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Synthesis of Hexahydro-1*H*-pyrrolo[1,2-c]imidazole Derivatives by Sequential Azomethine Ylide Cycloaddition and Urea Cyclization Reactions.

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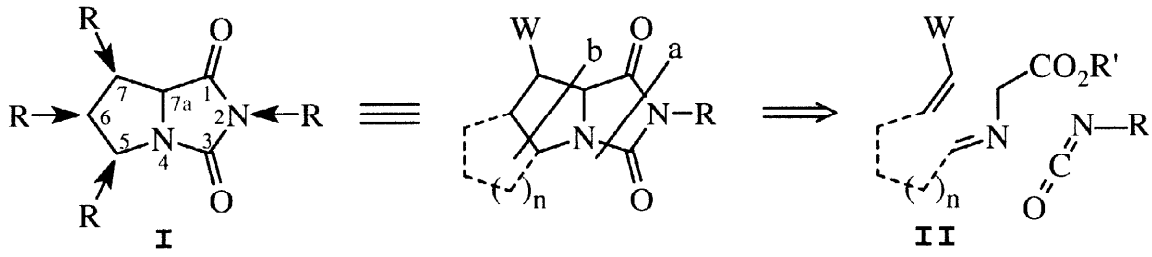
Abstract: *An efficient, diastereoselective route to 2,5,6,7-tetrasubstituted 1H-pyrrolo[1,2-c]imidazoles has been developed using azomethine ylide cycloaddition and urea cyclization reactions. Relative stereochemical assignments at the four contiguous pyrrolidine stereogenic centers were established by single-crystal X-ray analysis.*

As part of ongoing activities directed towards the preparation and biological evaluation of novel hydantoin-containing heterocycles,[2] we became intrigued by the scaffolding potential of the 1*H*-pyrrolo[1,2-c]imidazole ring system.[3] Herein we disclose our adaptation of azomethine ylide cycloaddition[4] and urea cyclization[5] protocols for the synthesis of 2,5,6,7-tetrasubstituted 1*H*-pyrrolo[1,2-c]imidazoles of generalized structure **I** (R→ = substitution points).



Our plan envisioned conversion of a proline-like intermediate (disconnection "a") to **I** by sequential urea formation and heterocyclization. The proline-like intermediate would be constructed (disconnection "b") from Schiff base **II** via an intramolecular azomethine ylide cycloaddition to an electron-deficient C,C-double bond. While numerous examples establish that tautomerization of an amino ester-derived Schiff base intermediate can deliver a Grigg-type azomethine ylide (-CH=N-CH_2-CO_2R' ⇌ -CH=N^+H-C^-H-CO_2R')[6] which efficiently adds to electron-deficient dipolarophiles in both bimolecular[7] and intramolecular[8] cycloadditions, we decided to explore the intramolecular variant where the azomethine ylide and dipolarophile are tethered.

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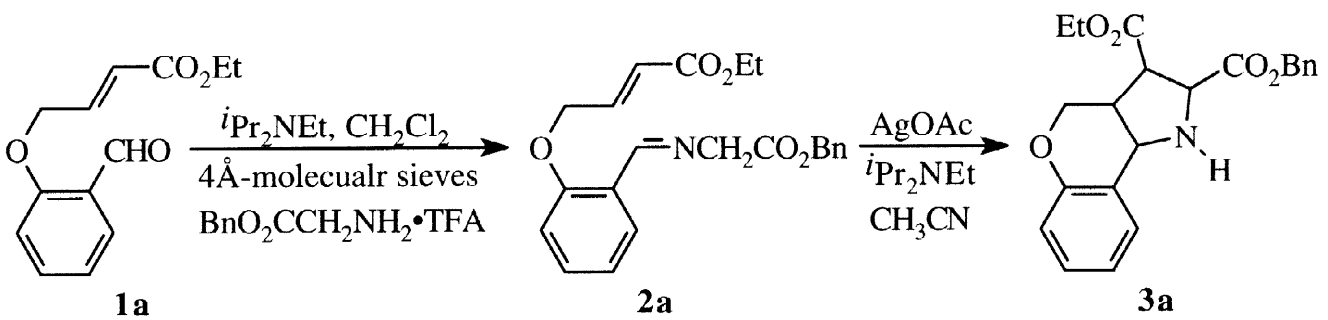
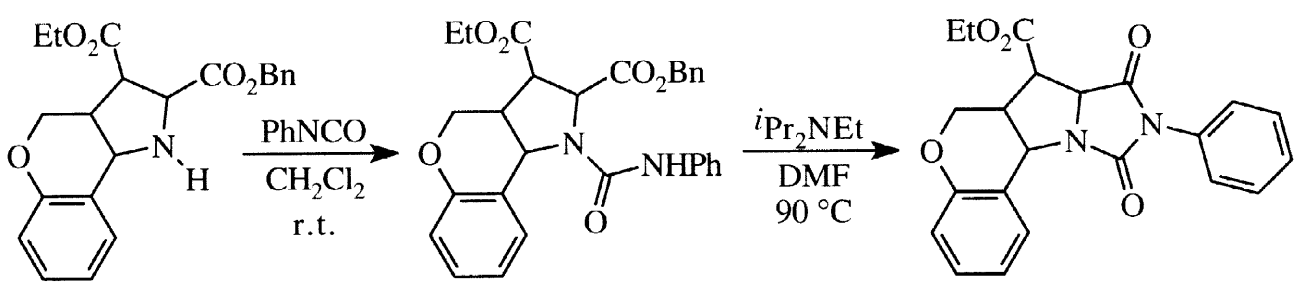
As with Grigg's pyrro[2,3-d]benzo[b]pyran studies,[9] we began by condensing glycine benzyl ester•TFA with salicylaldehyde derivative **1a**[10] to give benzylideneglycinate **2a** in 80% yield (≈4 mmol scale). Not surprisingly, only one diastereomeric isomer of **2a** (presumably the *E*-imine) was obtained as evidenced by its ^{1}H NMR spectrum; singlets were observed at 7.98 ppm (C<u>H</u>=N, 1 H) and 4.41 ppm (N–C<u>H</u>$_2$, 2 H). Treating the crude Schiff base at room temperature with silver acetate and *N,N*-diisopropylethylamine in acetonitrile (3 h) followed by an aqueous ammonium chloride quench, work-up, and flash chromatography (SiO_2, 1:4::EtOAc:hexanes) delivered the cycloadduct **3a** (≈4 mmol scale, 87% yield). Within the limits of ^{1}H NMR detection, proline derivative **3a** was obtained as a single isomer. Given that all four stereogenic centers occur on a 5-membered ring, we were reluctant to make coupling constant-based relative stereochemical assignments at this stage.



1a **2a** **3a**

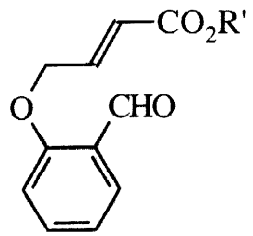
Treatment of proline derivative **3a** with phenyl isocyanate in dichloromethane at room temperature for 2 h afforded urea **4a** in 85% yield (≈4 mmol scale, mp 177-8°C). Hydantoin formation ensued upon heating (90°C) a DMF solution of **4a** with *N,N*-diisopropylethylamine. Hexahydro-1*H*-pyrrolo[1,2-c]imidazole **5a**[11] was obtained in 95% yield (≈2 mmol scale, mp 197-8°C) as a single isomer. The overall yield of **5a** from **1a** was excellent (56%).



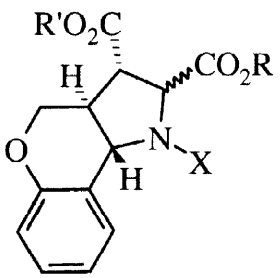
3a **4a** **5a**

Similar results were obtained when salicylaldehyde derivatives **1a** and **1b** were condensed with glycine ethyl ester•HCl. The subsequent cycloaddition reactions of

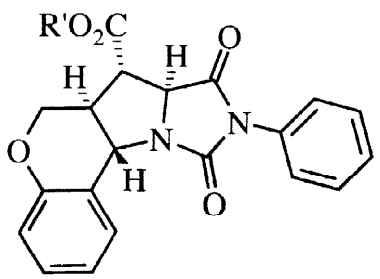
these two Schiff base intermediates were uneventful and delivered **3b** (83%) and **3c** (79%), respectively. However, we discovered that base-mediated cyclization reactions of the corresponding ureas (**4b** and **4c**, respectively) were somewhat sluggish, requiring 48 h for **4b**/**4c** → **5a**/**5b** whereas **4a** → **5a** occurred within 15 h. The yields of hexahydro-1*H*-pyrrolo[1,2-c]imidazoles **5a** (78% from **4b**) and **5b** (82% from **4c**) were lower (95% for **4a** → **5a**).



1a; R'= Et
1b; R'= Me

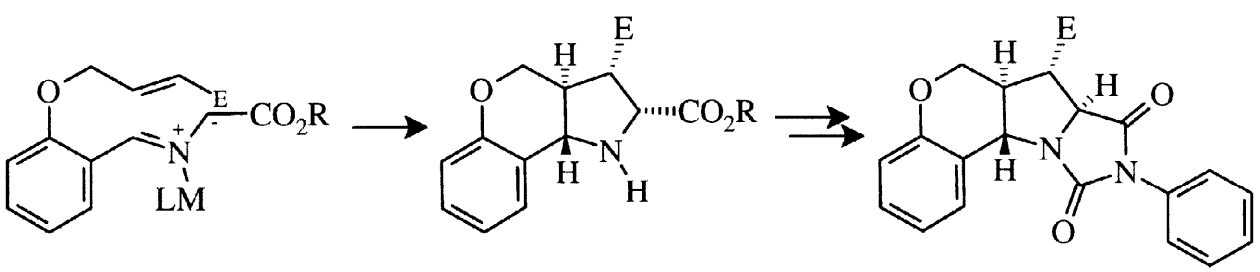


3a; R = Bn, R'= Et, X = H
4a; R = Bn, R'= Et, X = C(=O)NHPh
3b; R = Et, R'= Et, X = H
4b; R = Et, R'= Et, X = C(=O)NHPh
3c; R = Et, R'= Me, X = H
4c; R = Et, R'= Me, X = C(=O)NHPh



5a; R'= Et
5b; R'= Me

The relative stereochemical assignments at the four contiguous pyrrolidine stereogenic centers in **5** were established by single-crystal X-ray analysis (data submitted to the Cambridge Crystallographic Centre). It is interesting to note that both **5a** and **5b** are obtained as single isomers but that the stereochemistry at C7a (1*H*-pyrrolo[1,2-c]imidazole numbering) is not that expected from an *endo*-like transition-state. These results are consistent with the *endo*-like cycloaddition of a *trans,anti*-azomethine ylide followed by base-mediated C7a epimerization of the carboalkoxy moiety to the thermodynamically preferred *trans,anti,trans*-pyrrolidine arrangement found in **5**. This C7a epimerization may take place during the cycloaddition step (**2** → **3**) or during subsequent transformations (**3** → **4** or **4** → **5**); ^{1}H-NMR data for H-C7 and H-C7a in **3**, **4**, and **5** were inconclusive due to signal overlap.



Endo-like cycloaddition followed by epimerization.

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References and Notes:

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10 See reference 5b.

11 All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and EA. For **5a**: mp (hexanes/EtOAc) 197-8 °C, ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.48-6.75 (m, 9 H, Ar), 4.82 (d, 1 H, *J* = 10 Hz, NC<u>H</u>CO), 4.50 (m, 2 H, C<u>H</u>$_2$O), 4.33-4.19 (m, 3 H, ArC<u>H</u>N & OC<u>H</u>$_2$CH$_3$), 2.92 (m, 2 H), 1.25 (t, 3 H, *J* = 7 Hz, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.09, 168.47, 160.73, 152.56, 129.26, 129.18, 129.11, 128.43, 126.12, 125.71, 123.81, 120.72, 116.02, 68.03, 67.05, 62.17, 62.07, 47.46, 46.56, 14.16; IR (KBr) 1724, 1649, 1599 cm^{-1}. Anal. calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.69; H, 5.29; N, 7.13. For **5b**: mp (hexanes/EtOAc) 203-4 °C, ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.56-6.83 (m, 9 H, Ar), 4.90 (d, 1 H, *J* = 10 Hz, NC<u>H</u>CO), 4.60 (m, 2 H, C<u>H</u>$_2$O), 4.36 (t, 1 H, *J* = 10.5 Hz, C<u>H</u>CO$_2$), 3.85 (s, 3 H, OC<u>H</u>$_3$), 3.04 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.05, 168.99, 160.68, 152.54, 131.54, 129.29, 129.24, 129.20, 129.13, 128.45, 126.12, 125.68, 123.76, 120.73, 116.03, 67.99, 67.03, 62.06, 53.03, 47.47, 46.35; IR (KBr) 1722, 1677, 1600, 1203 cm^{-1}. Anal. calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.29; H, 4.71; N, 7.40.