SYNTHESIS OF NEW PHENYLPYRROLIZINONES *VIA* A MANNICH REACTION

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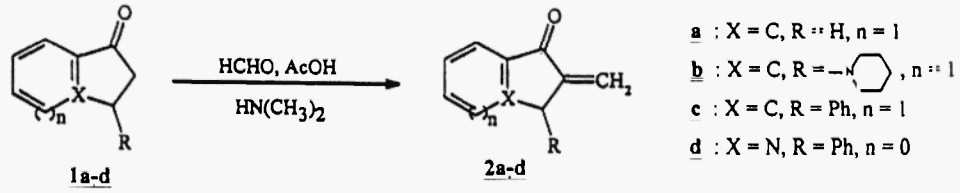
Abstract: The synthesis of 2-methylidene-3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one **2d** and subsequent Michael additions to this α,β-unsaturated ketone is described.

Introduction

In connection with our interest in chemical and biological properties of arylpyrrolizinones (1), we describe synthesis and reactivity of α,β-ethylenic ketone **2c-d** (Scheme 1). Gupta (2) and Muehlstaedt (3) described the synthesis of different 2-methylidenindan-1-ones **2a-b**. In a previous study we have synthesized the 2-methylidene-3-phenyl-indan-1-one **2c** *via* a Mannich reaction.

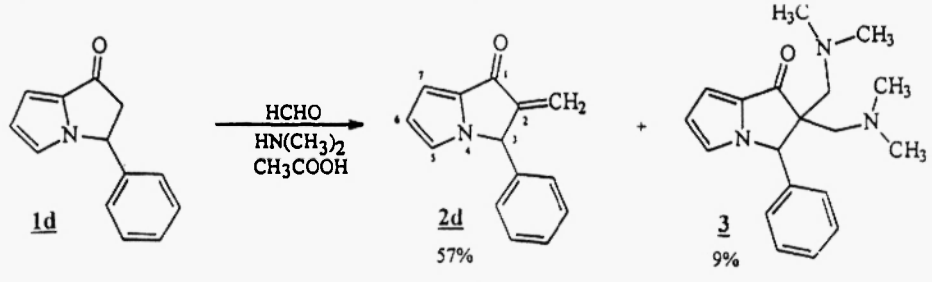


Scheme 1

The substrate 3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one **1d** (4) furnished 2-methylidene-3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one **2d**. We also investigated synthesis of 2-aminoalkyl and 2-alkoxy-derivatives. Reactions of various primary and secondary amines with this Michael-type substrate lead to the desired aminoalkyl derivatives. Finally, an original route was developed for the synthesis of alcohol addition products.

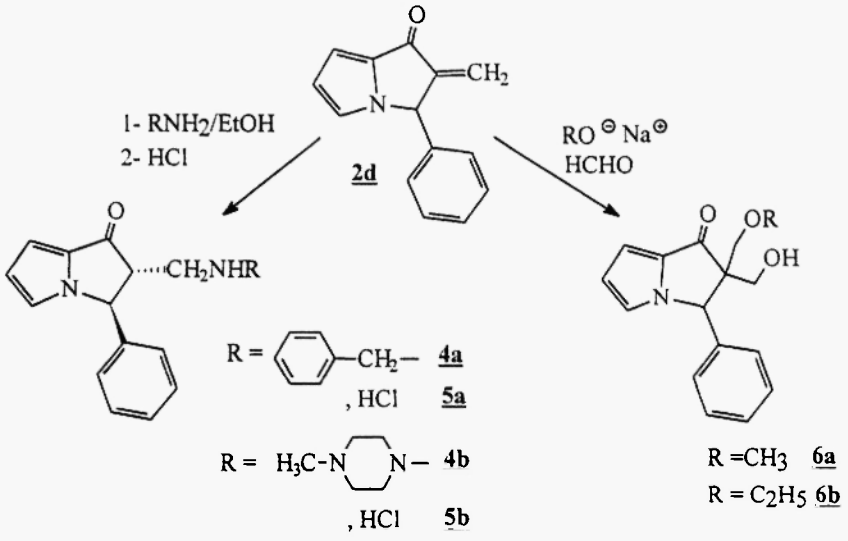
Results and discussion

The α,β-ethylenic ketone **2d** (5) was synthesized *via* a Mannich reaction. This compound **2d** was obtained together with the bis(aminoalkyl) product **3** (Scheme 2).



Scheme 2

1,4-Addition of primary and secondary amines such as benzylamine or *N*-methylpiperazine to **2d** proceeded in ethanol, leading to the expected **4a** and **4b** products with yields ranging from 85 to 96%(Scheme 3). These products were isolated as hydrochlorides **5a** and **5b**. Only the *trans* isomers were formed. The diastereoselectivity can be explained by steric factors.



Scheme 3

We have also developed an original and efficient one-pot synthesis of 2-alkoxypyrrolizinones **6a-b** starting from the α,β-unsaturated ketone **2d** (Scheme 3). The initial step is a 1,4-addition of an alcolate molecule to the unsaturated ketone **2d**, followed by a nucleophilic attack of the intermediate enolate on a molecule of formaldehyde.

Conclusion

We have designed the synthesis of the very useful synthon **2d**. It has already been used for the synthesis of various original compounds, whose biological properties are under investigation.

References

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(5) ^{1}H NMR were recorded on a JEOL JNM-LA 400 spectrophotometer at 40°C. Compound **2d** ($CDCl_3$) δ : 7.2 (m, 5H, Ph); 6.84 (dd, $^3J_{H\text{-}7\ H\text{-}6}$ = 3.7 Hz, $^4J_{H\text{-}7\ H\text{-}5}$ = 1.1 Hz, 1H, H-7); 6.77 (dd, $^3J_{H\text{-}5\ H\text{-}6}$ = 2.2 Hz, $^4J_{H\text{-}5\ H\text{-}7}$ = 1.1 Hz, 1H, H-5); 6.45 (dd, $^3J_{H\text{-}6\ H\text{-}7}$ = 3.7 Hz, $^3J_{H\text{-}6\ H\text{-}5}$ = 2.2 Hz, 1H, H-6); 6.15 (d, $^2J_{CH2\ CH2}$ = 1.3 Hz, 1H, CH_2); 5.81 (s, 1H, H-3); 5.22 (d, $^2J_{CH2\ CH2}$ = 1.3 Hz, 1H, CH_2).

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