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Synthesis of new indolylpyrrole derivatives via a four-component domino reaction between arylglyoxals, acetylacetone, indole and aliphatic amines in aqueous media

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ABSTRACT

A novel synthesis of indolylpyrrole derivatives is described by a four-component domino reaction between arylglyoxals, acetylacetone, indole and aliphatic amines in water as solvent at 60 °C without using any catalyst or promoter. The FT-IR, ^{1}H NMR, ^{13}C NMR spectral and elemental analysis confirm the structures of the products.

Introduction

Pyrrole ring is one of the most important chemical subunits which is widely found in the structure of many therapeutically active compounds [1]. Pyrrole ring also exists in the structure of a wide variety of natural products such as vitamin B12, pigments like bilirubine and biliverdine and the porphyrine of heme [2]. Access to pyrrole derivatives using multi-component reactions is particularly attractive from the synthetic efficiency and environmentally point of views [3].

Indole derivatives having a heterocyclic ring at C3 have recently attracted much attention from synthetic point of view for their presence at natural products such as martefagin A6 [4] and alkaloids, which are potent inhibitors of HIV-1 integrase [5–9]. Some indole derivatives containing a pyrrole substituent at their C3 position have been recently synthesized and proven to possess interesting biological activities [10–12].

Multi-component domino reactions (MDRs), particularly those performed in water have attracted much attraction from chemists for their synthetic power point of view and green characteristics. These reactions have been successfully utilized for synthesis of a wide variety of chemically and biologically important compounds [13].

Arylglyoxals have gained much attention for synthesis of heterocycles using multi-component reactions. The application of arylglyoxals for preparation of a wide range of three- to six-membered heterocycles has been recently reviewed [14]. In continuation of our previous studies on the application of arylglyoxals in synthesis of heterocyclic compounds [15–17], we report herein a green MDR approach for synthesis of some indole derivatives having a pyrrole functionality at their 3-position. Thus the four-component domino reaction between arylglyoxals, acetylacetone, indole and aliphatic amines in water as solvent in the absence of any catalyst or promoter afforded indole derivatives in excellent yields (Scheme 1).

At the beginning of our investigation, we carried out the reaction between 4-chlorophenylglyoxal monohydrate, acetylacetone, indole and benzylamine in water as solvent. After stirring for 1 h at 60 °C, the analysis of the reaction mixture by TLC showed the presence of only one product. Filtering the reaction mixture and simple washing of the product by diethyl ether afforded the indolylpyrrole derivative **5a** in nearly quantitative yield. The NMR, IR spectral, and combustion analytical data deduced the structure of product. The ^{1}H NMR spectrum of compound **5a** showed three sharp single signals at 1.7, 2.4 and 5.1 ppm which are related to two methyl and one methylene groups, respectively. The aromatic protons resonated between 6.8 and 7.3 ppm. The NH proton was observed at 10.9 ppm. The ^{13}C NMR spectrum of **5a** exhibited twenty-four distinct signals in agreement with the proposed structure, the carbonyl carbon resonated at 196.8 ppm. The proposed structure was also confirmed by the IR spectrum of **5a,** which

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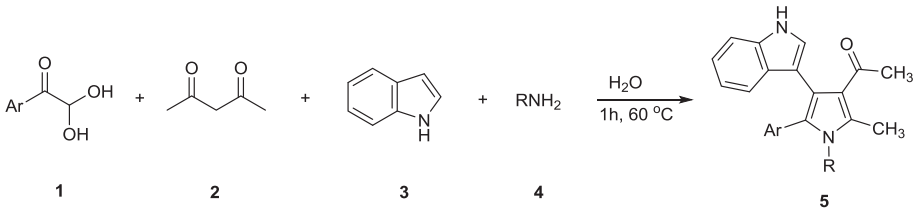
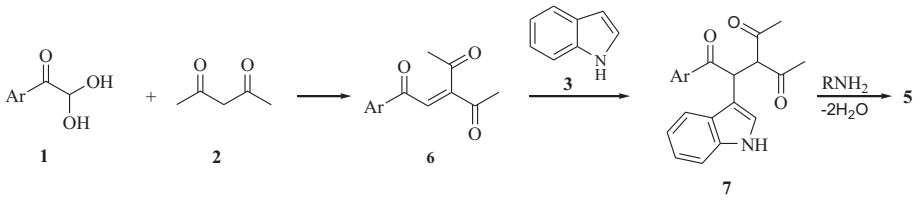
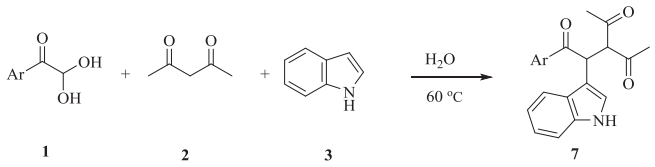


Scheme 1. Synthesis of indolylpyrrole derivatives by reaction between arylglyoxals, acetylacetone, indole and aliphatic amines.



Scheme 2. The possible reaction mechanism for synthesis of indolylpyrroles **5a-i**.



Scheme 3. Synthesis of 3-acetyl-1-aryl-2-(1H-indol-3-yl)pentane-1,4-dione **7.**

showed the absorption bands at 1635 cm^{-1} for carbonyl group and at 3359 cm^{-1} for NH bond.

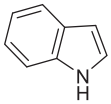
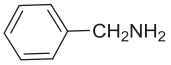
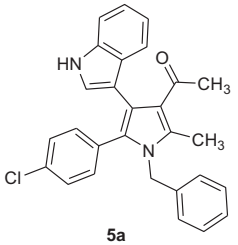
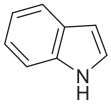
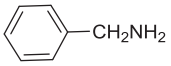
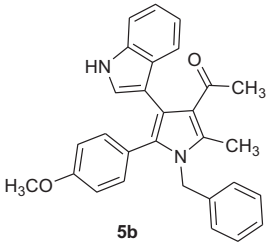
To define the scope and generality of the reaction, a series of substituted arylglyoxals and aliphatic amines were examined. To our delight, in each case the desired indolylpyrrole derivative was obtained in excellent yield. This method has some advantages, as the starting materials are simply available, the reaction conditions are simply accessible and the products were isolated in high yields by simple filtration and washing with diethyl ether.

When the aromatic amines such as aniline or 4-methoxyaniline were used as the amine component, complex mixtures were obtained and no pure product could be isolated. Similarly, no product could be isolated when cyclic diketones like dimedone or ketoesters such as ethyl acetoacetate were used instead of acetylacetone.

A plausible mechanism for the formation of compounds **5** is shown in Scheme 2. The Knovenagel condensation of arylglyoxal and acetylacetone afforded enone **6** which under the Michael addition of indole converted to trione derivative **7**. The reaction of benzyl amine with intermediate **7**, known as Paal-Knorr pyrrole synthesis, afforded the indolylpyrrole derivative **5**.

Continuing the process of our study, we decided to investigate the possibility of using the reaction conditions for preparing and isolating intermediate **7**. Thus, the reaction of arylglyoxals, acetylacetone and indole was carried out in water at 60 °C in the absence of any catalyst or promoter. As shown in Scheme 3 and Table 2 the indolyltrione derivatives **7a-g** were obtained in excellent yields. As shown in Table 1 the reaction is compatible

Table 1
Synthesis of indolylpyrrole derivatives **(5a- i)** by reaction of arylglyoxals, acetylacetone, indole and aliphatic amines.

Entry	Ar	Indole	RNH_2	Product	Yield%
1	4-ClC_6H_4			 **5a**	98
2	4-$OCH_3C_6H_4$			 **5b**	93

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