturated with cold methanol and collected by filtration, washed with 5 mL of methanol and crystallized from ethanol.

*Compound* **8a**. This compound was isolated (1.2 g, 60%), mp 240°C. IR: $\nu$ 3170 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 3.4 (s, 6H, $2SCH_3$), 7.2–7.9 (m, 4H, Ar—H), 10.3 (s, 1H, NH). $^{13}$C NMR: $\delta$ 45.5 (C-2), 56.7 ($SCH_3$), 110.2, 120.3, 124.2, 125.2, 140.1, 150.3 (aryl-C). MS: *m/z* (%) 213 ($M^+$, 15%), 185 (66), 120 (2), 108 (2), 92 (13), 77 (8), 64 (80), 52 (17). Anal calcd for $C_9H_{11}NOS_2$ (213.31): C, 50.68; H, 5.20; N, 6.57; S, 30.06. Found: C, 50.52; H, 5.05; N, 6.33; S, 29.86.

*Compound* **8b**. This was isolated (EtOH) in 0.4 g (57%), mp 295°C. IR: $\nu$ 3180 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 3.5 (s, 6H, $2SCH_3$), 7.2–7.9 (m, 3H, Ar—H), 9.2 (s, 1H, NH). MS: *m/z* (%) 247 ($M^+$, 17%). Anal calcd for $C_9H_{10}ClNOS_2$ (247.76): C, 43.64; H, 4.07; N, 5.66; S, 25.88; Cl, 14.31. Found: C, 43.36 ; H, 4.27; N, 5.44; S, 25.74; Cl, 14.01.

*Compound* **8c**. This was isolated (MeOH) in 0.5 g (66%), mp 280°C. IR: $\nu$ 3172 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 3.2 (s, 6H, $2SCH_3$), 7.1–7.9 (m, 3H, Ar—H), 10.2 (s, 1H, NH). MS: *m/z* (%) 258 ($M^+$, 25%). Anal calcd for $C_9H_{10}N_2O_3S_2$ (258.31): C, 41.85; H, 3.90; N, 10.85; S, 24.82. Found: C, 41.63; H, 3.76; N, 10.46; S, 24.66.

*Compound* **8d**. This was isolated (MeOH) in 0.5 g (58%), mp 210°C. IR: $\nu$ 3175 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 3.5 (s, 6H, $2SCH_3$), 7.1–7.9 (m, 8H, Ar—H), 11.3 (s, 1H, NH). MS: *m/z* (%) 289 ($M^+$, 19%). Anal calcd for $C_{15}H_{15}NOS_2$ (289.41): C, 62.25; H, 5.22; N, 4.84; S, 22.16. Found: C, 62.06; H, 5.01; N, 4.63; S, 22.01.

*Compound* **8e**. This was isolated (Dioxan/$H_2O$) in 0.2 g (40%), mp 110°C. IR: $\nu$ 1710 (C=O), 3180 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 1.4 (s, 6H, $2CH_3$), 7.1–7.9 (m, 4H, Ar—H), 12.5 (s, 1H, NH). MS: *m/z* (%) 205 ($M^+$, 15%). Anal calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.17; H, 5.23; N, 6.61.

### *General Procedure for 2-(1-Methyl-1-phenylpyrazole-5-one-4-yl)-benzazole derivatives* **16a–c**

Equimolar amounts (1 mmol) of **12** (1.0 g) and 2-aminothiophenol **2b** (0.45 g) were refluxed in 30 mL ethanol for 10–12 h in the presence of 0.5 mL of piperidine. The solid product isolated during reflux was filtered, and the residue was concentrated under vacuum till dryness and triturated with 3 mL methanol, and the solid formed was filtered and crystallized together with the first portion from DMF/ethanol to afford **16b**. Similarly, each of **2a** (0.39 g) and **2c** (0.39 g) reacted with **12** under the same conditions to yield **16a** and **16c**, respectively.

*2-(1-Methyl-1-phenylpyrazole-5-one-4-yl)-benzimidazole* **16a**. Yield: 0.3 g (65%), mp 100°C. IR: $\nu$ 1700 (C=O), 3177 (NH). $^1$H NMR (DMSO): $\delta$ 2.1 (s, 3H, $CH_3$), 7.1–7.9 (m, 9H, Ar—H), 9.8 (s, 2H, 2NH). MS: *m/z* (%) 290 ($M^+$, 25%). Anal calcd for $C_{17}H_{14}N_4O$ (290.33): C, 70.33; H, 4.86; N, 19.30. Found: C, 70.20; H, 4.64; N, 19.11.

*2-(1-Methyl-1-phenylpyrazole-5-one-4-yl)-benzothiazole* **16b**. Yield: 0.4 g (72%), mp 195°C. IR: $\nu$ 1628 (C=C), 1675 (C=O), 3215 (NH). $^1$H NMR (DMSO): $\delta$ 2.1 (s, 3H, $CH_3$), 7.2–7.9 (m, 9H, Ar—H), 9.2 (s, 1H, NH). $^{13}$C NMR (DMSO): 15.2 ($CH_3$), 121.2–130.3 (aryl-C), 142.6 (C-3-pyrazole), 145.2 (C-4-pyrazole), 172.5 (C-5-pyrazole), 185.2 (C-2-thiazole). MS: *m/z* (%) 307 ($M^+$, 100%). Anal calcd for $C_{17}H_{13}N_3OS$ (307.37): C, 66.43; H, 4.26; N, 13.67. Found: C, 66.25; H, 4.03; N, 13.55.

*2-(1-Methyl-1-phenylpyrazole-5-one-4-yl)-benzoxazole* **16c**. Yield: 0.3 g (60%), mp 95°C. IR: $\nu$ 1850 (C=O), 3185 (NH). $^1$H NMR ($CDCl_3$): $\delta$ 1.6 (s, 3H, $CH_3$), 7.1–7.9 (m, 9H, Ar—H), 10.5 (s, H, NH). MS: *m/z* (%) 291 ($M^+$, 35%). Anal calcd for $C_{17}H_{13}N_3O_2$ (291.31): C, 70.10; H, 4.50; N, 14.42. Found: C, 69.90; H, 4.26; N, 14.22.

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