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Indolizines, Triazolo[4,3-*a*]pyridines, Benzimidazo[1,2-*d*]oxadiazoles, and Pyrazolo[1,5-*c*]triazoles via Nitrogen and Sulfur Ylides

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ABSTRACT: *The pyridinium salts* **2a,b** *reacted with dimethyl acetylenedicarboxylate (DMAD) to give the indolizine derivatives* **6a,b**. *Pyridinium salts* **2a,b** *also reacted with pyrazole-5-diazonium salt to afford the hydrazonoyl bromides* **8a,b**, *which on treatment with aqueous ethanolic sodium carbonate furnished the 8a*H*-1,2,4-triazolo[4,3-a]pyridine* **10**. *When sulfonium bromide* **11** *was treated with nitrous acid and with pyrazole-5-diazonium salt, it afforded the new hydroximoyl and hydrazonoyl halides* **12** *and* **17**, *respectively. Compound* **12** *reacted with 2-methylthiobenzimidazole to furnish benzimidazo-[1,2-d]-1,2,4-oxadiazole derivative* **14**. *Treatment of either* **12** *with 3-phenyl-5-aminopyrazole or* **17** *with triethylamine resulted in the formation of the same product: pyrazolo[1,5-c]-1,2,4-triazole derivative* **16**. © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:432–436, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20037

INTRODUCTION

Indolizine derivatives are potential pharmaceutical candidates [1–3] and are useful as photographic sensitizers [4,5]. In addition, benzimidazole and benzothiazole derivatives were found to be effective anti-HIV and anticancer agents [6–8]. As part of our research interest toward developing new routes for the synthesis of fused heterocyclic systems having benzimidazole and benzothiazole moeities [9–12], we establish here a novel route to the incorporation of such moieties into the entitled bridged-head nitrogen heterocycles utilizing some new nitrogen and sulfur ylides.

RESULTS AND DISCUSSION

Thus, pyridinium bromide **2a**, which was recently reported by us [10], was treated with dimethyl acetylenedicarboxylate (DMAD) as dipolarophile in dry benzene at refluxing temperature, in the presence of triethylamine, and resulted in the formation of a single yellow-colored product as examined by thin-layer chromatography (TLC). Elemental analysis and mass spectra established the molecular formula of the product as $C_{20}H_{14}N_2O_5S$. Spectral data (IR, ^{1}H and ^{13}C NMR) were in complete agreement with the assigned indolizine structure **6a**, Scheme 1. The ^{1}H NMR spectrum of compound **6a** revealed two singlet signals at δ 3.56 and 3.85 due to two methyl ester groups in addition to the aromatic multiplets in the region δ 7.36–9.54. Its IR spectrum also showed two characteristic carbonyl absorptions at 1732 and 1695 cm^{-1}. In the same manner, pyridinium bromide **2b** reacted with DMAD under the same

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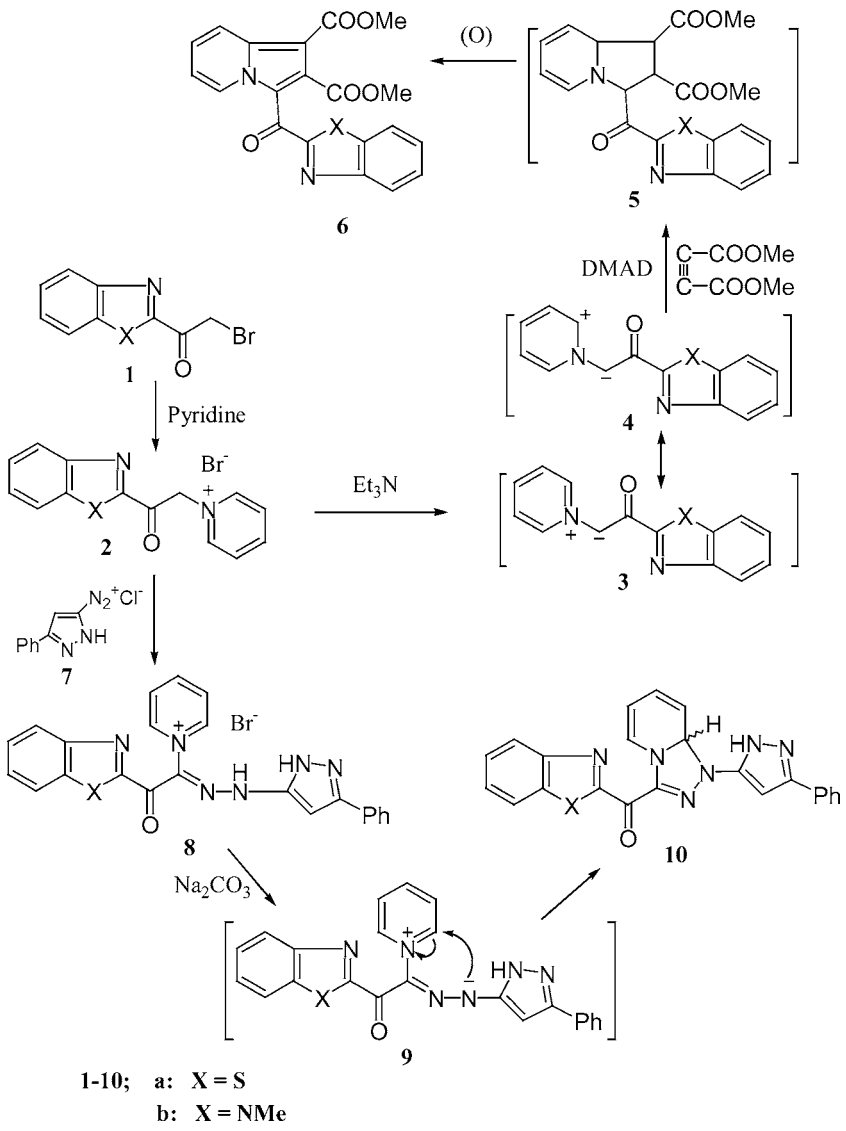


SCHEME 1

reaction conditions to afford the indolizine derivative **6b**, Scheme 1. Indolizine derivatives **6a,b** are assumed to be formed via 1,3-dipolar cycloaddition of DMAD to the nitrogen ylides **4a,b** (which were formed in situ) to give the nonisolable intermediates **5a,b**, which are oxidized under the reaction conditions to give the indolizine products **6a,b**. This reaction proceeded in a similar way as the one reported of carboxymethyl-pyridinium chloride with DMAD [13].

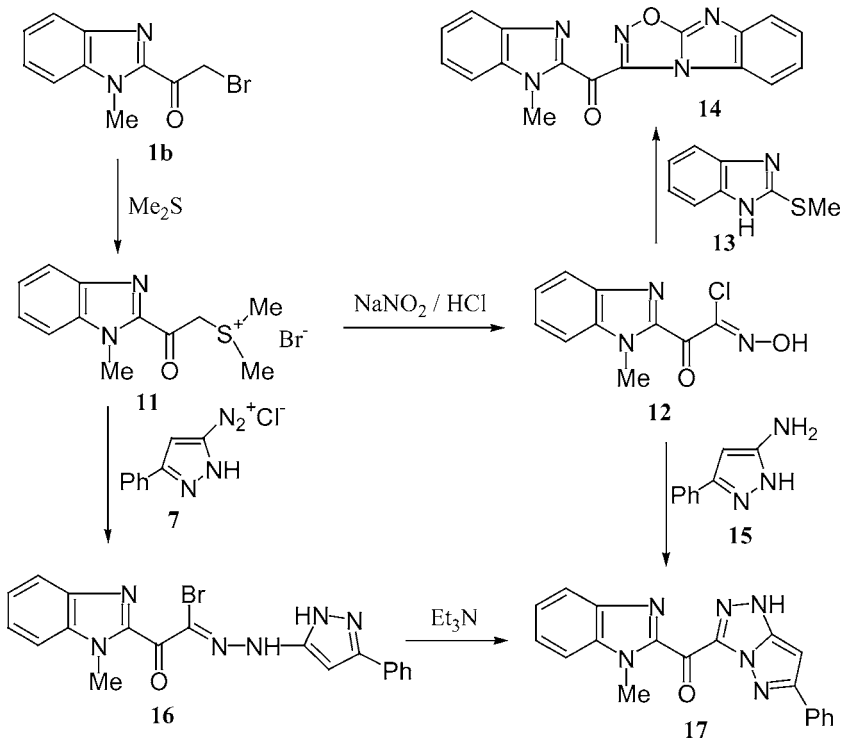
Reaction of the pyridinium bromide **2a** with pyrazole-5-diazonium chloride (**7**) in ethanol under neutral conditions afforded the corresponding hydrazonoyl bromide **8a** in a high yield. Treatment of the latter salt with sodium carbonate in aqueous ethanol at room temperature furnished a brown-colored product that was elucidated as 3-(2-benzothiazolylcarbonyl)-1-(3-phenyl-1*H*-pyrazol-5-yl)-8a*H*-1,2,4-triazolo[4,3-*a*]pyridine (**10a**), Scheme 1. The ^{1}H NMR spectrum of the latter product exhibited three singlet signals at δ 5.90, 6.61, and 9.44 (D_2O-exchangeable) due to triazoline-5-CH, pyrazole-4-CH, and pyrazole-NH protons, respectively, in addition to aromatic multiplets in the region δ 7.35–8.56. Similar treatment of the pyridinium bromide salt **2b** with pyrazole-5-diazonium chloride **7** under the same reaction conditions resulted in the formation of the corresponding hydrazonoyl pyridinium bromide salt **8b** in 85% yield. Treatment of the latter salt **8b** with sodium carbonate was performed similar to **8a**, to afford the corresponding 8a*H*-1,2,4-triazolo[4,3-*a*]pyridine derivative **10b**, as

outlined in Scheme 1. Formation of compounds **10a,b** from **8a,b** is assumed to take place through the elimination of the HBr molecule from **8a,b** to give the nonisolable nitrogen ylide **9a,b**, which undergoes an intramolecular 1,5-dipolar cycloaddition to give the triazolo[4,3-*a*]pyridine derivatives **10a,b**.

The reactivity of 1-(1-methylbenzimidazol-2-yl)-1-ethanone-2-dimethylsulfonium bromide (**11**) towards the synthesis of hydroximoyl and hydrazonoyl halides was also explored. Thus, treatment of the sulfonium bromide **11** with sodium nitrite in a mixture of dioxane/water in the presence of hydrochloric acid at room temperature afforded a good yield of a greenish-yellow-colored product that was identified as 2-(1-methylbenzimidazolyl) carbonylhydroximoyl chloride (**12**) (Scheme 2) on the basis of its elemental and spectral analyses. Compound **12** reacted with 2-methylthio-1*H*-benzimidazole (**13**) in ethanol/triethylamine at refluxing conditions to give a pale yellow colored product established as 3-[(1-methylbenzimidazol-2-yl)carbonyl]benzimidazo-[1,2-*d*]-1,2,4-oxadiazole (**14**) (Scheme 2) on the basis of the elemental and spectral analyses of the reaction product. The IR spectrum of compound **12** showed a carbonyl absorption at 1693 cm^{-1} and a broad OH band at 3350–3100 cm^{-1}; however, the IR spectrum of **14** showed only a carbonyl absorption at 1720 cm^{-1}.

Similarly, the hydroximoyl chloride **12** reacted with 5-amino-3-phenylpyrazole (**15**) in ethanolic triethylamine solution, at refluxing temperature, and furnished only one product as examined by TLC. The structure of the obtained product was substantiated from its elemental analysis and spectral data and identified as 3-[(1-methylbenzimidazol-2-yl)carbonyl]-6-phenylpyrazolo[1,5-*c*]-1,2,4-triazole (**16**), as depicted in Scheme 2. The IR spectrum of compound **16** showed C=O and NH absorption peaks at 1654 and 3153 cm^{-1}, respectively.

It is well known that sulfonium bromides couple easily with diazonium salts in the presence of sodium acetate as a basic medium to give the corresponding hydrazonoyl bromides [14]; however, in this work we could perform the coupling of the sulfonium bromide **11** with pyrazole-5-diazonium chloride (**7**) in ethanol under neutral condition to obtain the *hitherto* unreported α-oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-2-(1-methyl-benzimidazole)ethane-hydrazonoyl bromide (**17**), having heterocyclic rings at both *C*- and *N*-terminals, in a good yield (Scheme 2). The IR spectrum of the latter hydrazonoyl bromide revealed one carbonyl and two NH absorption bands at 1654, 3210, and 3146 cm^{-1}, respectively. Treatment of **17** with triethylamine in refluxing ethanol resulted in the formation of a product that was found to be identical in all respects (mp, mixed mp, and



SCHEME 2

spectral data) with compound **16** that was obtained above from the reaction of hydroximoyl chloride **12** with 5-amino-3-phenylpyrazole (**15**) as shown in Scheme 2.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Pyridinium salts **2a,b** [10], 5-aminopyrazole derivatives **7** and **10** [15], sulfonium salts **11a** [16] and **11b** [10], and 2-methylthio-1*H*-benzimidazole (**13**) [17] were prepared according to the procedures reported in the literature.

Indolizine Derivatives **6a,b**

To a mixture of **2a** or **2b** (2 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.57 g, 4 mmol) in dry benzene (30 mL), triethylamine (0.4 mL) was added and the reaction mixture was refluxed for 3 h, and then left to cool to room temperature. The triethylamine-hydrobromide salt was removed by filtration, and the filtrate was evaporated under vacuum. The residue was triturated with methanol, where a yellow-colored precipitate was formed that was filtered off, washed with methanol, and dried. Recrystallization from DMF/EtOH afforded **6a,b**.

6a: Yield 79%; mp 170–172°C; IR (KBr) ν 1732, 1695 (2 C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.56 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.36 (td, 1H, J = 7.2, 1.2 Hz); 7.61–7.72 (m, 3H), 8.12 (dd, 1H, J = 7.2, 2.4 Hz), 8.26 (dd, 1H, J = 6.9, 2.4 Hz), 8.30 (d, 1H, J = 8.7 Hz), 9.54 (d, 1H, J = 6.9 Hz); ^{13}C NMR (DMSO) δ 52.47, 53.06, 105.68, 117.86, 119.51, 120.03, 123.66, 125.41, 128.13, 128.43, 129.47, 130.47, 133.12, 136.72, 138.65, 153.13, 163.19, 165.34, 167.37, 175.99; MS *m/z*, 394 (M$^+$), 344, 285, 256, 160, 128, 96, 64. For $C_{20}H_{14}N_2O_5S$ Calcd: C, 60.91; H, 3.58; N, 7.10; S, 8.13%. Found: C, 61.14; H, 3.44; N, 7.21; S, 8.19%.

6b: Yield 83%; mp 238–240°C; IR (KBr) ν 1720, 1713 (2 C=O), 1608 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.64 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.26 (s, 3H, CH_3), 7.28 (m, 1H); 7.54–7.68 (m, 5H), 8.05 (d, 1H, J = 8.6 Hz), 8.63 (d, 1H, J = 7.2 Hz); MS *m/z*, 392 (M$^+$ + 1), 391 (M$^+$), 362, 332, 300, 246, 165, 143, 116, 77. For $C_{21}H_{17}N_3O_5$ Calcd: C, 64.45; H, 4.38; N, 10.74%. Found: C, 64.36; H, 4.21; N, 10.44%.

Hydrazonoyl Pyridinium Bromides **8a,b**

A mixture of **2a** or **2b** (5 mmol) and 3-phenylpyrazole-5-diazonium chloride (**7**) (1.03 g, 5 mmol) in absolute ethanol (50 mL) was left to stir at room temperature for 8 h. The orange-yellow-colored precipitated products were filtered off, washed with absolute ethanol, and dried. Recrystallization from acetic acid afforded **8a,b**.

8a: Yield 73%; mp >300°C; IR (KBr) ν 3404 (br 2NH), 1714 (C=O), 1629 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.49 (s, 1H), 7.36–7.80 (m, 7H); 8.16–8.23 (m, 2H), 8.46–8.61 (m, 3H), 9.32 (d, 2H, J = 6.27 Hz), 10.17 (br s, 1H, NH), 13.12 (br s, 1H, NH). For $C_{23}H_{17}BrN_6OS$ Calcd: C, 54.66; H, 3.39; N, 16.63; S, 6.34%. Found: C, 54.58; H, 3.37; N, 16.44; S, 6.38%.

8b: Yield 80%; mp >300°C; IR (KBr) ν 3226, 3132 (2NH), 1697 (C=O), 1616 (C=N) cm^{-1}. For $C_{24}H_{20}BrN_7O$ Calcd: C, 57.38; H, 4.01; N, 19.52%. Found: C, 57.50; H, 3.77; N, 19.81%.

1,2,4-Triazolo[4,3-a]pyridine **10a,b**

To a stirred solution of **8a** or **8b** (2 mmol) in ethanol (20 mL) and water (10 mL) was added sodium carbonate solution (0.3 g in 5-mL water) portionwise. The reaction mixture was left to stir at room temperature for 4 h. The brown-colored precipitate was filtered off, washed with water and then ethanol, and dried. Recrystallization from DMF afforded **10a,b**.

10a: Yield 66%; mp 238–240°C; IR (KBr) ν 3210 (NH), 1665 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.90 (s, 1H, triazoline-5-CH), 6.61 (s, 1H, pyrazole-4-CH), 7.35–7.83 (m, 6H); 8.05–8.20 (m, 3H), 8.33–8.56 (m, 4H), 9.44 (br s, 1H, NH). MS *m/z*, 425 (M$^+$ + 1), 424 (M$^+$), 345, 292, 212, 161, 135, 81, 77. For $C_{23}H_{16}N_6OS$ Calcd: C, 65.08; H, 3.80; N, 19.80; S, 7.55%. Found: C, 65.21; H, 3.84; N, 19.59; S, 7.47%.

10b: Yield 58%; mp 262–264°C; IR (KBr) ν 3192 (NH), 1670 (C=O), 1612 (C=N) cm^{-1}; MS *m/z*, 422 (M$^+$ + 1), 421 (M$^+$), 319, 290, 195, 128, 105, 79. For $C_{24}H_{19}N_7O$ Calcd: C, 68.40; H, 4.54; N, 23.26%. Found: C, 68.21; H, 4.84; N, 23.55%.

Hydroximoyl Chloride **12**

To a stirred mixture of **11** (3.15 g, 10 mmol) and sodium nitrite (0.7 g, 10 mmol) in dioxane/water (40 mL, 1:1) was added conc. HCl (50 mL) portionwise over a period of 1 h. The reaction mixture was left to stir for further 2 h at room temperature. The greenish-yellow-colored precipitate was filtered off, washed with water, and dried. Recrystallization from toluene afforded **12** in 63% yield; mp 178–180°C; IR (KBr) ν 3350–3100 (br OH), 1693

(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.22 (s, 3H), 7.44–7.61 (m, 2H); 8.05 (d, 1H, $J = 7.8$ Hz), 8.17 (d, 1H, $J = 8.1$ Hz), 9.1 (s, 1H). For $C_{10}H_8ClN_3O_2$ Calcd: C, 50.54; H, 3.39; N, 17.68%. Found: C, 50.48; H, 3.22; N, 17.45%.

Benzimidazo[1,2-d]-1,2,4-oxadiazole Derivative **14**

To a mixture of **12** (0.474 g, 2 mmol) and 2-methylthio-1*H*-benzimidazole (**13**) (0.33 g, 2 mmol) in ethanol (20 mL), triethylamine (0.2 mL) was added and the reaction mixture was refluxed for 6 h, then left to cool to room temperature. The reaction mixture was diluted with water and the so-formed precipitate was filtered off, washed with ethanol, and dried. Recrystallization from DMF/EtOH afforded **14** in 45% yield; mp 190–192°C; IR (KBr) ν 1720 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.21 (s, 3H), 7.28–7.65 (m, 6H); 8.10–8.21 (m, 2H); MS *m/z*, 317 (M^+), 282, 210, 131, 103, 76. For $C_{17}H_{11}N_5O_2$ Calcd: C, 64.35; H, 3.49; N, 22.07%. Found: C, 64.23; H, 3.38; N, 22.31%.

Hydrazonoyl Bromide **17**

A mixture of **11** (3.15 g, 10 mmol) and 3-phenylpyrazole-5-diazonium chloride (**7**) (2.06 g, 10 mmol) in absolute ethanol (20 mL) was left to stir at room temperature for 6 h. The orange-yellow-colored precipitate was filtered off, washed with water, and dried. Recrystallization from acetic acid afforded **17** in 59% yield; mp 205–207°C; IR (KBr) ν 3210, 3146 (2NH), 1654 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1 (s, 3H), 6.66 (s, 1H), 7.12–8.01 (m, 9H); 9.48 (br s, 1H, NH), 13.95 (br s, 1H, NH). For $C_{19}H_{15}BrN_6O$ Calcd: C, 53.91; H, 3.57; N, 19.86%. Found: C, 53.69; H, 3.24; N, 19.72%.

*3-[(1-Methylbenzimidazol-2-yl)carbonyl]-6-phenylpyrazolo[1,5-c]-1,2,4-triazole (***16***)*

Method A. To a mixture of **12** (0.474 g, 2 mmol) and 5-amino-3-phenylpyrazole (**15**) (0.312 g, 2 mmol) in ethanol (20 mL), triethylamine (0.2 mL) was added and the reaction mixture was refluxed for 6 h, then left to cool to room temperature. The precipitated product was filtered off, washed with water and ethanol, dried, and finally recrystallized from EtOH/DMF to afford **16** in 68% yield; mp 216–218°C; IR (KBr) ν 3153 (NH), 1654 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (s, 3H), 7.26–7.31 (m, 3H), 7.4–7.51 (m, 2H), 7.66–7.76 (m, 5H), 8.87 (s, 1H); MS *m/z*, 343 ($M^+ + 1$), 342 (M^+), 304, 276, 170, 155, 77. For $C_{19}H_{14}N_6O$ Calcd: C, 66.66; H, 4.12; N, 24.55%. Found: C, 66.58; H, 4.27; N, 24.38%.

Method B. To a solution of **17** (0.423 g, 1 mmol) in ethanol (20 mL), triethylamine (0.2 mL) was added and the reaction mixture was refluxed for 2 h, then left to cool to room temperature. The brown-colored precipitated product was filtered off, washed with water and ethanol, dried, and finally recrystallized from EtOH/DMF to afford a product identical in all respects (mp, mixed mp, and spectra) with the pyrazolo[1,5-*c*]-1,2,4-triazole derivative **16** in 74% yield.

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