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PYRROLIZINE AND INDOLIZINE DERIVATIVES FROM 1,6-DIOXO-2,4-DIENE BY INTER- AND INTRAMOLECULAR RING CLOSURE

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Abstract – A variety of 1-amino-alkyl esters and nitriles react with 1,6-dioxo-2,4-diene to give pyrrole derivatives in good yield. Mild basic conditions facilitate the further intramoleular Dieckmann or Thorpe like condensation giving pyrrolizine and indolizine derivatives. These reactions provide simple, two step sequence to pyrrolizine and indolizine derivatives with control of product dictated by the base used for the condensation reaction.

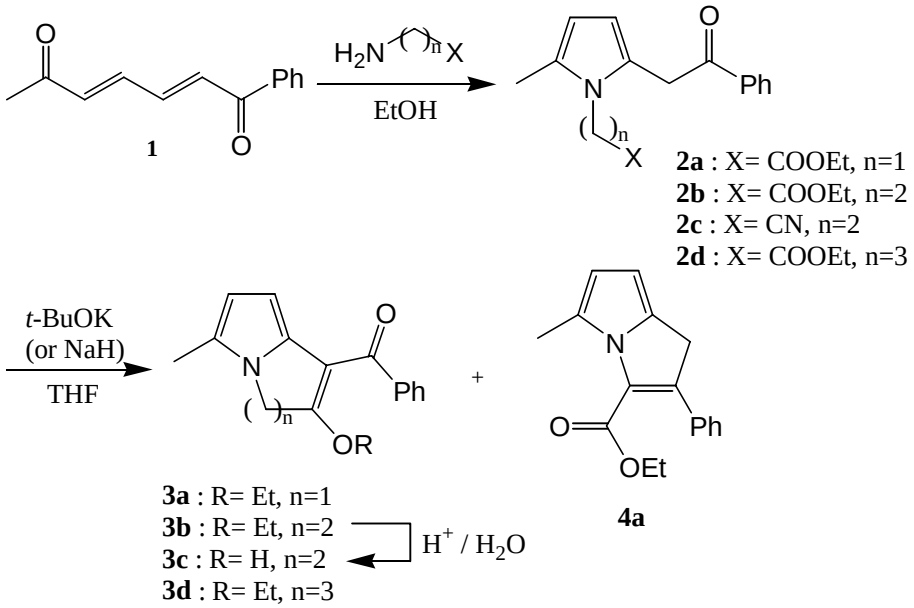
INTRODUCTION

The pyrrolizine and indolizine alkaloids constitute a very large family of natural product having a wide range of potent biological activities that are widely isolated from plants, insects, animals, oceanic lives and secondary metabolites of microbes. [1-3] In view of the intense interest in the pyrrolizine and indolizine alkaloids and the scarcity of natural samples, many new methodologies and strategies have been developed towards their synthesis.[4-12] We have recently reported the synthesis of 1,2,5-trisubstituted pyrrole derivatives from the reaction of 1,6-dioxo-2,4-diene with a variety of primary amines.[13] This prompt us to extend the synthetic potentiality of this method for the synthesis of pyrrolizine and

indolizine derivatives by synthesizing pyrrole derivatives with an appropriate N-substitution that can further undergo the second intramolecular condensation reaction to give fused[1,2-*a*]pyrroles.

RESULT AND DISCUSSIONS

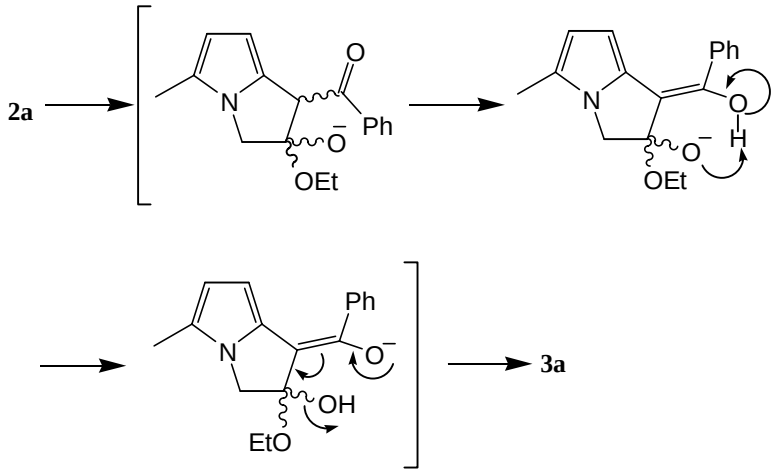
In our previous studies, [13] we have demonstrated that 1,6-dioxo-2,4-diene (**1**) react with ethyl glycinate to give pyrrole derivative (**2a**) in good yield, and this intermediate was used to test the practicality of the second intramolecular Dieckmann type cyclization[14] to synthesize pyrrolizine derivative. The treatment of **2a** with 1 equiv. of potassium butoxide (*tert*-BuOK) underwent cyclization to give **3a** in moderate yield (Scheme 1). It was found that under this reaction condition, the cyclization took place regio- and chemoselectively to give a single product. An interesting observation during the cyclization reaction was the expulsions of a hydroxy group rather than the usual ethoxy group to give the vinyl ether (**3a**), a diversion from the normal Dieckmann-type cyclization. The presence of an ethoxy group in **3a** was obvious by inspection of the ^{1}H NMR spectrum that showed a quartet and triplet at δ 4.30 (J = 4.6 Hz) and 1.32(J = 4.8 Hz) respectively. Apparently, the transient alkoxide anion formed was protonated readily under this reaction condition to form a hemiacetal, whereby in this case the hydroxy group became more susceptible to elimination as compared with the ethoxy group. The availability of a proton



Scheme 1. Synthesis of pyrrolizines and indolizines.

source for the instantaneous protonation of the transient alkoxide intermediate was attributed to the following sequence of events: (i) the enolization of the pyrrole-2-methylene carbonyl to the enol form, (ii) the transfer of a proton from the enol to the transient alkoxide anion *via* a six-member transitional state to form the requisite hemiacetal, and (iii) the expulsion of hydroxy group to give the vinyl ether (Scheme 2). In general, irrespectively of the base used, the cyclization reactions must proceed with the unusual elimination of the hydroxy group to give the vinyl ether.

We next study the judicious choice of base on the cyclization reaction. When **2a** was treated with 1 equiv. of sodium hydride (NaH) in THF, this afforded two products in a 1 : 2 ratio, one being the cyclized products (**3a**) (18%) and a new compound that was assigned **4a** (36%). Deprotonation by NaH can take placed at the two α-methylene ester groups in **2a** and these can undergo an intramolecular condensation to form **3a** and **4a**. The two regiosiomeric products (**3a**) and (**4a**) can be differentiated by their NMR spectra. The ^{13}C NMR spectrum with a chemical shift at δ 193 was in agreement for the presence of the ketogroup in **3a**. In contrast, the ^{13}C NMR spectrum of compound (**4a**) showed a typical ester chemical shift at δ 163. Furthermore, the ^{1}H NMR spectrum for the ring methylene protons in **3a** appears as a singlet at δ 5.19, consistent to that of pyrrolo[1,2-*a*]pyrrole reported,[11] and also indicative of the same regiochemistry at the double bond. On the other hand the ring methylene proton in **4a** showed germinal



Scheme 2. Formation of vinyl ether during cyclization reaction

coupling in the ^{1}H NMR spectrum. The 2D NMR (^{1}H and ^{13}C NMR) experiment for **3a** showed the

methylene proton resonance at δ_H 5.19 correlated with the carbon signal at δ_C 47.17; and for **4a** the methylene proton resonance at δ_H 5.18 and 4.91 correlated with the carbon signal at δ_C 47.31. The close proximity of the ^{13}C NMR for the methylene carbon in **3a** and **4a** can be accounted for from the fact that the ϒ–carbon for enolketone (**3a**) resonance at a higher field as compared to the ϒ-carbon of α,β-unsatutrated compound (**4a**), whereas conversely the α-carbon to nitrogen (**3a**) resonances at a lower field as compared to the α-carbon of a double bond (**4a**). These two opposing phenomenon accounts for the close proximity of the^{13}C NMR spectrum for **3a** and **4a**. Importantly, we have shown that the use of sodium hydride and potassium *tert*-butoxide as bases in the cyclization of **2a** occurred with different regiospecificity at the α-methylene ester groups. For the purpose of obtaining a single product, we therefore chose to use *tert*-BuOK for further studies.

The synthesis of the indolizine system requires the preparation of ethyl 1-pyrrolylpropionate (**2b)**. Treatment of **1** with β-alanine ethyl ester underwent the requisite intermoleuclar cylization smoothly to give 1-pyrrolepropionate (**2b)** in high yield. Indeed, the reaction of **2b** with 1 equivalent of *tert*-BuOK also underwent regioselective Dieckmann-type cyclization to give indolizidine derivative (**3b**) in moderate yield (60%). Importantly, this reaction also gave rise to the vinyl ether (**3b**), thus implying the generality for the elimination of the hydroxy group in this class of compounds. We next extend the scope of our study to the base catalyzed condensation of the enolate with an *N*-tethered cyano group, an intramolecular version of the Thrope-*type* cyclization. The reaction of **1** with 1-aminopropionitrile gave good yield of 1-pyrrolylpropionitrile (**2c**). The reaction of **2c** with 1 equivalent of *tert*-BuOK was found to undergo regioselective Thrope-like cyclization to give indolizidines ring system (**3c**) (in the enol form) in moderate yield (55%).

Attempt hydrolysis of the vinyl ether in **3b** to the enol (**3c**) was carried out. When **3b** was refluxed in water under acid catalysis (HCl) for a prolonged period, it was converted successfully to the enol (**3c**), and this rigorously proved their structures.

The scope of this new methodology can be extended for the synthesis of *N*-fused pyrrolo-ring system of larger ring size. The reaction of **1** with ethyl 4-aminobutanoate gave the pyrrole derivatives (**2d**) in

moderate yield (64%). Cyclization of **2d** with *tert*-BuOK gave **3d** in a lower yield (25%) The size of the ring being formed was found to have an influence on the yield of the cyclized product.

CONCLUSIONS

In conclusion, a rapid synthesis of pyrrolizine and indolizine ring system in two steps starting from 1,6-dioxo-2,4-diene has been achieved. This approach starts with the construction of an appropriately functionalized pyrrole ring from the reaction of 1,6-dioxo-2,4-diene with commercially available amines, followed by a subsequent intramolecular cyclization *via* Dieckmann or Thrope-like reaction. Moreover, the usual expulsion of an ethoxide to give the carbonyl group during Dieckmann type cyclization was not observed, but rather the hydroxy group was eliminated to give the vinyl ether.

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EXPERIMENTAL

Melting points reported were uncorrected. IR spectra were recorded by dissolving the compound in $CHCl_3$ and absorption maxima are given in cm^{-1}. ^1H NMR were recorded on a 200 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. MS spectral measurement and elemental analyses were carried out using the instrumentation center of NSC, Taiwan.

Compounds (**1**) and (**2a**)[13] were previously prepared in our laboratory.

General Procedure for the Preparation of Pyrrole Derivatives from 1,6-Dioxo-2,4-dienes and Amine. The appropriate amine hydrochloride salt (1.1 mmol) in ethanol (10 mL) was neutralized with sodium carbonate (116.6 mg, 1.1 mmol) at rt. A solution of the appropriate 1,6-dioxo-2,4-diene in ethanol (5 mL) was added and the reaction was stirred at rt for approximately 6 h (The reaction was monitor using TLC and terminated when other spots started to appear. Prolong reaction time led to a

lower yield of the product and many side products). The ethanol was first removed *in vacuo*, water added, and extracted with chloroform. The organic phase was washed with brine solution, dried (Na_2SO_4) and solvent removed on a rotatory evaporator. The crude product was purified by preparative thin layer chromatography (silica gel).

Ethyl 2-(2-Oxophenylethyl)-5-methyl(pyrrol-1-yl)propionate (**2b**). (EtOAc/ hexane, 1 : 5 as the eluent, yellow solid, mp 69-71^oC, 95%). IR ν_{max} 1723 and 1690 cm^{-1}. ^1H NMR δ 8.05 (d, J = 7.7 Hz, 2H), 7.57 (m, 1H), 7.50 (m, 2H), 5.89 (d, J = 3.4 Hz, 1H), 5.84 (d, J = 3.4 Hz, 1H), 4.29 (s, 2H), 4.14 (q, J = 6.7 Hz, 2H), 4.10 (t, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H). MS *m/z* 299. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.07; N, 4.68. Found: C, 72.50; H, 7.10; N, 4.70.

2-(2-Oxophenylethyl)-5-methyl(pyrrol-1-yl)propionitrile (**2c**). (EtOAc/ hexane, 1 : 5 as the eluent, yellow solid, mp 95-96^oC, 90%). IR ν_{max} 2015 and 1690 cm^{-1}. ^1H NMR δ 8.05 (d, J = 7.7 Hz, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 5.93 (d, J = 3.6 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 4.29 (s, 2H), 4.12 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H), 2.25 (s, 3H). MS *m/z* 252. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.15; H, 6.04; N, 11.11. Found: C, 76.18; H, 6.37; N, 11.07.

Ethyl 2-(2-Oxophenylethyl)-5-methyl(pyrrol-1-yl)butyrate (**2d**). (EtOAc/ hexane, 1 : 5 as the eluent, yellow solid, mp 82-83^oC, 64%). IR ν_{max} 1723 and 1690 cm^{-1}. ^1H NMR δ 8.04 (d, J = 7.8 Hz, 2H), 7.55 (m, 1H), 7.48 (m, 2H), 5.89 (d, J = 3.4 Hz, 1H), 5.82 (d, J = 3.4 Hz, 1H), 4.25 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.82 (t, J = 8.1 Hz, 2H), 2.32 (t, J = 6.9 Hz, 2H), 2.24 (s, 3H), 1.91 (m, 1H), 1.23 (t, J = 7.0Hz, 3H). MS *m/z* 313. Anal. Calcd for $C_{19}H_{23}NO_3$: 72.82; H, 7.40; N, 4.47. Found: C, 72.50; H, 7.25; N, 4.42.

General Procedure for the Preparation of Pyrrolizine and Indolizine Derivatives. To a solution of the appropriate *N*-tethered pyrrole (0.5 mmol) in THF (20 mL) was added *tert*-BuOK (56 mg, 0.5 mmol) at rt. The reaction was stirred for approximately 6 h. The THF was removed *in vacuo*, water added, extracted with chloroform, and extract was washed with brine, and dried (Na_2SO_4). The crude product was purified by preparative thin layer chromatography (silica gel).

The reaction with NaH was carried out using similar method whereby *tert*-BuOK is replaced with NaH.

(2-Ethoxy-5-methyl-3*H*-pyrrolizin-1-ly)-phenylmethanone (**3a**). (Ether/ hexane, 1 : 3 as the eluent, yellow liquid, 45%). IR ν_{max} 1670 cm^{-1}. ^{1}H NMR δ 7.98 (d, J = 7.3 Hz, 2H), 7.50 (m, 3H), 6.89 (d, J = 3.8 Hz, 1H), 6.09 (d, J = 3.8 Hz, 1H), 5.19 (s, 2H), 4.30 (q, J = 4.6 Hz, 2H), 2.28 (s, 3H), 1.32 (t, J = 4.8 Hz, 3H). ^{13}C NMR δ 193.11 (C), 182.90 (C), 168.31 (C), 142.08 (C), 134.23 (CH), 133.45 (C), 130.11 (CH), 128.71 (CH), 127.51 (C), 125.20 (CH), 110.93 (CH), 61.76 (CH_2), 47.17 (CH_2), 14.17 (CH_3), 12.17 (CH_3). MS *m/z* 267. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.68; H, 6.45; N, 5.26.

Ethyl 5-Methyl-2-phenyl-1*H*-pyrrolizine-3-carboxylate (**4a**). The cyclization was carried out using NaH. This give rise to a mixture of **3a** (18%) and **4a** (35%) (Ether/ hexane, 1 : 3 as the eluent). IR ν_{max} 1675 cm^{-1}. ^{1}H NMR δ 8.12 (d, J = 8.0 Hz, 2H), 7.52 (m, 1H), 7.41 (m, 2H), 7.17 (d, J = 4.0 Hz, 1H), 6.02 (d, J = 4.0 Hz, 1H), 5.18 (d, J = 10.5 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.14 (q, J = 2.4 Hz, 2H), 2.19 (s, 3H), 1.20 (t, J = 4.5 Hz, 3H). ^{13}C NMR δ 183.12 (C), 168.31 (C), 165.77 (C), 139.91 (C), 135.59 (C), 133.18 (CH), 129.96 (CH), 129.63 (CH), 128.76 (C), 120.85 (CH), 109.59 (CH), 61.45 (CH_2), 47.31 (CH_2), 13.99 (CH_3), 12.19 (CH_3). MS *m/z* 267. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.54; H, 6.42; N, 5.25.

(7-Ethoxy-3-methyl-5,6-dihydroindolizin-8-yl)phenylmethanone (**3b**). (Ether/ hexane, 1 : 3 as the eluent, yellow liquid, 60%). IR ν_{max} 1665 cm^{-1}. ^{1}H NMR δ 8.00 (d, J = 7.4 Hz, 2H), 7.60 (m, 1H), 7.50 (m, 2H), 6.85 (d, J = 4.2 Hz, 1H), 6.01 (d, J = 4.2 Hz, 1H), 4.60 (t, J = 7.2 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H). ^{13}C NMR δ 193.34 (C), 182.09 (C), 171.18 (C), 142.21 (C), 134.17 (C), 133.49 (CH), 129.99 (CH), 128.32 (CH), 126.88 (C), 125.61 (CH), 110.85 (CH), 60.77 (CH_2), 41.55 (CH_2), 35.26 (CH_2), 14.09 (CH_3), 12.35 (CH_3). MS *m/z* 281. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.58; H, 6.80; N, 4.86.

(7-Hydroxy-3-methyl-5,6-dihydroindolizin-8-yl)phenylmethanone (**3c**). (Ether/ hexane, 1 : 3 as the eluent, yellow liquid, 55%). IR ν_{max} 3457 and 1660 cm^{-1}. ^{1}H NMR δ 7.99 (d, J = 7.6, 2H), 7.62 (m, 1H), 7.52 (m, 2H), 6.89 (d, J = 4.4 Hz, 1H), 6.09 (d, J = 4.4 Hz, 1H), 4.64 (t, J = 4.2 Hz, 2H), 2.98 (t, J =

4.2 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR δ 192.88 (C), 182.41 (C), 142.41 (C), 134.35 (C), 133.24 (C), 129.96 (CH), 128.88 (CH), 126.91 (CH), 126.21 (C), 117.47 (CH), 111.56 (CH), 41.56 (CH_2), 19.46 (CH_2), 12.58 (CH_3). MS *m/z* 253. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.68; H, 5.93; N, 5.48.

{8-Ethoxy-3-methyl-5,6-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl}phenylmethanone (**3d**). (Ether/ hexane, 1 : 3 as the eluent, yellow liquid, 25%). IR ν_{max} 1668 cm^{-1}. ^{1}H NMR δ 8.00 (d, J = 7.2 Hz, 2H), 7.61 (m, 1H), 7.47 (m, 2H), 6.83 (d, J = 4.2 Hz, 1H), 6.02 (d, J = 4.2 Hz, 1H), 4.47 (t, J = 5.0 Hz, 2H), 4.16 (q, J = 5.0 Hz, 2H), 2.45 (t, J = 4.8 Hz, 2H), 2.35 (s, 3H), 2.12 (m, 2H), 1.26 (t, J = 5.0 Hz, 3H). ^{13}C NMR δ 193.39 (C), 182.24 (C), 172.89 (C), 142.04 (C), 134.12 (C), 133.60 (CH), 130.01 (CH), 128.69 (C), 126.89 (C), 125.40 (CH), 110.78 (CH), 60.55 (CH_2), 44.89 (CH_2), 31.04 (CH_2), 25.85 (CH_2), 14.22 (CH_3), 12.28 (CH_3). MS *m/z* 295. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.76; H, 7.17; N, 4.74. Found: C, 77.58; H, 7.13; N, 4.67.

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