A SHORT THREE COMPONENTS APPROACH TO FUSED PYRROLO[2,3-*b*]PYRROLIDINONE

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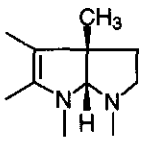
Abstract - 4-Methyl-4-dimethoxymethylpyrans (**5b**) and (**5c**) prepared from 1,3-cyclohexanediones (**2**), pyruvaldehyde dimethyl acetal (**3b**), and malononitrile (**4**), were subjected to hydrolysis with HCl to give fused furofuranones (**6**), which were treated with amines to give fused pyrrolopyrrolidinones (**9**).

Preparation of pyrrolopyrrolidines (**1**) including naturally occurring (-)-physostigmine and its analogues



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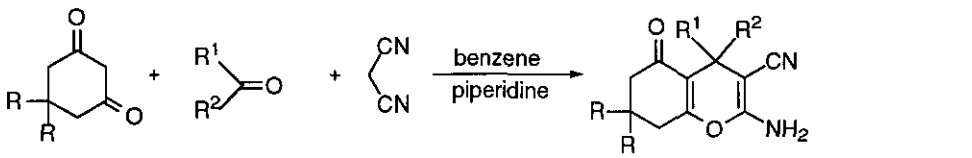
has received much attention because some of them are inhibitors of acetylcholinesterase[1] and therapeutic agents for treating Alzheimer's disease.[2] Consequently a number of approaches[3] to the synthesis of these compounds have been reported. However, these methods need several steps. It is known that three component reactions using cyclohexane-1,3-dione (**2a**), ketone (**3a**), and malononitrile (**4**) produce fused pyran derivatives (**5a**).[4] In the course of our work[5] on simple preparations of saturated polyheterocycles using dialdehyde, we attempted to apply this reaction to the preparation of pyrrolopyrrolidine derivatives by replacing **3a** with pyruvaldehyde dimethyl acetal (**3b**). Herein we wish to report a simple and unique preparation of pyrrolopyrrolidinone.



2a: R=H
b: R=CH_3

3a: R^1=R^2=CH_3
b: R^1=CH_3, R^2=$CH(OCH_3)_2$

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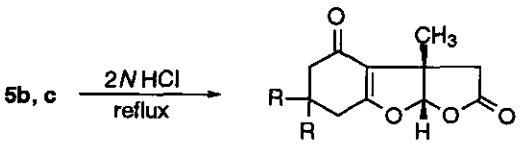
5a: R=H, R^1=R^2=CH_3
b: R=H, R^1=CH_3, R^2=$CH(OCH_3)_2$
c: R=CH_3, R^1=CH_3, R^2=$CH(OCH_3)_2$

Scheme 1

A solution of **2**, **3b**, and **4** in benzene was heated under reflux in the presence of piperidine to give 4-methyl-4-dimethoxymethylpyrans (**5b** and **5c**) in yields of 64 and 87 %, respectively (Scheme 1). The structure of **5c** was based on a characteristic acetal methine proton and carbon at δ 4.51 and 109 ppm in the

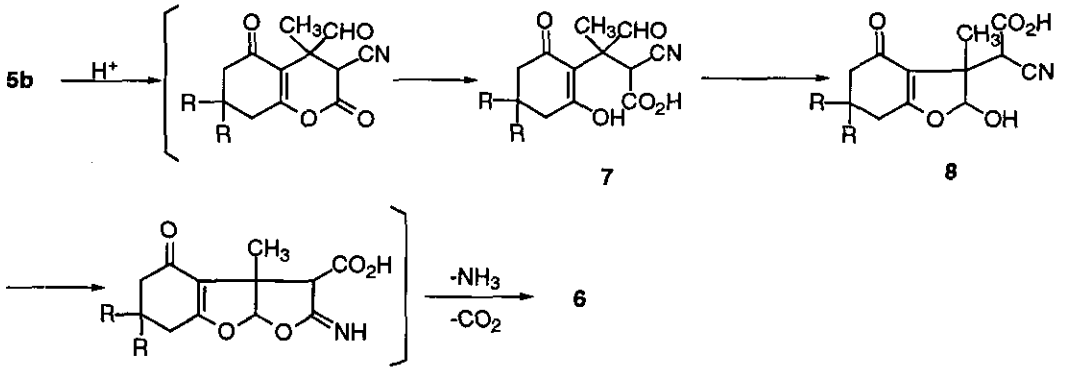
^{1}H- and ^{13}C-nmr spectra, respectively, and a molecular ion peak at *m/z* 278 in the mass spectrum. Hydrolysis of compound (**5b** and **c**) with 2*N* HCl gave the fused furo[2,3-*b*]furanones (**6a** and **b**) in 62-64 % yield (Scheme 2).[6] Structure of **6b** was determined as follows: The ^{1}H-nmr spectrum showed the acetal methine proton at δ 6.23 ppm and the ^{13}C-nmr spectrum indicated the acetal methine carbon at δ 112 ppm, with quaternary carbons at δ 34, 48, 116, and 173 ppm, respectively. The mass spectrum indicated a molecular ion at *m/z* 236. The ir spectrum showed carbonyl absorptions at 1650 and 1790 cm^{-1}.



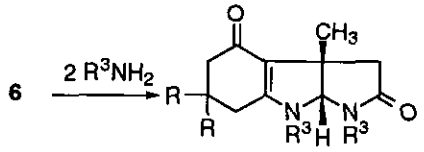
6a: R=H
b: R=CH_3

Scheme 2

A mechanistic rationalization of the formation of **6** from **5** involves an acid-catalyzed hydrolysis of the acetal and ring opening to give **7**. This step is then followed by formation of the hemiacetal (**8**), which undergoes recyclization and decarboxylation to **6** (Scheme 3).



Scheme 3



9a: R=H, R^3=H,
b: R=CH_3, R^3=H
c: R=CH_3, R^3=CH_3

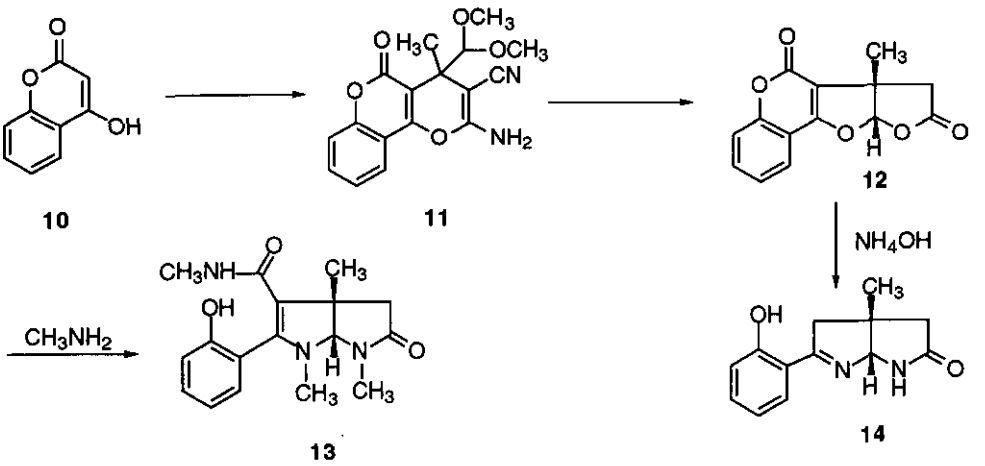
Scheme 4

Conversion of **6** to the fused pyrrolopyrrolidinone (**9**) was achieved in 47 - 89 % yield by heating with primary amines in EtOH (Scheme 4). These compounds were characterized by mass spectra and ^{1}H- and ^{13}C-nmr spectra.[7] All spectral data were consistent with the assigned structure.

As an application of this three component reaction, we next examined the reaction with 4-hydroxycoumarin (**10**). Thus, treatment of **10** with **3b** and **4** gave the pyranopyran (**11**) in 92 % yield. Hydrolysis of **11** with HCl produced the furofuranones (**12**) in 77 % yield. Compound (**12**) was treated with methylamine to give β-(2-hydroxyphenyl)pyrrolopyrrolidinone (**13**)[8] in 32 % yield (Scheme 5). Treatment of **12** with aqueous ammonia in a sealed tube afforded the imino compound (**14**)[9] in 63 % yield *via* decarboxylation of β-carboxyenamine.

Reduction of pyrrolopyrrolidinone to pyrrolopyrrolidine has been achieved by Marino.[10] A short approach to pyrrolopyrrolidinone using three components has been established.

Conversion of these compounds to related pyrrolopyrrolidine derivatives is being investigated.



Scheme 5

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6. A suspension of **5b** (0.61g, 2 mmol) in 2*N* HCl (20 ml) was refluxed for 12 h. The reaction mixture was extracted with CH_2Cl_2 (4 x 25 ml). The CH_2Cl_2 layer was washed with water (20 ml) and dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH = 50 : 1).

6b: yield 0.35 g (64 %); mp 85 - 87°C; ^{1}H-nmr (DMSO-d_6) δ 1.02 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.12 (1H, d, *J* = 16.17 Hz, C<u>H</u>H), 2.25 (1H, d, *J* = 16.17 Hz, CH<u>H</u>), 2.37 (1H, d, *J* = 18.14 Hz, C<u>H</u>H), 2.48 (1H, d, *J* = 18.14 Hz, CH<u>H</u>), 2.76 (1H, d, *J* = 18.14 Hz, C<u>H</u>H), 2.84 (1H, d, *J* = 18.14 Hz, CH<u>H</u>), 6.23 (1H, s, OCHO); ^{13}C-nmr (DMSO-d_6) δ 20.91, 27.25, 28.25 (CH_3), 36.15, 37.82, 50.64 (CH_2), 33.92, 47.92 (C), 111.97 (CH), 116.42, 173.11 (C = C), 173.38, 193.45 (C = O); ir (KBr) 1790, 1650 cm^{-1}; EI-ms *m/z* 236 (M^+).

7. A solution of **6b** (0.47 g, 2 mmol) and amine (10 mmol) in EtOH (20 ml) was refluxed for 12 h. The EtOH was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2: MeOH = 20 : 1).

9b: yield 0.42 g (89 %); mp 270 - 272°C; ^{1}H-nmr (DMSO-d_6) δ 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.91 (1H, d, *J* = 15.83 Hz, C<u>H</u>H), 2.05 (1H, d, *J* = 15.83 Hz, CH<u>H</u>), 2.14 (1H, d, *J* = 16.83 Hz, C<u>H</u>H), 2.21 (1H, d, *J* = 17.15 Hz, CH<u>H</u>), 2.23 (1H, d, *J* = 16.83 Hz, C<u>H</u>H), 2.53 (1H, d, *J* = 17.15 Hz, CH<u>H</u>), 4.83 (1H, s, NCHN), 7.94 (1H, s, NH), 8.21 (1H, s, NH); ^{13}C-nmr (DMSO-d_6) δ 23.74, 27.49, 28.71 (CH_3), 36.42, 41.36, 50.62 (CH_2), 33.80, 46.73 (C), 77.84 (CH), 112.05, 164.53 (C = C), 175.83, 188.89 (C = O); ir (KBr) 1690, 1680 cm^{-1}; EI-ms *m/z* 234 (M^+).

8. **13**: yield 0.20 g (32 %); mp 195 - 196 °C; ^{1}H-nmr (DMSO-d_6) δ 1.44 (3H, s, CH_3), 2.32 (1H, d, *J* = 17.49 Hz, C<u>H</u>H), 2.39 (3H, d, *J* = 4.62 Hz, CH_3), 2.68 (3H, s, CH_3), 2.73 (1H, d, *J* = 17.49 Hz, CH<u>H</u>), 2.82 (3H, s, CH_3), 4.64 (1H, s, NCHN), 5.30 (1H, br, NH), 6.90-7.49 (4H, m, ArH), 9.90 (1H, s, OH) ; ^{13}C-nmr (DMSO-d_6) δ 22.15, 25.57, 27.41, 34.82 (CH_3), 42.18 (CH_2), 47.52 (C), 88.73 (CH), 110.92, 118.09, 149.52, 155.02 (= C), 116.42, 119.52, 130.47, 131.12 (= CH) 165.21, 172.82 (C = O); ir (KBr) 3450, 1680, 1660 cm^{-1}; EI-ms *m/z* 315 (M^+).

9. A suspension of **12** (0.52 g, 2 mmol) in 28% ammonia solution (10 ml) was heated at 80 °C in a sealed tube for 2 h. The solid was filtered and recrystallized from EtOH to give **14**: yield 0.29 g (63 %); mp 218 - 219 °C; ^{1}H-nmr (DMSO-d_6) δ 1.34 (3H, s, CH_3), 2.14 (1H, d, *J* = 17.49 Hz, C<u>H</u>H), 2.40 (1H, d, *J* = 17.49 Hz, CH<u>H</u>), 3.02 (1H, d, *J* = 17.82 Hz, C<u>H</u>H), 3.37 (1H, d, *J* = 17.82 Hz, CH<u>H</u>), 5.30 (1H, s, CH), 6.90 - 6.97 (2H, m, Ar-H), 7.37 - 7.50 (1H, m, ArH), 8.69 (1H, s, NH), 13.26 (1H, br, OH); ^{13}C-nmr (DMSO-d_6) δ 24.74 (CH_3), 43.87, 48.08 (CH_2), 41.77 (C), 90.66 (CH), 116.29, 160.29 (= C), 116.58, 118.63, 130.37, 133.26 (= CH), 175.40, 177.48 (C = O and C = N); EI-ms *m/z* 230 (M^+).

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