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One-Pot Synthesis of Imidazo[1,2-b]pyrazole, Imidazo[1,2-b]-1,2,4-triazole, Imidazo[1,2-a]-pyridine, Imidazo[1,2-a]pyrimidine, Imidazo-[1,2-a]benzimidazole, and 1,2,4-Triazolo-[4,3-a]benzimidazole Derivatives

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ABSTRACT

Hydrazonoyl bromides **1a–c** *react with 5-amino-3-phenyl-1H-pyrazole, 5-amino-1H-1,2,4-triazole, 2-aminopyridine, 2-aminopyrimidine, and 2-aminobenzimidazole to afford the corresponding imidazo[1,2-b]pyrazoles* **10**, *imidazo[1,2-b]-1,2,4-triazoles* **11**, *imidazo[1,2-a]pyridines* **16**, *imidazo[1,2-a]pyrimidines* **17**, *and imidazo[1,2-a]benzimidazoles* **20**, *respectively. Compounds* **1a–c** *reacted also with 2-methylthiobenzimidazole to give 1,2,4-triazolo[4,3-a]benzimidazole derivatives* **21**.

INTRODUCTION

Several imidazo[1,2-b]pyrazole [1], imidazo[1,2-b]-1,2,4-triazole [2], imidazo[1,2-a]pyridine [3], imidazo[1,2-a]pyrimidine [4], and imidazo[1,2-a]benzimidazole [5] derivatives are of significant pharmaceutical and microbiological importance. As part of our ongoing program aiming at the synthesis of fused-ring heterocycles with a bridgehead nitrogen atom [6–8], we report here a facile synthesis of such ring systems incorporating a benzothiazole moiety that may enhance their biological activity.

Thus, when equimolar amounts of the hydrazonoyl bromides **1a–c** and 5-amino-3-phenyl-1H-pyrazole (**2**) were heated in ethanol under reflux, they afforded highly colored precipitates for which structures **10** or **12** seemed possible (Scheme 1). However, structure **10** was assigned to the isolated products on the basis of their elemental analyses and spectral data. Their IR spectra showed, in each case, the lack of a carbonyl absorption band and revealed an NH stretching absorption near 3240 cm^{-1}, whereas their ^1H NMR spectra displayed, in each case, a broad singlet signal (D_2O-exchangeable) near δ 11.5 due to the NH proton. These findings exclude the other possible structure **12**. The formation of structure **10** is assumed to proceed via displacement of the halogen atom by the most basic ring nitrogen atom, with elimination of hydrogen bromide, followed by cyclocondensation via loss of a water molecule. All attempts to isolate the acyclic intermediate **8** were unsuccessful.

Similarly, treatment of **1a–c** with 5-amino-1H-1,2,4-triazole (**3**) in refluxing ethanol furnished colored precipitates for which the two possible structures imidazo[1,2-b]-1,2,4-triazole **11** and 1,2,4-triazolo[5,1-c]-1,2,4-triazole **13** could conceivably be written (Scheme 1). The appearance of a characteristic NH absorption in the region 3400–

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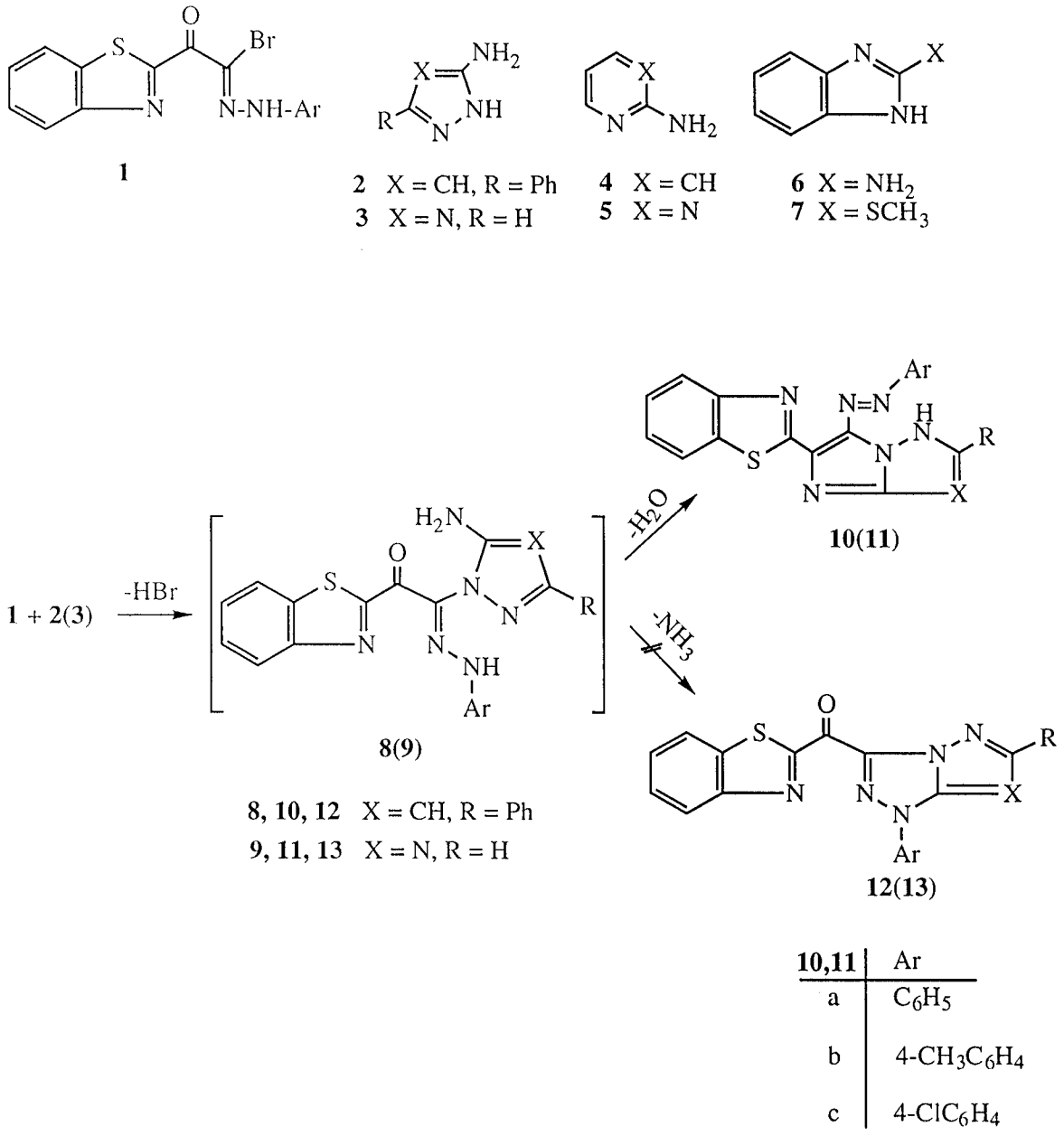
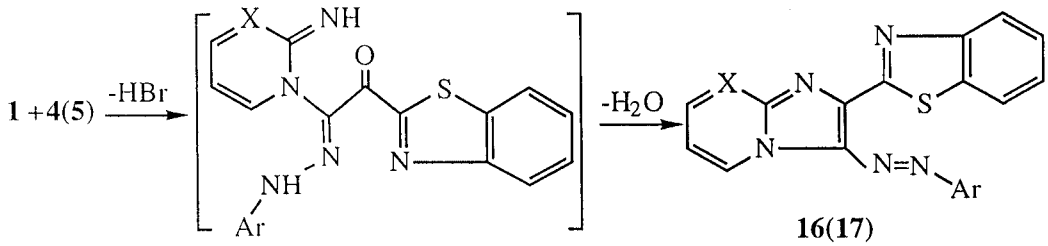


SCHEME 1

3200 cm^{-1} and lack of carbonyl absorption bands in the IR spectra of the isolated products and the presence of a D_2O-exchangeable broad signal near δ 11.3 (due to the NH proton) in their ^1H NMR spectra provided a firm support for structure **11** and ruled out the other possible structure **13**.

The hydrazonoyl bromides **1a–c** react also with 2-aminopyridine (**4**) in refluxing ethanol to afford the corresponding 3-arylazo-2-(benzothiazol-2-yl)imidazo[1,2-a]pyridines **16a–c** via the nonisolable intermediates **14**. The structures of the latter products were established on the basis of their elemental analyses and spectral data. The formation of **16** is assumed to proceed via displacement of the halogen atom by the most basic ring nitrogen atom of the pyridine moiety, followed by cyclocondensation via loss of a water molecule (Scheme 2). This behavior is similar to that reported for the reaction of α-haloketones with 2-aminopyridine [9,10]. Analogously, compounds **1a–c** react with 2-aminopyrimidine (**5**) under similar reaction conditions to give the 3-arylazo-2-(benzothiazol-2-yl)imidazo-



SCHEME 2

[1,2-a]pyrimidines**17a–c** via the nonisolable intermediates **15** (Scheme 2). The IR spectra of compounds **16a–c** and **17a–c** were free of both NH and CO absorption bands.

Treatment of the hydrazonoyl bromides **1a–c** with 2-aminobenzimidazole (**6**) in refluxing ethanol furnished highly colored products identified as 3-arylazo-2-(benzothiazol-2-yl)-1H-imidazo[1,2-a]benzimidazoles **20a–c.** Elemental analyses and spectral data of the isolated products were in complete agreement with structure **20** and not with the other possible structure **21**. The latter were independently prepared by another route, as described below (Scheme 3). The IR spectra of **20a–c** showed, in each case, the absence of carbonyl bands in the region 1800–1650 cm^{-1} and revealed an NH absorption band in the region 3400–3300 cm^{-1}. The ^1H NMR spectrum of **20b**, for example, exhibited, in addition to an aromatic multiplet at δ 7.38–8.24, a broad exchangeable signal at δ 8.72 and a singlet at δ 2.43 due to NH and CH_3 protons, respectively.

Compounds **1a–c** reacted also with 2-methylthiobenzimidazole (**7**) in either toluene or ethanol at reflux temperature and gave high yields of the corresponding 1-aryl-3-(benzothiazol-2-yl)carbonyl-1,2,4-triazolo[4,3-a]benzimidazoles **21a–c** (Scheme 3). The formation of **21a–c** is assumed to proceed via loss of hydrogen bromide, followed by cyclocondensation via elimination of methanethiol from the nonisolable intermediates **19**. Microanalyses and spectral data of the products isolated were in complete agreement with structure **21**. Their IR spectra revealed, in each case, a characteristic carbonyl absorption band near 1660 cm^{-1}. The ^1H NMR spectrum of **21b**, for example, exhibited a singlet at δ 2.35 and a multiplet at δ 7.4–8.37 assignable to methyl and aromatic protons, respectively.

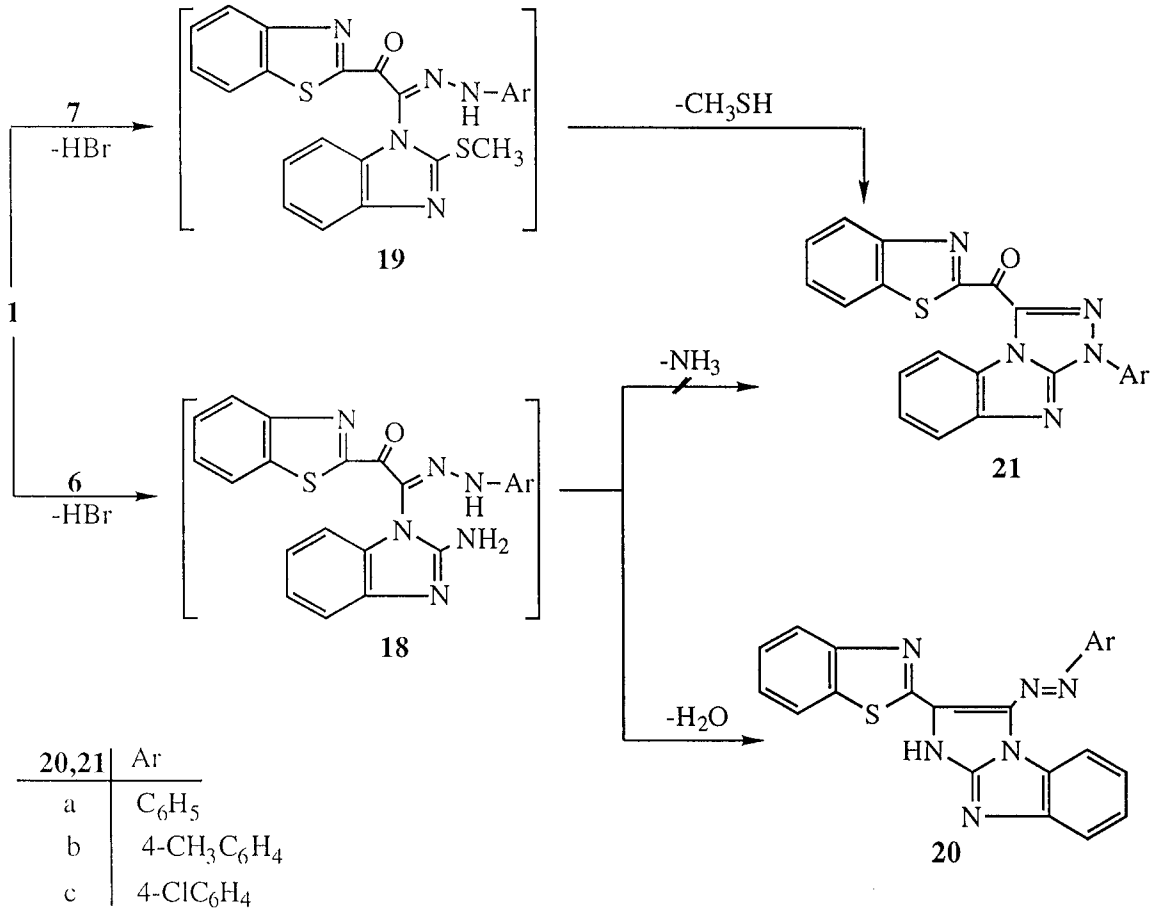
EXPERIMENTAL

Melting points were recorded on a Gallenkamp melting-point apparatus. IR spectra were measured as KBr pellets on a Pye-Unicam SP 3-300 spectrophotometer. ^1H NMR spectra were recorded in deuterated dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. N-Aryl-α-oxo-2-benzothiazoleethanehydrazonoyl bromides [11] **1a–c**, 5-amino-3-phenyl-1H-pyrazole [12] (**2**), and 2-methylthiobenzimidazole [13] (**7**) were prepared according to literature procedures.

Reactions of Hydrazonoyl Bromides **1a–c** *with Heterocyclic Amines*

General Procedure. A mixture of the appropriate hydrazonoyl bromide **1a–c** (2 mmol) and the appropriate heterocyclic amine **2**, **3**, **4**, **5**, or **6** (2.2 mmol) in ethanol (20 mL) was refluxed for 5–8 hours, then cooled. The solid that had formed was filtered off, washed with water, and dried. Recrystallization from dimethylformamide afforded **10a–c**, 11a–c, 16a–c, 17a–c, and **20a–c**, respectively.

10a (73%); mp. 241–243°C; IR (KBr) ν 3241 (NH) cm^{-1}; ^1H NMR (DMSO) δ 6.53 (1H, s), 7.36–8.30 (14H, m), 11.62 (1H, br). Found: C, 68.37; H, 3.80; N, 19.71. $C_{24}H_{16}N_6S$ requires C, 68.55; H, 3.83; N,



SCHEME 3

19.98; S, 7.62. **10b** (84%); mp. 227–229°C; IR (KBr) ν 3241 (NH) cm^{-1}; ^1H NMR (DMSO) δ 2.41 (3H, s), 6.72 (1H, s), 7.45–8.32 (13H, m), 11.3 (1H, br). Found: C, 68.82; H, 4.30; N, 19.62; S, 7.51. $C_{25}H_{18}N_6S$ requires C, 69.10; H, 4.17; N, 19.34; S, 7.37. **10c** (75%); mp. 247–249°C; IR (KBr) ν 3240 (NH) cm^{-1}; ^1H NMR (DMSO) δ 6.64 (1H, s), 7.38–8.30 (13H, m), 11.55 (1H, br). Found: C, 63.47; H, 3.18; N, 18.20; S, 7.10. $C_{24}H_{15}C1N_6S$ requires C, 63.36; H, 3.32; N, 18.47; S, 7.04. **11a** (70%); mp. 214–216°C; IR (KBr) ν 3322 (NH) cm^{-1}; ^1H NMR (DMSO) δ 6.2 (1H, s), 7.42–8.27 (9H, m), 11.0 (1H, br). Found: C, 59.05; H, 3.25; N, 28.16; S, 9.30. $C_{17}H_{11}N_7S$ requires C, 59.11; H, 3.21; N, 28.38; S, 9.28. **11b** (68%); mp. 221–223°C; IR (KBr) ν 3340 (NH) cm^{-1}; ^1H NMR (DMSO) δ 2.31 (3H, s), 6.11 (1H, s), 7.23–8.30 (8H, m), 11.5 (1H, br). Found: C, 59.89; H, 3.73; N, 26.95; S, 9.10. $C_{18}H_{13}N_7S$ requires C, 60.15; H, 3.64; N, 27.28; S, 8.92. **11c** (77%); mp. 226–228°C; IR (KBr) ν 3232 (NH) cm^{-1}; ^1H NMR (DMSO) δ 6.23 (1H, s), 7.41–8.32 (8H, m), 11.0 (1H, br). Found: C, 53.80; H, 2.66; N, 25.94; S, 8.50. $C_{17}H_{10}C1N_7S$ requires C, 53.75; H, 2.65; N, 25.81; S, 8.44. **16a** (66%); mp. 202–204°C; IR (KBr) ν 1605 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.2–8.31 (ArH, m). Found: C, 67.50; H, 3.72; N, 15.38; S, 9.13. $C_{20}H_{13}N_5S$ requires C, 67.58; H, 3.68; N, 15.76; S, 9.02. **16b** (80%); mp. 216–218°C; IR (KBr) ν 1608 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 2.33 (3H, s), 7.28–8.30 (12H, m). Found: C, 68.20; H, 4.15; N, 18.57; S, 8.70. $C_{21}H_{15}N_5S$ requires C, 68.27; H, 4.09; N, 18.96; S, 8.67. **16c** (68%); mp. 228–230°C; IR (KBr) ν 1626 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.2–8.3 (ArH, m). Found: C, 61.86; H, 3.0; N, 17.69; S, 8.10. $C_{20}H_{12}C1N_5S$ requires C, 61.61; H, 3.10; N, 17.96; S, 8.22. **17a** (80%); mp. 189–190°C; IR (KBr) ν 1610 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.26–8.35 (ArH, m). Found: C, 64.34; H, 3.40; N, 23.70; S, 8.90. $C_{19}H_{12}N_6S$ requires C, 64.02; H, 3.39; N, 23.58; S, 8.99. **17b** (86%); mp. 269–270°C; IR (KBr) ν 1610 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 2.41 (3H, s), 7.19–8.20 (11H, m). Found: C, 65.00; H, 3.72; N, 22.43; S, 8.49. $C_{20}H_{14}N_6S$ requires C, 64.84; H, 3.81; N, 22.69; S, 8.65. **17c** (78%); mp. 288–290°C; IR (KBr) ν 1605 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.25–8.30 (ArH, m). Found: C, 58.40; H, 2.67; N, 21.83; S, 8.27. $C_{19}H_{11}C1N_6S$ requires C, 58.38; H, 2.83; N, 21.50; S, 8.20. **20a** (56%);

mp. 318–320°C; IR (KBr) ν 3340 (NH) cm^{-1}; ^1H NMR (DMSO) δ 7.28–8.26 (13H, m), 9.0 (1H, br). Found: C, 66.80; H, 3.48; N, 21.52; S, 8.09. $C_{22}H_{14}N_6S$ requires C, 66.98; H, 3.57; N, 21.30; S, 8.12. **20b** (55%); mp. 316–318°C; IR (KBr) ν 3432 (NH) cm^{-1}; ^1H NMR (DMSO) δ 2.43 (3H, s), 7.38–8.24 (12H, m), 8.72 (1H, br). Found: C, 67.40; H, 3.68; N, 20.69; S, 7.78. $C_{23}H_{16}N_6S$ requires C, 67.62; H, 3.94; N, 20.57; S, 7.84. **20c** (60%); mp. 320–322°C; IR (KBr) ν 3320 (NH) cm^{-1}; ^1H NMR (DMSO) δ 7.4–8.2 (12H, m), 8.78 (1H, br). Found: C, 61.37; H, 3.10; N, 19.80; S, 7.61. $C_{22}H_{13}C1N_6S$ requires C, 61.60; H, 3.05; N, 19.59; S, 7.47.

Reaction of Hydrazonoyl Bromides **1a–c** *with 2-Methylthiobenzimidazole* (**7**).

General Procedure. A mixture of the appropriate hydrazonoyl bromide **1a–c** (2 mmol) and 2-methylthiobenzimidazole (**7**) (0.33 g, 2.2 mmol) in ethanol (20 mL) or in toluene (20 mL) was refluxed for 3 hours, then cooled. The precipitate so formed was collected by filtration, washed with water, dried, and finally recrystallized from dimethylformamide to afford 1-aryl-3-(benzothiazol-2-yl)carbonyl-1,2,4-triazolo[4,3-a]benzimidazoles **21a–c** in 75–85% yields.

21a (83%); mp. 235–237°C; IR (KBr) ν 1665 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 7.38–8.30 (ArH, m). Found: C, 66.71; H, 3.30; N, 17.42; S, 8.00. $C_{22}H_{13}N_5OS$ requires C, 66.82; H, 3.31; N, 17.71; S, 8.10. **21b** (75%); mp. 251–253°C; IR (KBr) ν 1658 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 2.35 (3H, s), 7.40–8.37 (12H, m). Found: C, 67.20; H, 3.48; N, 16.29; S, 7.45. $C_{23}H_{15}N_5OS$ requires C, 67.46; H, 3.69; N, 17.10; S, 7.83. **21c** (85%); mp. 255–257°C; IR (KBr) ν 1673 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 7.43–8.32 (ArH, m). Found: C, 61.72; H, 2.91; N, 16.07; S, 7.50. $C_{22}H_{12}C1N_5OS$ requires C, 61.46; H, 2.81; N, 16.29; S, 7.45.

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