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Bismuth nitrate-catalyzed novel synthesis of pyrrole-substituted indolinones

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Abstract—Synthesis of indole derivatives bound to pyrroles is a challenge. In this letter, an expeditious synthesis of these types of molecules starting from isatins and 4-hydroxy proline via a bismuth nitrate-catalyzed reaction is described.

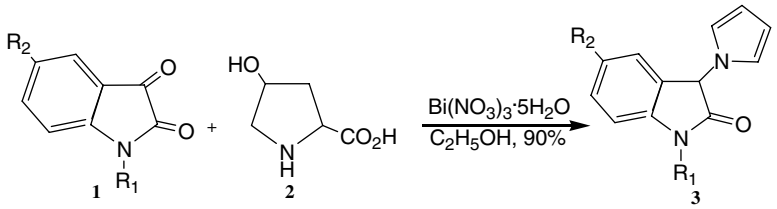
1. Introduction

Substituted pyrroles and indoles are important classes of heterocyclic compounds having different medicinal activities.[1] Many methods for the synthesis of substituted pyrroles are described in the literature.[2] Conjugate addition reactions have been used for the synthesis of polysubstituted pyrroles.[3] These compounds can also be prepared from transition metal intermediates,[4] reductive couplings,[5] aza-Wittig reactions,[6] and other multistep operations.[7] Apart from these new developments, the Paal-Knorr[8] reaction remains one of the most attractive methods for the synthesis of pyrroles. A clay-mediated[9] organic reaction and microwave irradiation method[10] have been used for the construction of pyrroles under Paal-Knorr conditions. In this paper, we describe a simple method for the synthesis of substituted pyrroles attached to indole skeleton by bismuth nitrate-catalyzed reaction.

We[11] performed a structure-activity relationship study of various polyaromatic derivatives easily prepared from their corresponding amines in a projected route toward the development of novel anticancer agents. It was reported that modification of the heterocyclic ring is crucial in determining the biological activity of these derivatives. Based on the biological activities of these derivatives, we became interested in the synthesis of pyrroles bound to the aromatic system of different structures.

Isatin derivatives are commercially available. Reaction of 4-hydroxy proline (**2**) with isatin (**1**) in the presence of catalytic amount of bismuth nitrate in tetrahydrofuran produced (**3**) in low yield (20%). The progress of the reaction was also slow. A dramatic change was observed when the reaction was performed in ethanol (Scheme 1).

Under similar conditions and in ethanol, the reaction was completed within 30 min and the products were



a: R_1=R_2=H; b: R_1=H; R_2=CH_3; c: R_1=CH_3, R_2=H; d: R_1=H, R_2=OCF_3

Scheme 1.

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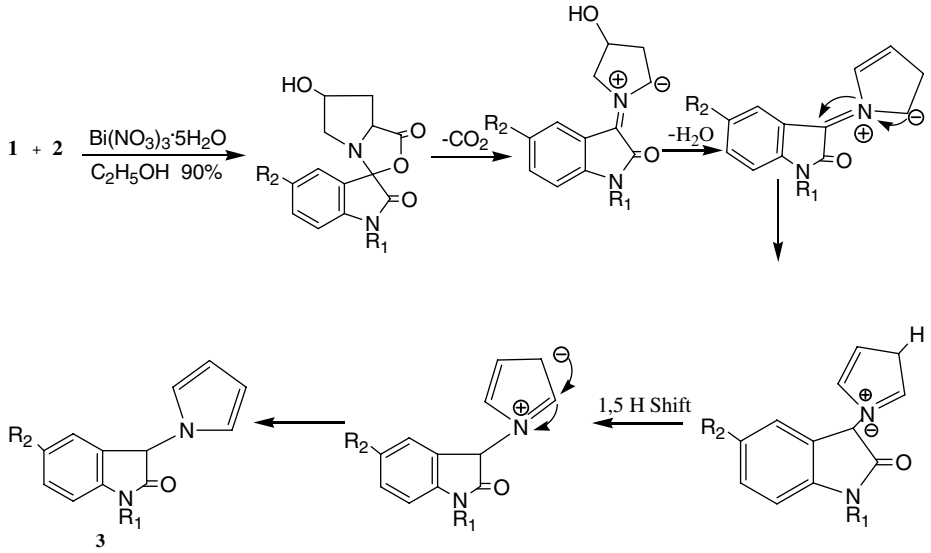

Scheme 2.

obtained in 90% yield. The reaction did not proceed without bismuth nitrate. The structure of the product has been confirmed by NMR spectra. The singlet at δ 8.15 indicates the presence of NH-group. The presence of 8-aromatic hydrogens is also established from the NMR spectra. The peaks at δ 6.9 and 6.7 indicate the presence of pyrrole moiety. The characteristic peak at δ 5.5 confirms the presence of methine hydrogen connected to a pyrrole and electron withdrawing amide carbonyl group.

The reaction mechanism of this procedure is not established yet. However, based on the structure, a most probable mechanism may be postulated. The amino and the carboxy group in (**2**) are ideally located to undergo a condensation reaction to the highly reactive keto group of the indolinone moiety in the presence of bismuth nitrate.[12] At high temperature, this intermediate can form azomethine ylide via decarboxylation. Mild acid-induced dehydration at reflux temperature may then yield a conjugated product. A 1,5-proton shift may then occur to afford the more stable zwitterion intermediate, which can easily transform to the most stable product to gain aromatic character.[13] This indicates the capability of the bismuth nitrate as an activator in catalyzing several spontaneous processes (Scheme 2). Bismuth chloride also produced the product in low yield (50%). Bismuth oxide failed to produce a product. Since bismuth salts are inexpensive and environmentally friendly, this simple method for the preparation of heterocyclic compound using a single step is very important.[14]

We believe that our method can be used with other activated keto-compounds. Studies in this area will be reported from our laboratory in due course.

2. Experimental

To isatin (1 mmol), hydroxyproline (1 mmol), and bismuth nitrate pentahydrate (20 mg) was added ethanol (2 mL), and the suspension was refluxed for 30 min. The reaction was diluted with water (10 mL) and extracted with dichloromethane (25 mL), washed with saturated sodium bicarbonate (5 mL) and dried with sodium sulfate. Pure product was isolated through column chromatography (ethyl acetate/hexane = 1:4).

Compound **1a**: mp: 140 °C, IR (KBr) (υ_{max}, cm^{-1}): 3295, 3190, 1711, 1614, 1482; ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 6.51 (1H, s, CH), 6.25 (2H, br s, CH), 6.70 (2H, br s, CH), 6.85–7.34 (4H, m, ArH), 8.87 (1H, br s, NH); compound **1b**: mp: 161 °C, IR (KBr) (υ_{max}, cm^{-1}): 3200, 1708, 1619, 1487; ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 4.93 (3H, s, CH_3), 5.58 (1H, s, CH), 6.25 (2H, t, $J = 1.96$ Hz, CH), 6.71 (2H, t, $J = 2.01$ Hz, CH), 6.79–7.31 (4H, m, ArH), 9.09 (1H, br s, NH); compound **1c**: mp: 135 °C, IR (KBr) (υ_{max}, cm^{-1}): 1712, 1606, 1486; ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.23 (3H, s, CH_3), 5.48 (1H, s, CH), 6.22 (2H, br s, CH), 6.68 (2H, br s, CH), 6.89–7.42 (4H, m, ArH).

Acknowledgements

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