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Catalyst-free synthesis of functionalized dihydro-2-oxypyrroles by the reaction of enaminones and *N*,*N*′-bis(phenylmethylidene) phenylmethane

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ABSTRACT

A catalyst-free and convenient approach for the preparation of substituted dihydro-2-oxypyrrole is described. This three-component reaction between primary amines, dialkyl acetylenedicarboxylate, and *N*,*N*′-bis(phenylmethylidene)phenylmethane proceeds in MeOH under reflux conditions in good to excellent yields.

1. Introduction

Substituted pyrrole derivatives are very important heterocycles. Many biologically active compounds, potent pharmaceuticals, and natural products contain the pyrrole structural motif [1]. Among the pyrrole derivatives, dihydro-2-oxoypyrroles show such versatility and they are important substructures in a variety of pharmacy, including products active against viral infections (HIV [2,3], influenza [4] cytomegalovirus [5]), anticancer agents [6] and products active against microbiological diseases [7–9] (bacterial or fungal). Furthermore, dihydro-2-oxoy-pyrrole derivatives have been used as PI-091 [10], which is a novel platelet aggregation inhibitor, and EBPC, which is a highly specific aldose reductase inhibitor [11], as shown in Fig. 1. Besides, the well-known 5-alkyl-2-oxopyrroles [12], first described in 1890 by Emery [13], relatively little attention was given toward 5-aryl-2-oxopyrrole derivatives in the open literature.

As part of our continuing effort into design of new routes for the preparation of biologically active compounds using *N*,*N*′-bis(phenylmethylidene)phenylmethane and application of this reagent in the synthesis of numerous organic compounds, especially aza-cyclic compounds [14], herein, we describe a simple, one-pot, three-component synthesis of 5-phenyl-2-oxopyrrole derivatives **3** by the three-component reaction of *N*,*N*′-bis(phenylmethylidene)phenylmethane, primary amines **1** and dialkyl acetylenedicarboxylate **2** (Scheme 1).

2. Results and discussion

Firstly, an easily available starting material *N*,*N*′-bis (phenylmethylidene)phenylmethane was reacted with benzylamine **1a** and diethyl acetylenedicarboxylate **2a** in MeOH under refluxing temperature for 6 h. The 5-phenyl-2-oxopyrrole **3a** was successfully obtained in 85%

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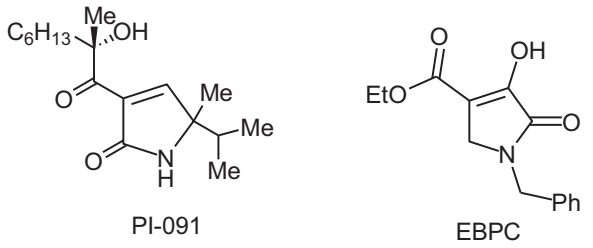
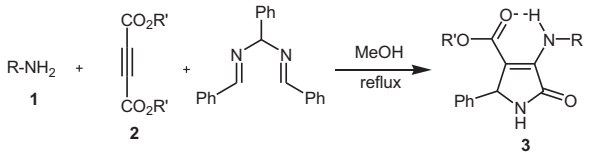


Fig. 1. Biologically active compounds having dihydro-2-oxypyrrole unit.



Scheme 1. Synthesis of 5-phenyl-2-oxopyrrole derivatives.

yield (Scheme 1). Different types of amines, such as benzyl and aliphatic amines were used to investigate the scope and limitation of the reaction.

A variety of benzylamines with substitutents Me, Cl at *para* position and aliphatic amines, such as propyl- and isobutylamine, were examined with DMAD and *N*,*N*′-bis(phenylmethylidene)phenylmethane under the same conditions and the corresponding dihydro-2-oxypyrrole derivatives **3a–i** were obtained in good yields as shown in Table 1.

Dialkyl acetylenedicarboxylate also showed very high reactivity in this reaction under the same conditions. All new compounds **3a–i** were fully characterized on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The structure of product **3h** was further confirmed by X-ray crystallographic analysis (Fig. 2). The mass spectrum of **3a** displayed the molecular ion peak at the appropriate *m/z* value. The IR spectrum of compound **3a** showed two absorption bands due to the NH stretching

Table 1
5-Phenyl-2-oxopyrrole derivatives were prepared by the mentioned reaction.

Entry	Product	R	R′	Time (h)	Yield (%)
1	**3a**	Bn	Et	6	85
2	**3b**	4-Cl-Bn	Me	6	81
3	**3c**	4-Cl-Bn	Et	7	74
4	**3d**	4-Me-Bn	Me	5	77
5	**3e**	4-Me-Bn	Et	6	82
6	**3f**	Propyl	Me	6	74
7	**3g**	Propyl	Et	5	75
8	**3h**	Isobutyl	Me	5	80
9	**3i**	Isobutyl	Et	5	79

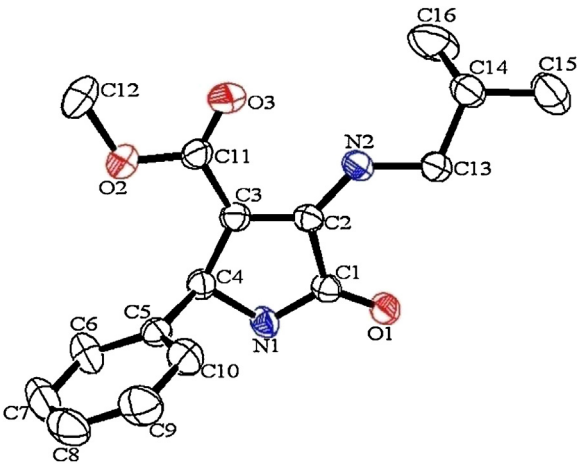
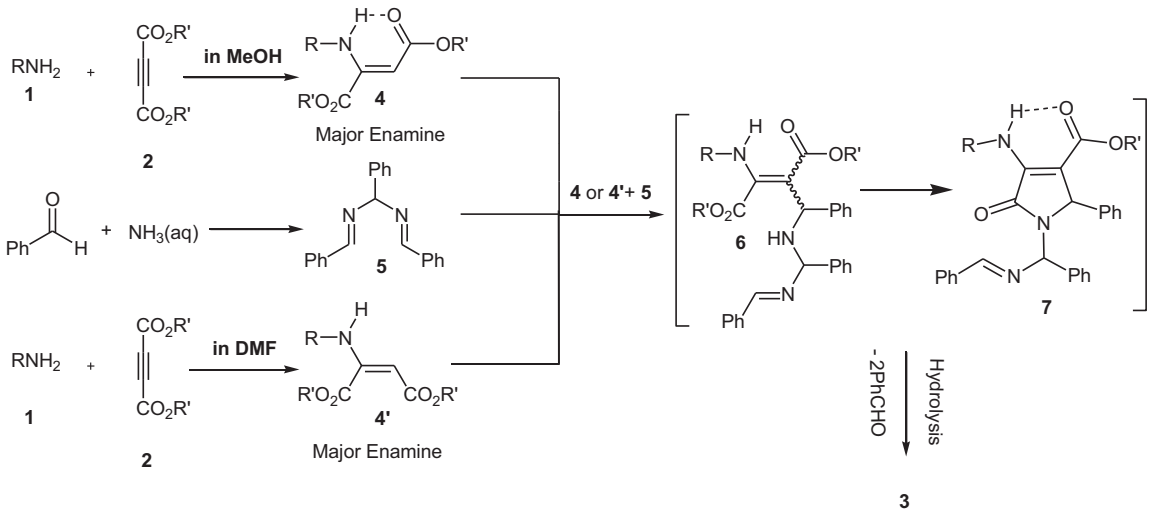


Fig. 2. X-ray crystal structure of compound **3h**.

frequency at 3338 and 3192 cm^{-1}, respectively. Absorption bands at 1705 and 1666 cm^{-1} are due to the COOEt and CONH groups, respectively. The ^{1}H NMR spectrum of **3a** showed a triplet for the CH_3 group (δ = 1.02 ppm, $^{3}J_{HH}$ = 7.1 Hz), three singlets for the two NH and CH groups



Scheme 2. Probing the mechanism for the formation of title compounds.