

Heterocyclic Synthesis via Enaminones: Regioselective Synthesis of Some Novel Pyrazole, Isoxazole, Pyrimidine, Pyrido [1,2-*a*]benzimidazole and Pyrazolo[1,5-*a*]pyrimidine Derivatives

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ABSTRACT: 2-Acetylbenzothiazole (**1**) reacts with dimethylformamide dimethylacetal (DMF-DMA) to afford the enaminone **2**. Compound **2** reacts regioselectively with some nitrilimines **5a–d** and nitrile oxides **6b–d** to afford the novel pyrazole and isoxazole derivatives **11a–d** and **12b–d**, respectively, which react with hydrazine hydrate to give the new pyrazolo[3,4-*d*]pyridazine and isoxazolo[3,4-*d*]pyridazine derivatives **13a–d** and **14b–d**, respectively. The enaminone **2** reacts with 1*H*-benzimidazole-2-acetonitrile (**17**) to afford the pyrido[1,2-*a*]benzimidazole derivatives **19**. Compound **2** reacts also with 5-amino-3-phenylpyrazole (**20**) and with guanidine to afford the new pyrazolo[1,5-*a*]pyrimidine and the 2-aminopyrimidine derivatives **22** and **24**, respectively. © 1999 John Wiley & Sons, Inc. *Heteroatom Chem* 10: 417–422, 1999

INTRODUCTION

Enaminone derivatives are highly reactive intermediates and are extensively used for the synthesis of heterocyclic compounds [1–3]. On the other hand, a great deal of interest has been focused on the synthesis of functionalized benzothiazole derivatives because of their synthetic and biological potentialities

[4–6]. In continuation of our interest in the synthesis of a wide variety of heterocycles containing a benzothiazole moiety for biological screening [7], we report here on the synthesis of 1-(benzothiazol-2-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**) and the regioselectivity in the 1,3-dipolar cycloaddition reactions of the latter compound with some nitrilimines **5a–d** and nitrile oxides **6b–d**. The behavior of compound **2** toward some nitrogen nucleophiles is also investigated.

Thus, treatment of 2-acetylbenzothiazole (**1**) with dimethylformamide dimethylacetal (DMF-DMA) in dry xylene under reflux afforded a bright red crystalline product that was identified as (*E*)-1-(benzothiazol-2-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**) in high yield. The structure of the latter product was established on the basis of its elemental analysis and spectral data. For example, its ¹H NMR spectrum displayed a singlet at δ 3.05 due to *N,N*-dimethyl protons and two doublets at δ 6.22 and 8.06 ($J = 12.2$ Hz) due to olefinic protons, in addition to an aromatic multiplet in the region δ 7.33–7.92. The value of the coupling constant ($J = 12.2$ Hz) for the ethylenic protons indicates that the enaminone **2** exists *all* in the *E*-configuration.

1,3-Dipolar cycloaddition of nitrilimines and nitrile oxides with alkenes is well documented [8,9]. In this work, we studied the regioselectivity in 1,3-dipolar cycloaddition of some nitrilimines **5a–d** and

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nitrile oxides **6b–d** with the enaminone **2**. Thus, reaction of the enaminone **2** with the nitrilimine **5a** (generated in situ by the action of triethylamine on the hydrazonoyl chloride **3a**) in dry benzene at room temperature afforded a single product (as examined by TLC and ^1H NMR spectroscopy) for which the two regioisomeric cycloadducts **9a** and **15a** seemed possible (Scheme 1). However, the regioisomer **9a** was assigned for the reaction product on the basis of its ^1H NMR spectrum and its chemical transformation outlined in Scheme 1. The ^1H NMR spectrum of the isolated product revealed two singlets at δ 2.73 and 9.03 due to acetyl- CH_3 and pyrazole-5- CH protons, respectively, in addition to an aromatic multiplet in the region δ 7.14–8.19. A further confirmation of the

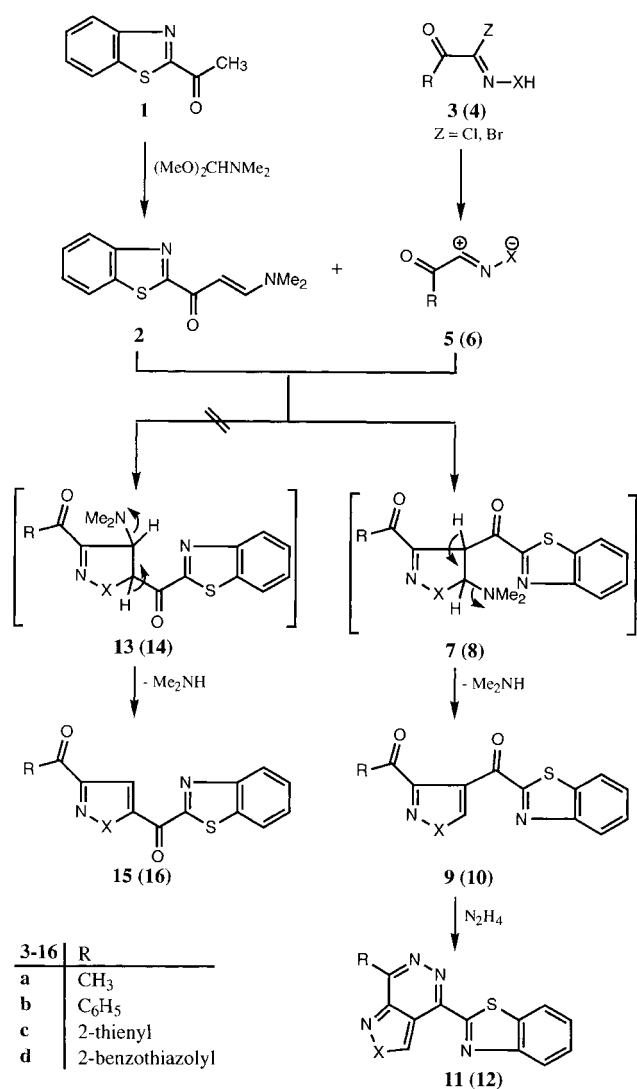
structure of compound **9a** comes from its reaction with hydrazine hydrate to afford a high yield of a yellow-colored product, which was identified as 4-(benzothiazol-2-yl)-7-methyl-2-phenylpyrazolo[3,4-*d*]pyridazine (**11a**) (Scheme 1). The formation of the 5-unsubstituted pyrazole **9a** is assumed to take place via a regioselective 1,3-cycloaddition of the nitrilimine intermediate **5a** to the enaminone **2** to form the nonisolable intermediate **7a**, followed by elimination of dimethylamine under the reaction conditions. The IR spectrum of compound **9a** showed two carbonyl absorption bands at 1710 and 1641 cm^{-1} , which disappeared in the IR spectrum of the product **11a**.

Prompted by these results and in order to generalize this reaction, the enaminone **2** was allowed to react with the nitrilimines **5b–d** under the same experimental conditions, where it afforded similarly the corresponding pyrazole derivatives **9b–d**. The latter products underwent cyclocondensation upon treatment with hydrazine hydrate in refluxing ethanol to give the pyrazolo[3,4-*d*]pyridazine derivatives **11b–d** (Scheme 1). The structure of the products **9b–d** and **11b–d** was established on the basis of their elemental analyses and spectral data (see Experimental section).

Alternatively, compound **2** reacts with nitrile oxide **6b** (generated in situ by the action of triethylamine on the hydroximoyl chloride **4b**) in dry benzene at room temperature to afford a single product for which the cycloadduct **10b** or **16b** can be formulated. However, the appearance of a singlet signal at δ 10.04 in the ^1H NMR spectrum of the reaction product is attributed to the isoxazole-5- CH proton, as in structure **10b**, rather than the isoxazole-4- CH proton in structure **16b**. Moreover, product **10b** underwent cyclocondensation with hydrazine hydrate in refluxing ethanol to give a product identified as 7-phenyl-4-(benzothiazol-2-yl)isoxazolo[3,4-*d*]pyridazine (**12b**). This result provided additional evidence for the regioisomeric cycloadduct **10b** and ruled out the other possible regioisomer **16b**.

In the same manner, the enaminone **2** reacts regioselectively with the nitrile oxides **5c,d** under the same experimental conditions to afford the isoxazoles **10c,d**, respectively. The latter products underwent cyclocondensation upon reaction with hydrazine hydrate in refluxing ethanol to afford the isoxazolo[3,4-*d*]pyridazine derivatives **12c,d** (Scheme 1). The structure of these products was established on the basis of their elemental analyses and spectral data (see Experimental section).

Next, the behavior of the enaminone **2** toward some nitrogen nucleophiles was also explored. Thus,



3, 5, 7, 9, 11, 13, 15 : X = N-Ph
4, 6, 8, 10, 12, 14, 16: X = O

SCHEME 1

heating equimolar amounts of compound **2** and 1*H*-2-benzimidazoleacetonitrile (**17**) in ethanol in the presence of a catalytic amount of piperidine resulted in the formation of a single product (as examined by TLC). The structure of the isolated product was identified as 3-(benzothiazol-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**19**) on the basis of its spectral data and elemental analysis. For example, the IR spectrum of compound **19** revealed a nitrile absorption band at 2191 cm^{-1} , whereas its $^1\text{H NMR}$ spectrum displayed only an aromatic multiplet in the region δ 6.96–8.40.

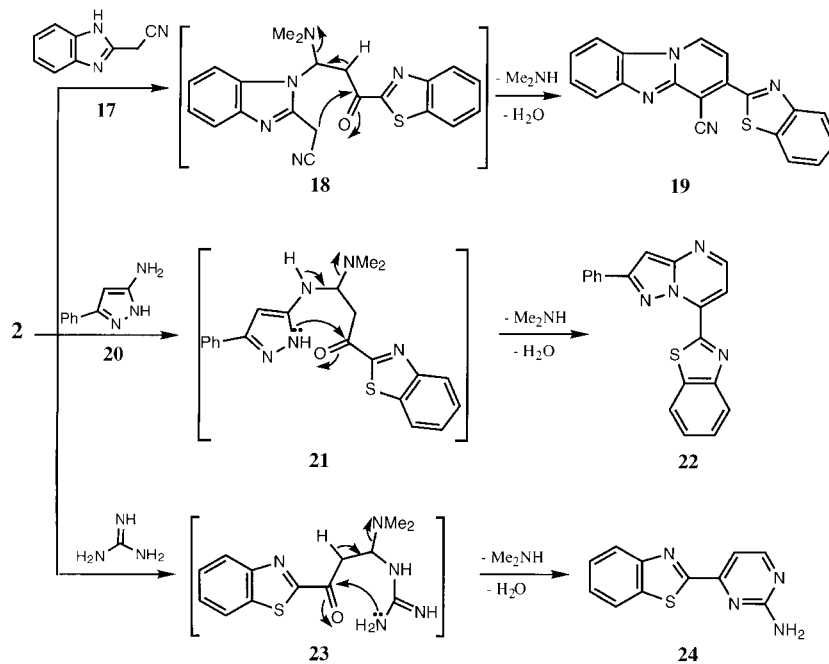
On the other hand, compound **2** reacted with 5-amino-3-phenylpyrazole (**20**) under the same reaction conditions and gave only one isolable product, which was identified as 7-(benzothiazol-2-yl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (**22**) (Scheme 2). The spectral data of the isolated product **22** were in complete agreement with the assigned structure. For example, the IR spectrum of the reaction product revealed no bands due to amino or carbonyl functions. Moreover, its $^1\text{H NMR}$ spectrum revealed an aromatic multiplet in the region δ 7.13–8.22, in addition to a singlet signal at δ 8.57, which is due to the 5-CH proton in structure **22**. Although the endocyclic nitrogen in compound **20** is the most nucleophilic site [10,11], it is a sterically hindered site. Formation of compound **22** is therefore assumed to take place via the addition of the exocyclic amino group in **20** to the activated double bond in **2** to give the

acyclic nonisolable intermediate **21**, which undergoes cyclization and aromatization via the loss of dimethylamine and water molecules to afford the final isolable product **22** as depicted in Scheme 2.

Enaminone **2** also reacted with guanidine nitrate in refluxing ethanol in the presence of anhydrous potassium carbonate and afforded a high yield of a colorless product to which the 2-amino-4-(benzothiazol-2-yl)pyrimidine structure **24** is assigned based on its elemental analysis and spectral data. The IR spectrum of **24** showed two absorption bands at 3467 and 3120 cm^{-1} due to the amino group. A plausible mechanism for the formation of compound **24** is outlined in Scheme 2 and compound **24** is assumed to be formed via an initial Michael-type addition of an amino group of guanidine to the activated double bond in **2** followed by elimination of dimethylamine and water molecules from the intermediate **23**.

EXPERIMENTAL

Melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye-Unicam SP 3-300 spectrophotometer. $^1\text{H NMR}$ spectra were recorded in deuterated chloroform or dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference, and results are expressed as δ values. Mass spectra were performed on a Shi-



SCHEME 2

madzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Hydrazonoyl halides **3a** [12], **3b** [13], **3c** [14], and **3d** [15], hydroximoyl chlorides **4b** [16], **4c** [17], and **4d** [18], 2-acetylbenzothiazole (**1**) [19], 1*H*-2-benzimidazoleacetonitrile (**17**) [20], and 5-amino-3-phenylpyrazole (**20**) [21] were prepared according to procedures in the literature.

1-(Benzothiazol-2-yl)-3-(*N,N*-dimethylamino)-2-propen-1-one (**2**)

A mixture of 2-acetylbenzothiazole (**1**) (3.54 g, 20 mmol) and DMF-DMA (2.66 mL, 20 mmol) in dry xylene (20 mL) was refluxed for 8 hours, then left to cool to room temperature. The reddish-brown precipitated product was filtered off, washed with petroleum ether, and dried. Recrystallization from benzene afforded the enaminone **2** in 91% yield (4.0 g), m.p. 159–160°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1637 (conjugated C=O), 1558 (C=C); $^1\text{H NMR}$ (CDCl_3) δ 3.05 (s, 6H), 6.22 (d, 1H, $J = 12.2$ Hz), 7.33–7.92 (m, 4H), 8.06 (d, 1H, $J = 12.2$ Hz); MS, m/z 232 (M^+); Found: C, 62.16; H, 5.10; N, 11.98; S, 13.77%. $\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS}$ requires C, 62.05; H, 5.21; N, 12.06; S, 13.80%.

3-Aroyl-4-(benzothiazol-2-yl)carbonyl-1-phenylpyrazoles **9a–d** and 3-Aroyl-4-(benzothiazol-2-yl)carbonyl isoxazoles **10b–d**

General Procedure. To a stirred solution of the appropriate hydrazonoyl halide **3a–d** or hydroximoyl chloride **4b–d** (2 mmol) and the enaminone **2** (0.464 g, 2 mmol) in dry benzene (20 mL) was added triethylamine (0.2 mL) portionwise over a period of 30 minutes, and the mixture was stirred at room temperature for 24 hours. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with ethanol. The solid product, so formed in each case, was collected by filtration, washed with water, and dried. Recrystallization from ethanol afforded the corresponding pyrazole or isoxazole derivatives **9a–d** and **10b–d**, respectively.

Compound 9a. Yield (69%); m.p. 146–148°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1710, 1641 (two C=O), 1596 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 2.72 (s, 3H, CH_3CO), 7.41–8.19 (m, 9H, ArH's), 9.03 (s, 1H, pyrazole-5-CH); MS, m/z 348 ($\text{M}^+ + 1$), 347 (M^+); Found: C, 65.76; H, 3.65; N, 11.98; S, 9.30%. $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ requires C, 65.70; H, 3.77; N, 12.10; S, 9.23%.

Compound 9b. Yield (76%); m.p. 161–163°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1676, 1637 (two C=O), 1596

(C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.4–8.06 (m, 14H, ArH's), 9.12 (s, 1H, pyrazole-5-CH); Found: C, 70.34; H, 3.61; N, 10.20; S, 7.93%. $\text{C}_{24}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ requires C, 70.46; H, 3.69; N, 10.26; S, 7.83%.

Compound 9c. Yield (75%); m.p. 135–137°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1647 (br, two overlapped C=O), 1596 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.16–8.07 (m, 12H, ArH's), 9.24 (s, 1H, pyrazole-5-CH); MS, m/z 416 ($\text{M}^+ + 1$), 415 (M^+); Found: C, 63.64; H, 3.05; N, 10.16; S, 15.40%. $\text{C}_{22}\text{H}_{13}\text{N}_3\text{O}_2\text{S}_2$ requires C, 63.60; H, 3.15; N, 10.12; S, 15.43%.

Compound 9d. Yield (81%); m.p. 235–237°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1689, 1635 (two C=O), 1596 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.32–8.13 (m, 13H, ArH's), 9.18 (s, 1H, pyrazole-5-CH); Found: C, 64.29; H, 3.05; N, 11.86; S, 13.81%. $\text{C}_{25}\text{H}_{14}\text{N}_4\text{O}_2\text{S}_2$ requires C, 64.37; H, 3.02; N, 12.01; S, 13.74%.

Compound 10b. Yield (75%); m.p. 140–141°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1681, 1658 (two C=O), 1596 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.48–8.08 (m, 9H, ArH's), 10.04 (s, 1H, isoxazole-5-CH); Found: C, 64.68; H, 2.85; N, 8.42; S, 9.60%. $\text{C}_{18}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$ requires C, 64.67; H, 3.01; N, 8.38; S, 9.59%.

Compound 10c. Yield (86%); m.p. 110–112°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1673, 1651 (two C=O), 1594 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.17–8.09 (m, 7H, ArH's), 9.96 (s, 1H, isoxazole-5-CH); Found: C, 56.58; H, 2.31; N, 8.35; S, 18.79%. $\text{C}_{16}\text{H}_8\text{N}_2\text{O}_3\text{S}_2$ requires C, 56.47; H, 2.37; N, 8.23; S, 18.84%.

Compound 10d. Yield (85%); m.p. 218–220°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1687, 1656 (two C=O), 1592 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 7.51–8.20 (m, 8H, ArH's), 10.02 (s, 1H, isoxazole-5-CH); MS, m/z 392 ($\text{M}^+ + 1$), 391 (M^+); Found: C, 58.36; H, 2.24; N, 10.66; S, 16.38%. $\text{C}_{19}\text{H}_9\text{N}_3\text{O}_3\text{S}_2$ requires C, 58.31; H, 2.32; N, 10.74; S, 16.38%.

Reactions of **9a–d** and **10b–d** with Hydrazine Hydrate

General Procedure. A mixture of the appropriate pyrazole **9a–d** or isoxazole **10b–d** (1 mmol) and hydrazine hydrate (80%, 0.2 mL) in absolute ethanol (20 mL) was refluxed for 1 hour then left to cool to room temperature. The orange-yellow precipitated product was filtered off, washed with ethanol, and dried. Recrystallization from dimethylformamide (DMF) afforded the pyrazolo[3,4-*d*]pyridazine and the isoxazolol[3,4-*d*]pyridazine derivatives **11a–d** and **12b–d**, respectively.

Compound 11a. Yield (89%); m.p. 250–252°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1590 (C=N); $^1\text{H NMR}$ (CDCl_3) δ 3.05 (s, 3H, CH_3), 7.45–8.16 (m, 9H, ArH's), 9.37 (s, 1H, 3-CH); Found: C, 66.52; H, 3.71; N, 20.55; S, 9.34%. $\text{C}_{19}\text{H}_{13}\text{N}_5\text{S}$ requires C, 66.46; H, 3.81; N, 20.39; S, 9.34%.

Compound 11b. Yield (96%); m.p. 255–257°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1590, (C=N); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 7.46–8.15 (m, 14H, ArH's), 9.21 (s, 1H, 3-CH); MS, m/z 406 ($\text{M}^+ + 1$), 405 (M^+); Found: C, 71.18; H, 3.38; N, 17.39; S, 7.91%. $\text{C}_{24}\text{H}_{15}\text{N}_5\text{S}$ requires C, 71.10; H, 3.73; N, 17.27; S, 7.90%.

Compound 11c. Yield (87%); m.p. 296–298°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1587, (C=N); $^1\text{H NMR}$, insoluble in the common solvents; MS, m/z 412 ($\text{M}^+ + 1$), 411 (M^+); Found: C, 64.11; H, 3.14; N, 16.96; S, 15.60%. $\text{C}_{22}\text{H}_{13}\text{N}_5\text{S}_2$ requires C, 64.23; H, 3.18; N, 17.02; S, 15.57%.

Compound 11d. Yield (92%); m.p. >300°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1587 (C=N); $^1\text{H NMR}$, insoluble in the common solvents; MS, m/z 463 ($\text{M}^+ + 1$), 462 (M^+); Found: C, 64.78; H, 3.11; N, 18.19; S, 13.83%. $\text{C}_{25}\text{H}_{14}\text{N}_6\text{S}_2$ requires C, 64.91; H, 3.05; N, 18.17; S, 13.86%.

Compound 12b. Yield (89%); m.p. 266–268 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1608 (C=N); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 7.46–8.12 (m, 9H, ArH's), 10.13 (s, 1H, 3-CH); MS, m/z 332 ($\text{M}^+ + 2$), 331 ($\text{M}^+ + 1$), 330 (M^+); Found: C, 65.32; H, 3.10; N, 16.94; S, 9.71%. $\text{C}_{18}\text{H}_{10}\text{N}_4\text{OS}$ requires C, 65.45; H, 3.05; N, 16.96; S, 9.70%.

Compound 12c. Yield (87%); m.p. 256–258°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1589 (C=N); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 7.23–8.06 (m, 7H, ArH's), 10.03 (s, 1H, 3-CH); MS, m/z 338 ($\text{M}^+ + 2$), 337 ($\text{M}^+ + 1$), 336 (M^+); Found: C, 57.00; H, 2.36; N, 16.54; S, 19.00%. $\text{C}_{16}\text{H}_8\text{N}_4\text{OS}_2$ requires C, 57.14; H, 2.40; N, 16.66; S, 19.05%.

Compound 12d. Yield (98%); m.p. >300°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1587 (C=N); $^1\text{H NMR}$, insoluble; Found: C, 58.93; H, 2.31; N, 18.02; S, 16.54%. $\text{C}_{19}\text{H}_9\text{N}_5\text{OS}_2$ requires C, 58.90; H, 2.34; N, 18.08; S, 16.55%.

3-(Benzothiazol-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**19**) and 7-(Benzothiazol-2-yl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (**22**)

General Procedure. To a mixture of the enaminone **2** (0.464 g, 2 mmol) and 1*H*-2-benzimida-

zoleacetonitrile (**17**) or 5-amino-3-phenyl-1*H*-pyrazole (**20**) (2 mmol) in absolute ethanol (20 mL) was added piperidine (0.3 mL). The mixture was refluxed for 12 hours then left to cool to room temperature. The precipitated product was filtered off, washed with ethanol, and dried. Recrystallization from DMF afforded the corresponding pyrido[1,2-*a*]benzimidazole **19** and pyrazolo[1,5-*a*]pyrimidine **22** derivatives in 86% and 72% yield, respectively.

Compound 19. m.p. 233–235°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 2191 (C≡N), 1632 (C=N), 1610 (C=C); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 6.96–8.40 (m, 10H, ArH's, H-1 and H-2); Found: C, 69.82; H, 3.10; N, 17.29; S, 9.80%. $\text{C}_{19}\text{H}_{10}\text{N}_4\text{S}$ requires C, 69.92; H, 3.09; N, 17.17; S, 9.82%.

Compound 22. m.p. 230–232°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1600 (C=N); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 7.15–8.02 (m, 11H, ArH's, H-3 and H-6), 8.38 (s, 1H, H-5); MS, m/z 328 (M^+); Found: C, 69.55; H, 3.58; N, 17.16; S, 9.78%. $\text{C}_{19}\text{H}_{12}\text{N}_4\text{S}$ requires C, 69.49; H, 3.68; N, 17.07; S, 9.76%.

2-Amino-4-(benzothiazol-2-yl)pyrimidine (**24**)

To a mixture of the enaminone **2** (0.464 g, 2 mmol) and guanidine nitrate (0.28 g, 2.3 mmol) in absolute ethanol (20 mL), potassium carbonate anhydrous (0.552 g, 4 mmol) was added. The mixture was refluxed for 10 hours then allowed to cool to room temperature then diluted with water (10 mL). The solid product so formed was filtered off, washed with water, and dried. Recrystallization from DMF afforded lustrous crystals of compound **24** in 88% yield (0.4 g); mp. 275–277°C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3467, 3120 (NH_2), 1625 (C=N); $^1\text{H NMR}$, insoluble; MS, m/z 228 (M^+); Found: C, 57.91; H, 3.55; N, 24.41; S, 14.12%. $\text{C}_{11}\text{H}_8\text{N}_4\text{S}$ requires C, 57.88; H, 3.53; N, 24.54; S, 14.04%.

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