The Synthesis of 5-Azaindole Derivatives *via* Mesoionic Oxazolium 5-Oxides.

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A synthesis of 5-azaindole derivatives is described. This synthetic approach involves the preparation of an appropriately substituted pyrrole derivative by a 1,3-dipolar cycloaddition reaction of dimethyl acetylenedicarboxylate with a mesoionic oxazolium 5-oxide. The pyrrole intermediate contains a protected β-aminoethyl substituent, and subsequent removal of the phthalimido protecting group results in cyclization to yield the corresponding 5-azaindole. This approach has been used for both acyclic and cyclic amino acid precursors of the 1,3-dipole which is ultimately used in the sequence.

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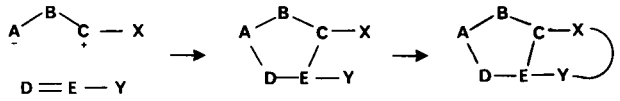
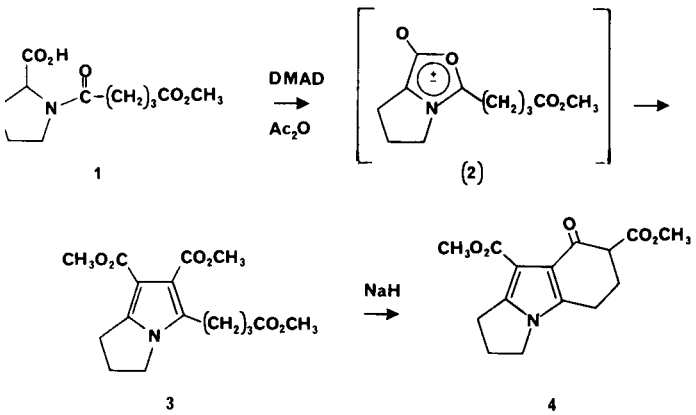
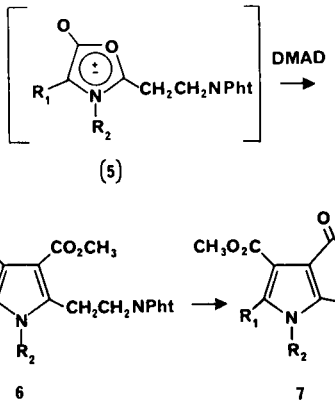
A general synthesis of fused heterocyclic systems, which involves a 1,3-dipolar cycloaddition followed by a subsequent ring closure reaction has been described by Lown and Landberg (1). In this approach, the selection of appropriate 1,3-dipoles and dipolarophiles requires that suitable functional groups (X and Y) are present in substituent side chains so that the ring closure step, which follows, can take place.



In previous studies, we had demonstrated that 5-keto-4,5,6,7-tetrahydroindoles could be prepared using this logic (2). For example, the 1,3-dipolar cycloaddition reaction of the mesoionic oxazolium 5-oxide, (**2**), with dimethyl acetylenedicarboxylate (DMAD) furnished the tetrahydropyrrolizine, **3**. Due to the high reactivity of the oxazolium 5-oxide system, (**2**) was generated *in situ* from its acyl amino acid precursor, **1**. (3) The ring closure step was achieved here by employing a Dieckmann condensation, thereby yielding the tetrahydroindole, **4**. Recently, Rebek has utilized this strategy in the synthesis of mitosene type compounds (4).



This paper will describe a second application of this general approach, namely, a 1,3-dipolar cycloaddition reaction of an appropriately sustituted oxazolium 5-oxide (**5**) to furnish a pyrrole intermediate, **6**, which is then capable of undergoing a second cyclization (lactamization) to form a 5-azaindole, **7**.



Two examples of this sequence are described here, and involve the use of acyclic and cyclic amino acid precursors to the mesoionic system. In the first case, an acyclic amino acid, *N*-methylglycine (sarcosine) was chosen as the starting material. Conversion of sarcosine to its benzyl ester *p*-toluenesulfonate (2), followed by acylation with β-phthalimidopropionyl chloride (5), and removal of the benzyl ester by hydrogenolysis resulted in the formation of the requisite acyl amino acid, **8**, in 36% overall yield. Treatment of **8** with DMAD in acetic anhydride provided the pyrrole diester, **9**, in 59% yield, *via* the mesoionic oxazolium 5-oxide.

This pyrrole derivative now contained a protected β-aminoethyl side chain on one of the α-positions of the pyrrole ring with an ester group at an adjacent β-position. When the amine protecting group was removed, lactamization occured without the isolation of the intermediate free amine. In this particular case, **9** was allowed to react

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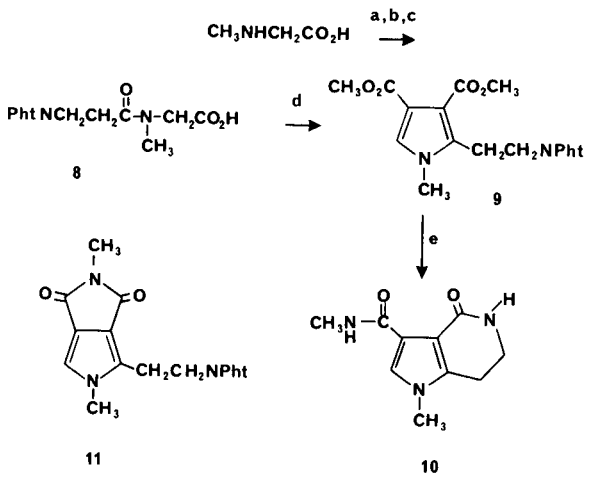
with excess aqueous methylamine using conditions previously described by Wolfe and Hasan. (6) These conditions resulted in deprotection, cyclization, and further aminolysis of the second ester group on the pyrrole ring to yield the azaindole amide, **10**, in 53% yield. Alternatively, **10** might have been formed from an intermediate imide (**11**) with subsequent removal of the phthalimido protecting group.



a, ϕCH_2OH/ TsOH ; b, $PhtNCH_2CH_2COCl/Et_3N$; c, H_2/Pd ; d, DMAD/Ac_2O
e, 40% CH_3NH_2/H_2O

The second example cited here involves the cyclic use of amino acid, 1,2,3,4-tetrahydroiosquinoline-3-carboxylic acid, **12**. We have previously described the use of such cyclic systems in the formation of novel ring-fused pyrroles. (7) Treatment of **12** with β-phthalimidopropionyl chloride in the presence of triethylamine afforded the acyl amino acid, **13**, as an impure gum. Rather than attempt to extensively purify this intermediate, it was found to be experimentally expedient to react this impure material with DMAD in acetic anhydride and isolate the crystalline pyrrole, **14**, (in a 33% overall yield from **12**). Deprotection of the amine in **14** with excess aqueous methylamine afforded the tetracyclic amide, **15**, while reaction of **14** with one equivalent of hydrazine hydrate in methanol furnished the corresponding ester, **16**, in 89% yield.

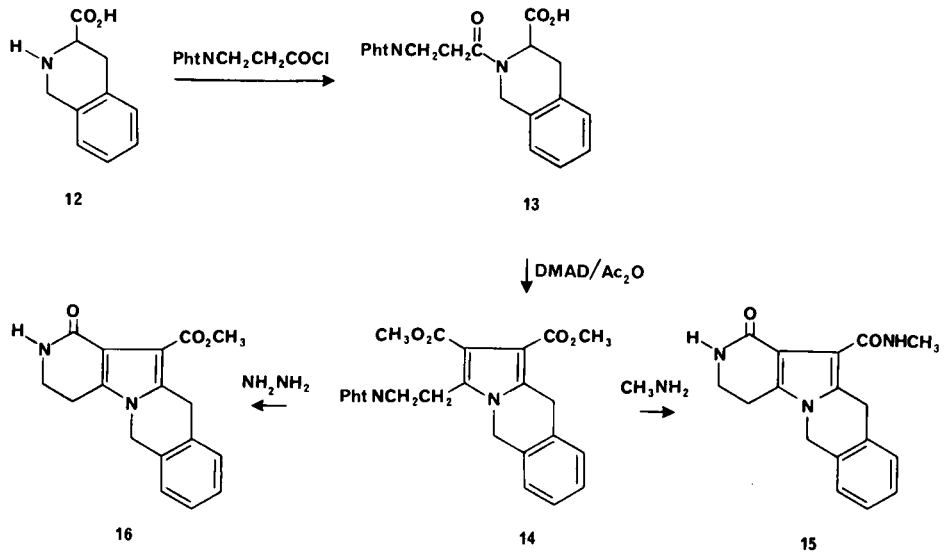
These studies demonstrate that the 1,3-dipolar cycloaddition reaction of mesoionic oxazolium 5-oxides is compatible with the presence of a protected (phthalimido) β-aminoethyl substituent, and that when this protecting group is subsequently removed, lactamization will occur. Furthermore, the scheme is applicable to both acyclic and cyclic amino acid precursors of the 1,3-dipole.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover Unimelt capillary apparatus which was calibrated against known standards. Infrared spectra were determined in chloroform solutions or potassium bromide discs on a Beckman IR-12 spectrometer; ^1H nmr spectra were obtained on a Varian Associates A-60 or T-60 spectrometer usually from deuteriochloroform solutions using tetramethylsilane as an internal standard. (The use of alternate solvents for ^1H nmr determinations will be clearly stated.) Mass spectra were run on an AEI MS-30 by Dr. Jeremy Hribar, Searle Laboratories, and microanalyses were performed by the Searle Laboratories Microanalytical Department.

N-[3-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-1-oxopropyl]-*N*-methylglycine Phenylmethyl Ester.

A suspension of *N*-methyl glycine benzyl ester *p*-toluenesulfonate (2) (105.3 g. 0.30 mole) in chloroform (750 ml.) was cooled to 10° and triethylamine (60.6 g., 0.60 mole) was added. The resultant light yellow solution was then cooled to 0° and a solution of β-phthalimidopropionyl chloride (70.1 g., 0.297 mole) in chloroform (300 ml.) was added in dropwise portions over a one hour period. The reaction mixture was stirred at room temperature overnight (18 hours), then washed with dilute (5%) hydrochloric acid (300 ml.), 2% sodium hydroxide solution (300 ml.), and water (300 ml.). The chloroform layer was dried over sodium sulfate, and evaporated to dryness *in vacuo*. A light-tan solid (104.1 g., 91%), m.p.



95-100.5°, was obtained. Recrystallization of this solid from ethanol furnished a colorless crystalline solid, m.p. 104-106°; ν C=O (chloroform): 1775, 1750, 1720, and 1660 cm^{-1}; δ 2.65-3.10 (CH_2CO, m); 3.07 (CH_3N, s); 3.85-4.20 (CH_2N, m); 4.18 (CH_2N, s); 5.17 ($OCH_2\phi$, s); 7.35 (5 aromatic H, s); 7.60-7.95 (4 aromatic H, A_2B_2).

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.26; H, 5.41; N, 7.60.

N-[3-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-1-oxopropyl]-*N*-methylglycine, **8**.

A solution of the aforementioned benzyl ester (72 g., 0.189 mole) in ethyl acetate (1200 ml.) and ethanol (200 ml.) was hydrogenated in a Parr Shaker apparatus at room temperature using 5% palladium on carbon (7.2 g.) as the catalyst. After three days, the mixture was filtered and the filtrate was evaporated to dryness. Trituration of the residue with anhydrous ether (500 ml.) furnished a colorless solid (27.95 g., 51%), m.p. 160-168°; ν OH (chloroform): 3700 and 3300-3000 (broad band) cm^{-1}; ν (C=O) (chloroform): 1775, 1725, and 1660 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.98; H, 4.87; N, 9.66. Found: C, 57.87; H, 5.10; N, 9.63.

1-Methyl 2-[2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]-1*H*-pyrrole-3,4-dicarboxylic Acid Dimethyl Ester, **9**.

A mixture consisting of **8** (5.80 g., 0.02 mole), dimethyl acetylenedicarboxylate (3.55 g., 0.025 mole), and acetic anhydride (100 ml.) was stirred and heated to 85° for 5 hours. The resultant orange solution was then cooled, evaporated to dryness, and the residue washed once with cyclohexane (100 ml.). Recrystallization of the residue from ethanol afforded light-tan crystals (4.40 g., 59%), m.p. 159-161°; ν C=O (chloroform): 1775 and 1720 cm^{-1}; δ 3.15 (CH_2, broad t); 3.73 and 3.75 (NCH_3 and OCH_3, s); 3.92 (CH_2, broad t); 7.13 (pyrrole H, s); 7.70-7.85 (4 aromatic H, m).

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.35; H, 4.85; N, 7.47.

N,1-Dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine 3-carboxamide, **10**.

A mixture of **9** (18.5 g., 0.05 mole) and 40% aqueous methylamine solution (350 ml.) was stirred at room temperature. Within the first 30 minutes, complete solution had occurred, but with continued stirring, a precipitate began to form. After 5 hours, the mixture was filtered and a light-gray solid was obtained. On concentrating the mother liquor to *ca* 175 ml., a second crop of solid was obtained. Recrystallization of the combined precipitate (7.4 g.) from 2-butanone afforded colorless needles (5.3 g., 51%), m.p. > 275°; ν N-H (potassium bromide): 3240 cm^{-1}; ν C=O (potassium bromide): 1650 cm^{-1}; M+ 207; δ (deuterium oxide): 2.67 (CH_2, t); 2.83 (NCH_3, s); 3.47 (OCH_3, s); 3.50 (CH_2, t); 7.10 (pyrrole H, s).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.04; H, 6.47; N, 20.45.

3-[2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]-5,10-dihydropyrrolo-[1,2-*b*]isoquinoline-1,2-dicarboxylic Acid Dimethyl Ester, **14**.

A suspension of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (64.10 g., 0.30 mole) in chloroform (750 ml.) was cooled to 10° and triethylamine (60.6 g., 0.60 mole) was added. A solution of β-phthalimidopropionyl chloride (71.2 g., 0.30 mole) in chloroform (350 ml.) was then added in dropwise portions over a 2 hour period. The reaction mixture was allowed to return to room temperature and was stirred overnight. After washing the mixture with 10% hydrochloric acid (500 ml.), the organic phase was dried (sodium sulfate) and the volatile components were removed by evaporation *in vacuo*. This left **13** as a light-brown gum (105.3 g.); ν OH (chloroform): 3400-3100 cm^{-1} (broad band); ν C=O (chloroform): 1780, 1720 and 1660 cm^{-1}.

This impure material (**13**, 104.0 g.) was dissolved in acetic anhydride (500 ml.) containing dimethyl actylenedicarboxylate (45.0 g., 0.32 mole) and the mixture was heated to 80° overnight. The orange solution was cooled, evaporated to dryness *in vacuo* and the residue was recrystallized from ethanol. Compound **14** was isolated as a light-yellow solid (42.40 g., 33% from **12**), m.p. 175-177.5°; ν C=O (chloroform): 1775 and 1720 cm^{-1}; δ 3.22 (CH_2, broad t); 3.77 (OCH_3, s); 3.82 (OCH_3, s); 3.95 (CH_2, broad t); 4.30 (CH_2, t, J = 1.5 Hz); 5.15 (CH_2, t, J = 1.5 Hz); 7.32 (4 aromatic H, s); 7.65-8.00 (4 aromatic H, A_2B_2.

Anal. Calcd. for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.05; H, 4.86; N, 6.03.

N-Methyl-7-Oxo-5,7,8,9,10,11,12-hexahydropyrido[3′,4′:4,5]pyrrolo-[1,2-*b*]isoquinoline-6-carboxamide, **15**.

A suspension of **14** (4.10 g., 0.0089 mole) in 40% aqueous methylamine (100 ml.) was stirred at room temperature overnight. The suspension, which now consisted of a colorless solid in place of the original light-yellow solid, was filtered and the solid that was collected (2.6 g.) was recrsytallized from ethanol. Compound **15** was obtained as a light-pink solid (1.60 g., 61%), m.p. > 260°; δ: 2.85-3.10 (CH_2, m); 2.93 (NCH_3, d, J = 5 Hz); 3.40-3.80 (CH_2, m); 3.88 (NH, s); 4.30-4.42 (CH, m); 4.60-4.75 (CH, m); 4.95 (CH_2, t, J = 2 Hz); 5.65-5.95 (NH, broad s); 7.20-7.45 (4 aromatic H, m).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.10; H, 5.94; N, 14.09.

Methyl 7-Oxo-5,6,7,8,9,10,11,12-hexahydropyrido[3′,4′:4,5]pyrrolo-[1,2-*b*]isoquinoline-6-carboxylate, **16**.

A mixture of **14** (45.85 g., 0.10 mole) in methanol (800 ml.) was treated with hydrazine hydrate (8.0 ml., 0.10 mole) and the reaction mixture was stirred and heated to reflux for 24 hours. The hot methanolic mixture was filtered and the filtrate was evaporated to dryness. Sodium carbonate solution (10%, 200 ml.) was added to the solid residue and the suspension that formed was heated on a steam bath for three hours. The mixture was filtered and the solid that was collected was washed with water (200 ml.), dried, and then recrystallized from ethanol to furnish **16** as a light-tan crystalline solid (26.55 g., 89%), m.p. 216-218°; ν N-H (chloroform): 3430 cm^{-1}; ν C=O (chloroform): 1710 and 1660 cm^{-1}; δ (DMSO-d_6): 2.65-3.00 (CH_2, broad t); 3.20-3.55 (CH_2, m); 3.70 (OCH_3, s); 4.17 (CH_2, s); 5.03 (CH_2, s); 7.00 (NH, broad s); 7.27 (4 aromatic H, s).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.87; H, 5.72; N, 9.42.

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