Novel Selective Heterocyclization of the Michael Adducts of Ene-hydrazines with Dimethyl Acetylenedicarboxylate

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Cyclization of the Michael adducts **1** and **6** formed from ene-hydrazines and dimethyl acetylenedicarboxylate (DMAD) in the presence of polyphosphoric acid (PPA) produced the fused 1,2-diazepine rings **2** and **7**. However, the adducts when heated in 1,2,3,4-tetrahydronaphthalene (tetralin) preferentially provided the fused pyridone rings **4** and **10** and the fused pyrrole rings **5** and **11**.

Because of their nucleophilic bifunctionality, ene-hydrazines exhibit versatility in the preparation of nitrogen-containing heterocycles.[1]

As a result of our interest in this area, earlier we investigated the cyclization of the Michael adducts of hydrazinopyridazinones, compounds containing an ene-hydrazine moiety, with DMAD and found that they unexpectedly underwent secondary cyclization to afford pyridazino-pyridones and -pyrroles rather than the expected pyridazinopyridazines.[2]

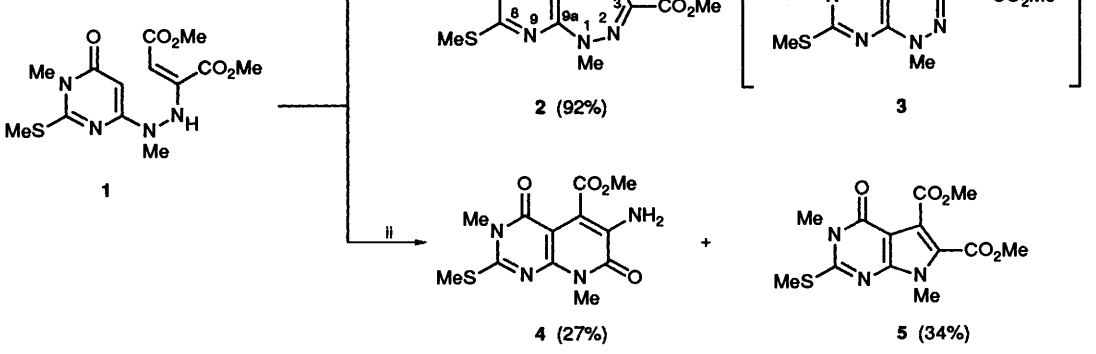
We describe here the novel heterocyclization of the Michael adducts of ene-hydrazines with DMAD to the fused 1,2-diazepines. The Michael adduct **1** when heated in toluene at 90 °C in the presence of a large excess of PPA gave pyrimido[4,5-*c*]-1,2-diazepine **2** (92%) as the sole product, the structure of which was assigned on the basis of spectral data and elemental analysis. Although cyclization through nucleophilic attack of the negatively polarized C-5 in the pyrimidine ring on the carbonyl group of a further ester could have given the isomeric product **3**, the latter was discounted on the basis of spectral evidence. Thus, the UV spectrum of compound **2** (maxima at 233 and 299 nm) was compared with that of the known compound, 7-amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione, structurally similar to **3**,[3] and shown to be quite different. Moreover, the ^1H-^{13}C long-range correlation spectrum of the product exhibited a clear cross peak arising from three-bond coupling between the methylene hydrogen (δ_H 3.67) and C-5a (δ_C 102.5).

In contrast, the adduct **1** when heated in tetralin at 200 °C provided pyrido[2,3-*d*]pyrimidine **4** (27%) and pyrrolo[2,3-*d*]-pyrimidine **5** (34%) in yields similar to those afforded by the reaction of hydrazinopyridazinones with DMAD (Scheme 1). The structural assignments for **4** and **5** were established on the basis of their spectral data and elemental analyses and their formation is presumed to proceed through an initial 3,3-sigmatropic reaction with cleavage of the N–N bond followed by cyclization and elimination of methanol or ammonia.

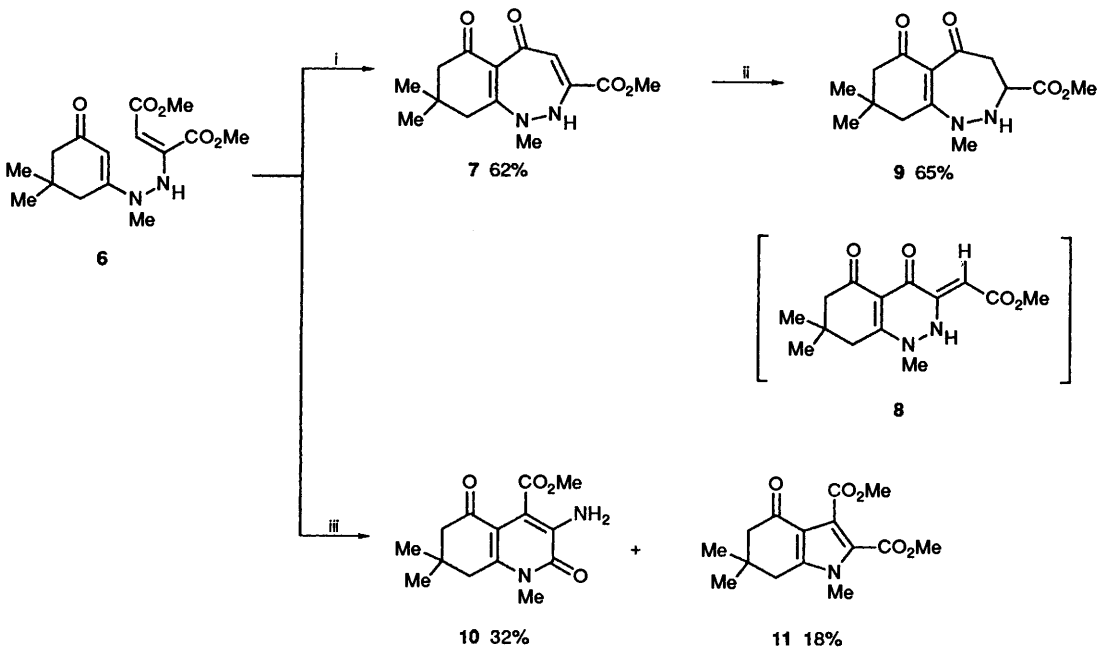
Cyclization of the adduct **6** of hydrazinocyclohexenone and DMAD in the presence of PPA gave cyclohexa[*c*]-1,2-diazepine **7**, and in tetralin at 200 °C, cyclohexa[*b*]pyridone **10** and cyclohexa[*b*]pyrrole **11**. Structure **7** was established and distinguished from an alternative possible isomer, **8**, by the reduction with sodium borohydride of its double bond to give **9**. The IR spectrum of the latter showed ester carbonyl and NH absorptions at 1720 and 3465 cm^{-1}, respectively, and the absence of a hydrogen bond. The ^1H NMR spectrum showed δ_H 3.27 (dd, *J* 14.8, 7.9, geminal 4-H), 3.38 (dd, *J* 14.8, 3.8, geminal 4-H) and 4.61 (dd, *J* 7.9, 3.8, methine 3-H).

Experimental

Michael Adduct **1** *of* 3-*Methyl*-6-(1-*methylhydrazino*)-2-*methylthiopyrimidin*-4(3H)-*one with DMAD*.—To a stirred solution of 3-methyl-6-(1-methylhydrazino)-2-methylthiopyrimidin-4(3*H*)-one[4] (1.00 g, 5 mmol) in MeOH (20 cm^3) was added dropwise DMAD (0.74 cm^3, 6 mmol) at room temperature. The mixture was stirred for 2 h, after which it was evaporated under reduced pressure and the residue was treated with ether (20 cm^3). The resulting precipitate was recrystallized from dichloromethane–isopropyl ether to give the crystalline Michael adduct **1** (1.51 g, 88%), m.p. 117–121 °C (Found: C, 45.8; H, 5.3; N, 16.15. $C_{13}H_{18}N_4O_5S$ requires C, 45.61; H, 5.30; N, 16.36%); ν_{max}(KBr)/cm^{-1} 1735 (C=O), 1705 (C=O) and 1655 (C=O); δ_H($CDCl_3$) 2.48 (3 H, s, SMe), 3.29 (3 H, s, NMe), 3.43 (3 H, s, NMe), 3.73 (3 H, s, OMe), 3.76 (3 H, s, OMe), 5.29 (1 H, s, CH=), 5.41 (1 H, s, CH=) and 9.22 (1 H, s, NH); *m*/*z* 342 (M^+).



Scheme 1 *Reagents and conditions:* i, PPA, toluene, 80–90 °C; ii, tetralin, 200 °C



Scheme 2 *Reagents and conditions:* i, PPA, toluene, 80–90 °C; ii, MeOH, $NaBH_4$; iii, tetralin, 200 °C

4,5-*Dihydropyrimido*[4,5-c]-1,2-*diazepine*-5,6(1H,7H)-*dione* **2**.—To PPA (4.06 g) at 80–90 °C was added dropwise a solution of the Michael adduct **1** (1.03 g, 3 mmol) in toluene (10 cm^3) and the reaction mixture was kept at 80–90 °C. After being stirred for an additional 30 min at 90 °C, the toluene layer was decanted from the reaction mixture, and the oily residue diluted with water whilst being stirred. The resulting crystals were filtered off and recrystallized from methanol to give compound **2** (0.86 g, 92%), m.p. 244–245 °C (decomp.) (Found: C, 46.5; H, 4.55; N, 17.8. $C_{12}H_{14}N_4O_4S$ requires C, 46.44; H, 4.55; N, 18.05%); ν_{max}(KBr)/cm^{-1} 1710sh (C=O) and 1695 (C=O); δ_H($CDCl_3$) 2.63 (3 H, s, SMe), 3.46 (3 H, s, NMe), 3.67 (2 H, s, CH_2), 3.84 (3 H, s, NMe) and 3.91 (3 H, s, OMe); δ_C($CDCl_3$) 15.03, 30.15, 43.50, 46.63, 53.61, 102.52, 145.26, 155.74, 158.86, 162.14, 164.63 and 176.99; *m/z* 310 (M^+).

Methyl 3-*Amino*-1,6-*dimethyl*-7-*methylthio*-2,5-*dioxo*-1,2,5,6-*tetrahydro*[2,3-d]*pyrimidine*-4-*carboxylate* **4** *and Dimethyl* 1,5-*Dimethyl*-6-*methylthio*-4-*oxo*-4,5-*dihydro*-1H-*pyrrolo*[2,3-d]-*pyrimidine*-2,3-*dicarboxylate* **5**.—A solution of compound **1** (1.03 g, 3 mmol) in tetralin (20 cm^3) was heated at 200 °C for 1 h and then evaporated, the residue was chromatographed on silica gel with benzene–ethyl acetate (5:1) as eluent to give compounds **4** and **5**, analytical samples of which were obtained by recrystallization from an appropriate solvent. *Compound* **4** (0.25 g, 27%), m.p. 271–273 °C (MeCN) (Found: C, 46.4; H, 4.5; N, 17.9. $C_{12}H_{14}N_4O_4S$ requires C, 46.44; H, 4.55; N, 18.05%); ν_{max}(KBr)/cm^{-1} 3430 (NH), 3340 (NH), 1715 (C=O) and 1660 (C=O); δ_H([$^2H_6$]DMSO) 2.62 (3 H, s, SMe), 3.41 (3 H, s, NMe), 3.65 (3 H, s, NMe), 3.79 (3 H, s, OMe) and 5.55 (2 H, s, NH_2); *m/z* 310 (M^+).

Compound **5** (0.33 g, 34%), m.p. 168–170 °C (ethyl acetate) (Found: C, 48.0; H, 4.65; N, 12.8. $C_{13}H_{15}N_3O_5S$ requires C, 47.99; H, 4.65; N, 12.92%); ν_{max}(KBr)/cm^{-1} 1735 (C=O), 1710 (C=O) and 1685(C=O); δ_H($CDCl_3$) 2.64 (3 H, s, SMe), 3.55 (3 H, s, NMe), 3.87 (3 H, s, NMe), 3.96 (3 H, s, OMe) and 3.98 (3 H, s, OMe); *m/z* 325 (M^+).

3-*Methoxycarbonyl*-1,8,8-*trimethyl*-2,5,6,7,8,9-*hexahydro*-1,2-*benzodiazepin*-5,6-(1H)-*dione* **7**.—Compound **6** (3.10 g, 10 mmol) was heated in the presence of PPA (13.52 g) for 40 min in the same manner as described for the preparation of compound **2**. The crude product was recrystallized from dichloromethane–isopropyl ether to give compound **7** (1.73 g, 62%), m.p. 154.5–155.5 °C (Found: C, 60.5; H, 6.55; N, 10.0. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07%); ν_{max}(KBr)/cm^{-1} 3420 (NH), 1720 (C=O) and 1660 (C=O); δ_H($CDCl_3$) 1.14 (6 H, s, Me × 2), 2.36 (2 H, s, CH_2), 2.67 (2 H, s, CH_2), 3.81 (3 H, s, NMe), 3.87 (3 H, s, OMe), 7.15 (1 H, s, CH=) and 10.22 (1 H, br, NH); *m/z* 278 (M^+).

Reduction of Compound **7**.—To a solution of compound **7** (1.39 g, 5 mmol) in MeOH (5 cm^3) was added sodium borohydride (0.19 g, 5 mmol) at room temperature. After being stirred for 10 min, the mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with chloroform–methanol (25:1) as eluent to give compound **9** (0.91 g, 65%), m.p. 98–99 °C (Found: C, 59.7; H, 7.2; N, 10.0. $C_{14}H_{20}N_2O_4$ requires C, 59.99; H, 7.19; N, 9.99%); ν_{max}(KBr)/cm^{-1} 3470 (NH), 1720 (C=O) and 1655 (C=O); δ_H([$^2H_6$]DMSO) 1.12 (3 H, s, Me), 1.13 (3 H, s, Me), 2.34 (2 H, s, CH_2), 2.63 (2 H, s, CH_2), 3.27 (1 H, dd, *J* 14.8, 7.9, CH_2), 3.38 (1 H, dd, *J* 14.8, 3.8, CH_2), 3.75 (6 H, s, NMe and OMe), 4.15 (1 H, br, NH) and 4.61 (1 H, dd, *J* 7.9, 3.8, CH); *m/z* (CI-MS) 281 (M^+ + 1).

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