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Heterocyclic Synthesis *via* Enaminonitriles: A Convenient Route to Some New Pyrazole, Isoxazole, Pyrimidine, Pyrazolo[1,5-*a*]pyrimidine, Pyrimido [1,2-*a*]benzimidazole and Pyrido[1,2-*a*]benzimidazole Derivatives†

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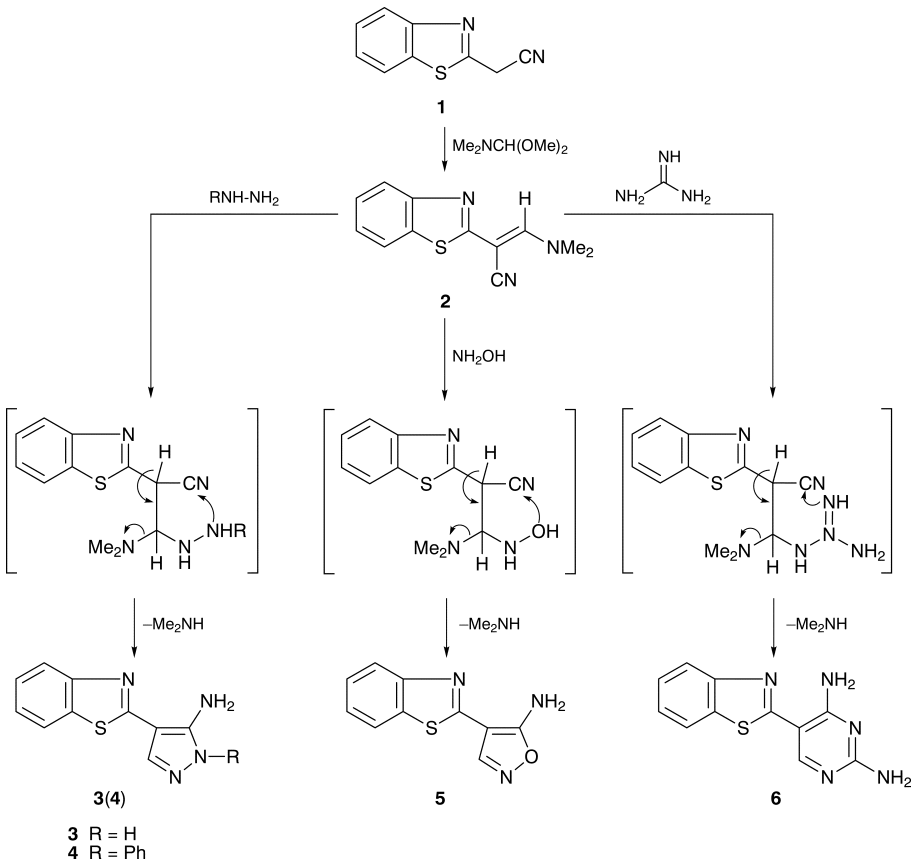
The utility of enaminonitrile **2** in the synthesis of some new pyrazole, isoxazole, pyrimidine, pyrazolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole and pyrido[1,2-*a*]benzimidazole derivatives is reported.

In continuation of our current interest in the synthesis of polysubstituted heterocycles incorporating a benzothiazole moiety,[1–5] we disclose here a facile synthesis of the highly versatile, hitherto unreported 2-(benzothiazol-2-yl)-3-(*N*,*N*-dimethylamino)prop-2-enenitrile **2** and the results of its utility as a building block for the synthesis of the title compounds.

Thus, treatment of 2-benzothiazoleacetonitrile **1** with dimethylformamide–dimethyl acetal (DMF–DMA) in refluxing xylene afforded the corresponding enaminonitrile **2** in excellent yield. The ^{1}H NMR spectrum of the isolated product exhibited two singlets at δ 3.29 and 7.98 due to the *N*,*N*-dimethylamino and methine protons, respectively, in addition to an aromatic multiplet in the region δ 7.18–7.77.

The reactivity of compound **2** towards some nitrogen nucleophiles was investigated. Thus, when **2** was treated with hydrazine hydrate and with phenylhydrazine in refluxing ethanol the novel aminopyrazoles **3** and **4**, respectively were produced (Scheme 1). Thus, the IR spectra of compounds **3** and **4** were free of nitrile function and showed absorption bands for NH_2 in the region 3400–3150 cm^{-1}; **3** also showed an absorption due to NH at 3112 cm^{-1}.

Similarly, the enaminonitrile **2** reacts with hydroxylamine in refluxing ethanol, to afford one isolable product identified as 5-amino-4-(benzothiazol-2-yl)isoxazole **5** (Scheme 1). The



Scheme 1

IR spectrum of **5** showed two absorption bands at 3360 and 3174 cm^{-1} due to the amino group. Prompted by the aforementioned results, we have also investigated the reactivity of the enaminonitrile **2** towards guanidine and some

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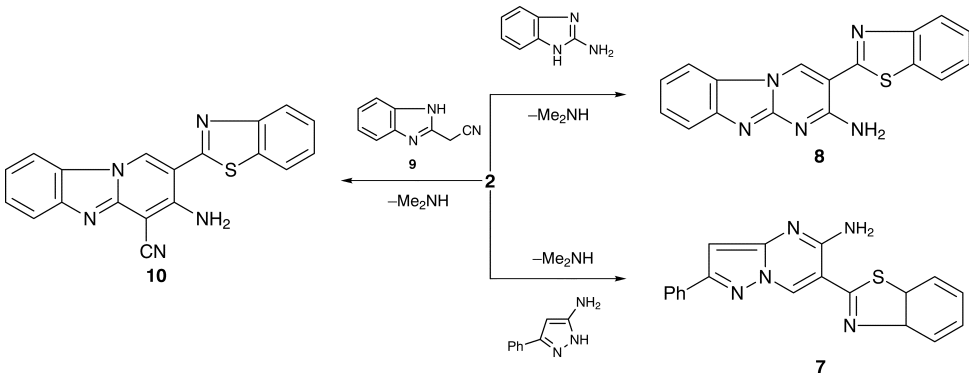

Scheme 2

heterocyclic amines. Thus, when compound **2** was treated with guanidine, it afforded an excellent yield of a product which was identified as 5-(benzothiazol-2-yl)-2,4-diaminopyrimidine **6** on the basis of its spectral data. Compounds **3**–**6** are assumed to be formed *via* addition of the amino group of hydrazines or guanidine to the activated ethylenic double bond of **2** followed by cyclization and elimination of a dimethylamine molecule as depicted in Scheme 1.

When enaminonitrile **2** was treated with 5-amino-3-phenyl-1*H*-pyrazole in refluxing ethanol, in the presence of piperidine, it afforded a green product identified as 5-amino-6-(benzothiazol-2-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine **7** (Scheme 2). The IR spectrum of compound **7** showed two characteristic absorption bands at 3385 and 3210 cm^{-1} due to the amino group and no bands due to the nitrile function.

In a similar manner, compound **2** reacted with 2-aminobenzimidazole under the same experimental conditions gave a red product in good yield. The structure of the obtained product was assigned as pyrimido[1,2-*a*]benzimidazole derivative **8** (Scheme 2). The presence of an amino group in structure **8** was evidenced by the appearance of two absorption bands at 3321 and 3100 cm^{-1} in the IR spectrum of the reaction product.

Note that the enaminonitrile **2** reacts smoothly with 2-(1*H*)-benzimidazoleacetonitrile **9** in refluxing ethanol in the presence of a catalytic amount of piperidine to afford only one isolable product, identified as 3-amino-2-(benzothiazol-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile **10**. The IR spectrum of the latter product revealed bands at 3404, 3115 and 2218 cm^{-1} due to the amino and nitrile functions, respectively.

Experimental

2-(*Benzothiazol-2-yl*)-3-(*N,N-dimethylamino*)*prop-2-enenitrile* **2**.—A mixture of 2-benzothiazoleacetonitrile **1** (4.04 g, 20 mmol) and dimethylformamide dimethyl acetal (2.66 ml, 20 mmol) in dry xylene (30 ml) was refluxed for 3 h, then cooled. The orange–yellow precipitated product was filtered off, washed with light petroleum and dried. Recrystallization from toluene gave compound **2** in 96% yield (4.39 g); mp 167–168 °C; ν_{max}(KBr)/cm^{-1} 2189 (C≡N); δ_H ($CDCl_3$) 3.29 (6 H, s, $2CH_3$), 7.18–7.77 (4 H, m, Ar′H), 7.98 (1 H, s, alkenic) (Found: C, 62.68; H, 4.90; N, 18.41; S, 13.87%. $C_{12}H_{11}N_3S$ requires C, 62.86; H, 4.83; N, 18.32; S, 13.98%).

Reaction of **2** *with Hydrazines*.—To a solution of the enaminonitrile **2** (0.458 g, 2 mmol) in ethanol (20 ml), hydrazine hydrate (80%, 0.2 ml) or phenylhydrazine (0.2 ml, 2 mmol) was added. The reaction mixture was refluxed for 4 h, then cooled. The solid product so formed was filtered off, washed with ethanol and dried. Recrystallization from dimethylformamide–ethanol afforded bright yellow needles of the corresponding 5-amino-4-(benzothiazol-2-yl)-1*H*-pyrazole **3** and its 1-phenyl derivative **4** in 88% and 83% yields, respectively. **3**: mp 230–232 °C; ν_{max}(KBr)/cm^{-1} 3394, 3284 (NH_2, 3112 (NH); δ_H (DMSO) 6.05 (2 H, br), 7.34–7.86 (4 H, m), 8.02 (1 H, s), 8.77 (br, 1 H) (Found: C, 55.32; H, 3.66; N, 25.87; S, 14.88%. $C_{10}H_8N_4S$ requires C, 55.54; H, 3.72; N, 25.90; S, 14.82%). **4**: mp 218–219 °C; ν_{max}(KBr)/cm^{-1} 3404, 3292 (NH_2); δ_H ($CDCl_3$) 5.88 (2 H, br, NH_2), 7.29–7.86 (10 H, m, Ar′H); *m/z* 292 (M^+) (Found: C, 65.69; H, 4.02; N, 19.18; S, 10.88%. $C_{16}H_{12}N_4S$ requires C, 65.73; H, 4.13; N, 19.16; S, 10.96%).

5-*Amino*-4-(*benzothiazol*-2-*yl*)*isoxazole* **3** *and* 5-(*Benzothiazol*-2-*yl*)-2,4-*diaminopyrimidine* **6**.—To a mixture of the enaminonitrile **2** (0.458 g, 2 mmol) and hydroxylamine hydrochloride or guanidine nitrate (2.3 mmol) in ethanol (30 ml), anhydrous potassium carbonate (0.552 g, 4 mmol) was added. The resulting mixture was refluxed for 6 h and then allowed to cool to room temperature and diluted with water (20 ml). The solid product so formed was collected by filtration, washed with water and dried. Recrystallization from DMF afforded the 5-aminoisoxazole **5** and 2,4-diaminopyrimidine **6**, respectively. The products are insoluble in the common NMR solvents. **5**: (72% yield); mp > 300 °C; ν_{max}(KBr)/cm^{-1} 3370, 3174 (NH_2); *m/z* 217 (M^+) (Found: C, 55.28; H, 3.35; N, 19.26; S, 14.71%. $C_{10}H_7N_3OS$ requires C, 55.30; H, 3.23; N, 19.35; S, 14.75%). **6**: (88% yield); mp > 300 °C; ν_{max}(KBr)/cm^{-1} 3371, 3269, 3210, 3118 (2 NH_2); *m/z* 243 (M^+) (Found: C, 54.21; H, 3.75; N, 28.84; S, 13.20%. $C_{11}H_9N_5S$ requires C, 54.30; H, 3.73; N, 28.79; S, 13.18%).

Reaction of **2** *with Heterocyclic Amines*.—A mixture of the enaminonitrile **2** (0.458 g, 2 mmol) and the appropriate heterocyclic amine (2.2 mmol) in ethanol (30 ml) in the presence of a few drops of piperidine was refluxed for 8 h, then left to cool to room temp. The precipitated product was filtered off, washed with ethanol and dried. Recrystallization from DMF afforded the corresponding pyrazolo-[1,5-*a*]pyrimidine and pyrimido[1,2-*a*]benzimidazole derivatives **7** and **8**, respectively. The products are insoluble in the common NMR solvents. **7**: (66% yield); mp 268–270 °C; ν_{max}(KBr)/cm^{-1} 3385, 3210 (NH_2); *m/z* 343 (M^+) (Found: C, 66.41; H, 3.77; N, 20.30; S, 9.4%. $C_{19}H_{13}N_5S$ requires C, 66.45; H, 3.82; N, 20.39; S, 9.34%). **8**: (58% yield); mp > 300 °C; ν_{max}(KBr)/cm^{-1} 3321, 3100 (NH_2); *m/z* 317 (M^+) (Found: C, 64.27; H, 3.42; N, 22.20; S, 10.24%. $C_{17}H_{11}N_5S$ requires C, 64.34; H, 3.49; N, 22.07; S, 10.16%).

3-*Amino*-2-(*benzothiazol*-2-*yl*)*pyrido*[1,2-*a*]*benzimidazole*-4-*carbonitrile* **10**.—A mixture of the enaminonitrile **2** (0.458 g, 2 mmol) and (1*H*)-2-benzimidazoleacetonitrile **9** (0.314 g, 2 mmol) in ethanol (30 ml) was heated to reflux temperature. To the resulting hot solution, a catalytic amount of piperidine (0.1 ml) was added and the reflux was continued for 4 h, then allowed to cool to room temp. The precipitated product was filtered off, washed with ethanol, dried and finally recrystallized from DMF to give the pyrido[1,2-*a*]benzimidazole derivative **10** in 81% yield (0.55 g); mp > 300 °C; insoluble in the common NMR solvents; ν_{max}(KBr)/cm^{-1} 3404, 3115 (NH_2), 2218 (C≡N); *m/z* 341 (M^+) (Found: C, 66.79; H, 3.26; N, 20.37; S, 9.40%. $C_{19}H_{11}N_5S$ requires C, 66.84; H, 3.24; N, 20.51; S, 9.39%).

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