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Rapid synthesis of tetrahydro-4*H*-pyrazolo[1,5-*a*]diazepine-2-carboxylate☆

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Abstract—Hydrazines condense with dimethyl 2-pyrrolidino-4-oxo-2-pentenedioate in the presence of aq. HCl to form *N*-substituted pyrazole-3,5-dicarboxylates **2**. Complex bicyclic derivatives, such as pyrazolo-oxazine **3a**, pyrazolo-oxazepine **3b**, pyrazolo-pyrazine **4a**, and pyrazolo-diazepine **4b**, were generated using 2-hydrazinoethanol, 3-hydrazinopropanol, 2-hydrazinoethylamine, and 3-hydrazinopropylamine.

1. Introduction

The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages. Pyrazole-3,5-dicarboxylate offers linkage opportunities via the carbonyl groups as well as the pyrazole nitrogens, and is an important feature of oral fibrinogen antagonist **1** (see Fig. 1).[1] An alternate approach that allows an efficient and flexible synthesis of substituted *N*-substituted pyrazole dicarboxylates **2** or more complex bicyclic derivatives such as pyrazolo-oxazine **3a**, pyrazolo-pyrazine **3b**, pyrazolo-oxazepine **4a**, or pyrazolo-diazepine **4b** (see Fig. 2) was highly desirable,[2] with pyrazolo-diazepin **4b** being the prize goal as a key intermediate for the synthesis of oral fibrinogen antagonist **1**.[1b]

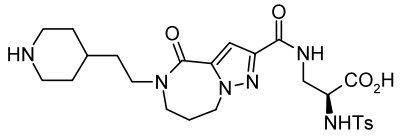

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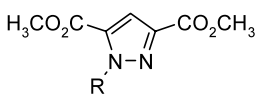
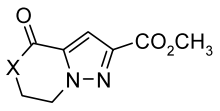
Figure 1. Oral fibrinogen antagonist **1**.

2. Results and discussion

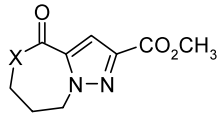
The ease of condensation of hydrazines with β-dicarbonyls[3a] and β-enaminones[3b] is well documented. A study to extend this condensation to dimethyl 2,4-dioxo-pentanedioate, **6**, for the preparation of a variety of *N*-substituted-3,5-dicarboxy-pyrazoles was initiated. The synthesis of diketone **6** has been previously reported.[4] The dimethylamino enamine of methyl pyruvate was prepared using stoichiometric amounts of



2a: R = H
b: R = methyl
c: R = benzyl
d: R = phenyl
e: R = 2-pyridyl
f: R = 4-carboxyphenyl



3a: X = O
b: X = NH



4 a: X = O
b: X = NH

Figure 2. Substituted pyrazole dicarboxylates.

Keywords: aminohydrazines; hydroxyhydrazines; pyrazole formation; pyrazolo-diazepine.
☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01417-5
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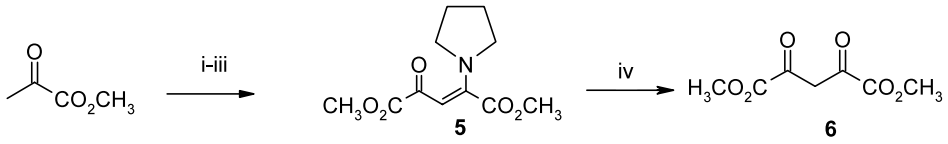
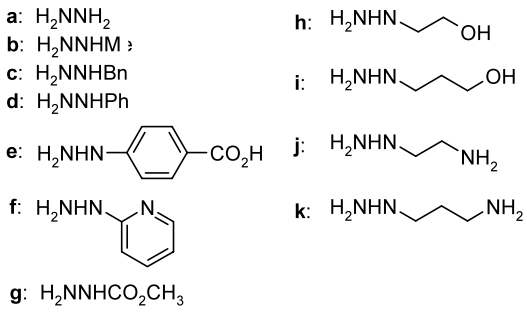


Figure 3. Synthesis of dimethyl 2,4-di-oxo-pentanedioate (**6**).

$AsCl_3$, then treated with methyl oxalyl chloride and hydrolyzed to the diketone. The replacement of $AsCl_3$, an environmentally unsatisfactory reagent, was achieved with the use of more benign trimethylborate, $B(OMe)_3$, in *tert*-butyl methylether (MTBE) or methylene chloride for the formation of the pyrrolidine enamine. Treatment of the reaction solution with triethylamine and methyl oxalylchloride produced crystalline enaminoketone **5** in ~50% overall yield (see Fig. 3).[5]

It was found that condensations of hydrazines with enaminoketone **5** were facile and obviated the need to convert the stabile crystalline enaminoketone into diketone **6**, an unstable oil. Condensations of hydrazines with enaminoketone **5** were carried out in methanol at 25–50°C, in the presence of a small amount of aq HCl.[6] Simple alkyl hydrazines **7a**–**f** (Table 1) gave pyrazoles **2a**–**f** as crystalline solids in yields of 70–90%. Hydrazine **7g** failed to cyclize, and the corresponding hydrazone was isolated.

Table 1. Hydrazines **7** used in condensations



Hydrazines **7h**–**k** were prepared by displacement of the corresponding chloride or bromide with hydrazine hydrate.[7,8] Isolation and purification was achieved by crystallization of the hydrazines as bis-*p*-toluenesulfonic acid salts, which were stable and non-hygroscopic.[9] Condensation of enaminoketone **5** with the hydrazines **7h**–**k** (as the Tosic acid salts) in methanol,

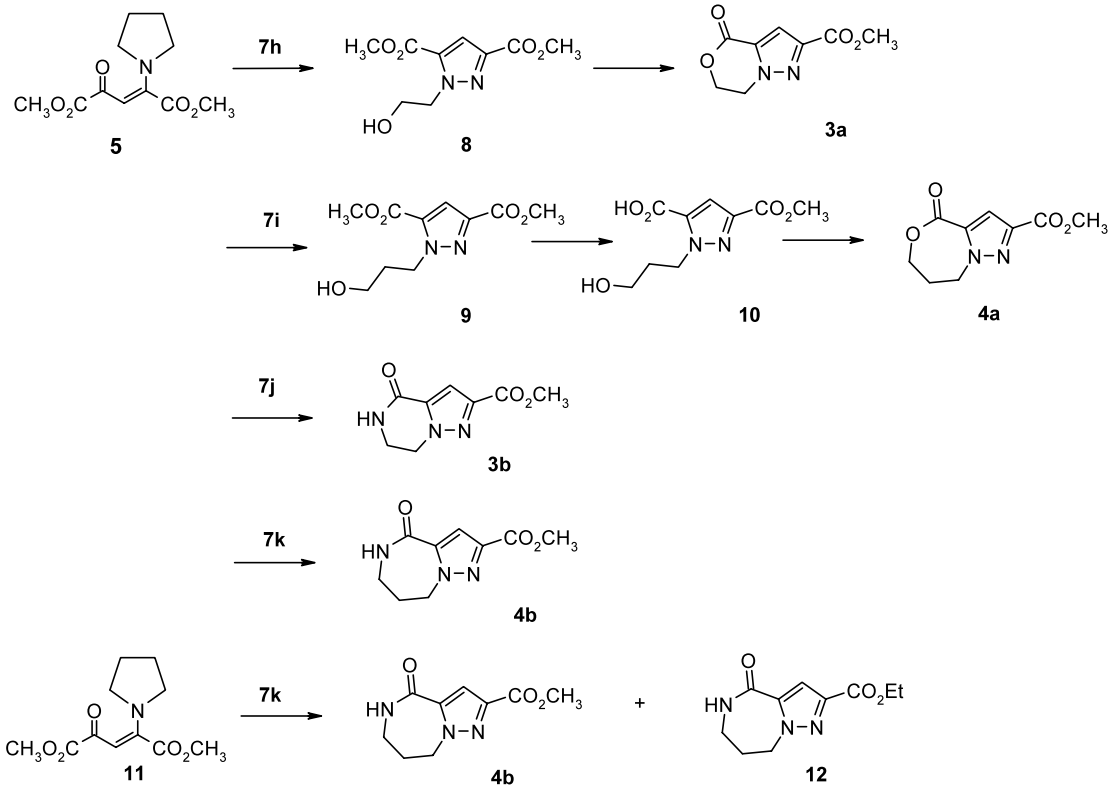


Figure 4. Pyrazole lactone and amide syntheses.

ethanol or water failed. In the presence of sodium acetate decomposition occurred with little or no desired product formation. In the presence of 1N HCl rapid formation of pyrazoles occurred.

Condensation with hydrazino-alcohols **7h** and **7i** produced the corresponding alcohols **8** and **9**, which were converted to lactones **3a** and **4a**, respectively. Alcohol **8** readily lactonized to pyrazolo-oxazine **3a** using DBU in THF. Alcohol **9**, however, failed to cyclize under acidic or basic conditions. When treated with potassium hydroxide in THF at 2°C,[10] ester hydrolysis produced acid **10**, which cyclized upon subsequent treatment with EDC and HOBt (see Fig. 4).[11]

Aminohydrazines **7j** and **7k** produced the bicyclic pyrazole-pyrazine **3b** and pyrazolo-diazepine **4b** directly. Thus, in a two-step synthesis, the key bicyclic intermediate **4b** used in the synthesis of oral fibrinogen antagonist **1** was achieved in 40% overall yield.

The need to add 1N HCl to effect hydrazine condensation to enaminoketone **5** suggested the intermediacy of diketone **6**. When the pyrrolidine enamine of methyl pyruvate was reacted with ethyl oxalyl chloride, the mixed ester enaminoketone **11** was isolated. Addition of hydrazine **7k** produced a 1:1 mixture of isomeric esters **4b** and **12**. It was otherwise anticipated that a differentiation between a 1,4- and 1,2-addition would have resulted in a biased ratio.

Thus, complex *N*-substituted pyrazole dicarboxylates **2** and bicyclic pyrazoles **3** and **4** were rapidly formed by the addition of hydrazines to enaminoketone **5** in typically 70–90% yields.

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5. **Dimethyl 2-pyrrolidino-4-oxo-2-pentenedioate (5)**. A solution of pyrrolidine (12.6 ml, 0.151 mol) in MTBE (100 ml) was cooled to −10°C. A solution of methyl pyruvate (13.6 ml, 0.151 mol) in MTBE (100 ml) was added dropwise over 30 min and stirred for 15 min. Trimethylborate (8.0 ml, 0.071 mol) was added dropwise over 2 min and the solution was stirred for 2 h at −10°C. The solution was treated with triethylamine (55 ml, 395 mmol), forming a precipitate, then a solution of methyl oxalylchloride (24.6 ml, 0.267 mol) in MTBE (50 mL) was added dropwise over 30 min to form a thick slurry. The resulting slurry was stirred for 30 min, treated with saturated sodium bicarbonate (250 mL) and methylene chloride (200 ml) and the phases separated. The aqueous phase was extracted with methylene chloride (2×100 ml). The combined organic phases were evaporated in vacuo to give an oil which was triturated with MTBE to produce 15.75 g of yellowish solids (45% yield). A sample was recrystallized from toluene/cyclohexane. Mp 80.3–82.0°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.70 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.46 (br t, $J=6.5$, 2H), 3.32 (br t, $J=6.7$, 2H), 2.04–1.90 (m, 4H). ^{13}C NMR (100.613 MHz, $CDCl_3$): δ 175.8, 165.2, 163.9, 154.9, 90.8, 53.2, 52.4, 49.0, 48.7, 25.1, 24.5. Anal. calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.73; H, 6.27; N, 5.74.
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9. Typical procedure: **3-Hydrazino-1-propanol bis-tosic acid salt (7i)**. A solution of 3-bromo-1-propanol (13.9 g, 0.10 mol) in ethanol (20 mL) was added to hydrazine hydrate (40 mL) at 65°C dropwise over 2 h, then stirred for 2 h. The mixture was concentrated in vacuo (27 in Hg, 90°C bath), dissolved in water (200 mL), and passed through a column of IRA-400 resin (285 mL, on base cycle). The column was eluted with water (4 bed volumes) and the eluate was concentrated in vacuo to an oil (7.3 g). The oil was evaporatively dried with ethanol (2×100 mL), dissolved with ethanol (100 mL) and *p*-TsOH hydrate (26 g) was added. After stirring for 1 h, crystalline product was filtered, washed with cold EtOH, and dried to give 18.6 g of off-white crystals of the bis-*p*-toluenesulfonic acid salt. Mp 125.0–126.1°C. ^{1}H NMR (400.13 MHz, D_2O): δ 7.54 (td, $J=8.3$, 2.0, 4H), 7.20 (td, $J=8.3$, 2.0, 4H), 4.71 (s, 6H), 3.53 (t, $J=6.1$, 2H), 3.08 (t, $J=7.3$, 2H), 2.21 (s, 6H), 1.75 (m, 2H). ^{13}C NMR (100.61 MHz, D_2O): δ 142.3, 139.3, 129.3, 125.2, 58.8, 49.0, 26.6, 20.3. Anal. calcd for $C_{17}H_{26}N_2S_2O_7$: C, 46.99; H, 6.03; N, 6.45; S, 14.76. Found: C, 47.00; H, 5.92; N, 6.23; S, 14.86. NMR and analytical data for compounds **7h**, **7j**, and **7k** can be found in the Supplementary Data.
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11. **Methyl 4-oxo-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-a][1,4]-diazepine-2-carboxylate (4b)**. Enaminoketone **5** (1.22 g, 5.0 mm) was dissolved in methanol (10 mL) and added 3-hydrazino-1-propylamine bis-Tosic acid salt (**7k**) (2.22 g, 5.1 mm). 2N aq HCl (0.5 mL) was added and the mixture was stirred 8 h. This was partitioned between methylene chloride (20 mL) and aq bicarbonate (20 mL). The aqueous phase was extracted with methylene chloride

(3×20 mL), and the extracts were evaporated to solids (0.80 g). The solids were dissolved into acetonitrile at 60°C and DBU (10 μl) was added to complete cyclization. After evaporation, lactam **4b** was isolated and found to be identical to known lactam. Additional experimental, NMR and Analytical data for compounds **3a**,**b**, **4a**, **8**, **9**, and **10** can be found in the Supplementary Data.