

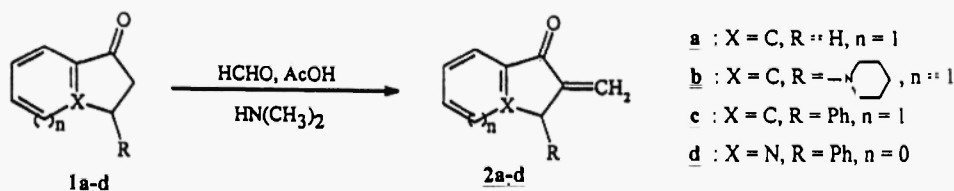
SYNTHESIS OF NEW PHENYLPYRROLIZINONES VIA A MANNICH REACTION

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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.

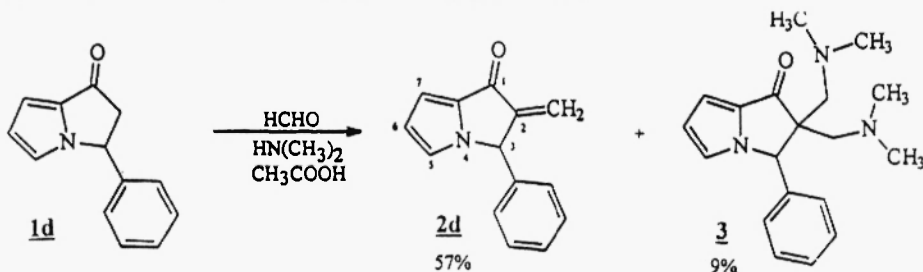


Scheme 1

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.

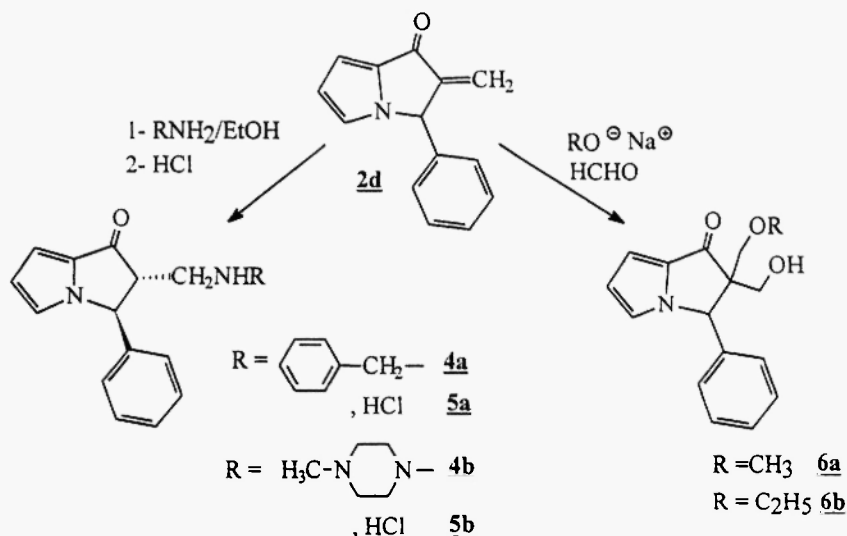
Results and discussion

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 alkolate 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) ^1H 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, $^3J_{\text{H-7 H-6}} = 3.7$ Hz, $^4J_{\text{H-7 H-5}} = 1.1$ Hz, 1H, H-7); 6.77 (dd, $^3J_{\text{H-5 H-6}} = 2.2$ Hz, $^4J_{\text{H-5 H-7}} = 1.1$ Hz, 1H, H-5); 6.45 (dd, $^3J_{\text{H-6 H-7}} = 3.7$ Hz, $^3J_{\text{H-6 H-5}} = 2.2$ Hz, 1H, H-6); 6.15 (d, $^2J_{\text{CH}_2 \text{CH}_2} = 1.3$ Hz, 1H, CH_2); 5.81 (s, 1H, H-3); 5.22 (d, $^2J_{\text{CH}_2 \text{CH}_2} = 1.3$ Hz, 1H, CH_2).

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