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A one-pot three-component approach to synthesis of novel dihydroxyoxoindeno[1,2-*b*]pyrrole derivatives

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ABSTRACT

A new class of 2-arylamino-dihydroxyindenopyrroles were prepared by the one-pot multicomponent reaction of ninhydrin, *N*-methyl-1-(methylthio)-2-nitroethenamine and aromatic amines in EtOH at room temperature. The advantages of this procedure are short reaction times, good to high yields, easy separation of products and good functional group tolerance.

Introduction

Pyrrolines, especially the fused pyrrolines, are one of the most important categories of heterocyclic compounds that are found in the skeleton of many pharmaceutical molecules.[1] For example, drugs including Pemetrexed, Moxifloxacin and Zopiclone, which exhibit anti-tumor, anti-bacterial or analgesic activities, contain the fused multicyclic pyrrolines.[2–4]

Indanones have also been found in natural products, drugs, pesticides and other biologically active molecules, exhibiting anti-tumor, anti-hypertension, antiallergy and other biological activity.[5] The importance of considering both these two frameworks, combining them with a facile synthesis would rapidly lead to excellent structures that potentially represent diverse or increased activities. Polyhydroxylated indenopyrroles are also interesting heterocycles that act as powerful inhibitors of glycosidases,[6] potassium channel openers,[7] DNA intercalators[8] and estrogenic agents.[9]

Development of synthetic method of indeno[1,2-*b*]pyrrole from easily accessible reactants is greatly required. In the last decade, the synthesis of dihydroxyoxoindeno[1,2-*b*]pyrrole derivatives has been carried out by the reaction of ninhydrin with various enamines (Fig. 1). Based on these procedures, heterocyclic ketene aminals **A**, **B** have been synthesized separately from the reaction of diamines with 3,3-bis(methylthio)-1-arylpropenone[10] or 1,1-bis(methylthio)-2-nitroethene[11] and then the reaction with ninhydrin has been examined. Reaction of 2-nitromethylenepyrrolidine **C** with ninhydrin also has been reported.[12] The reaction of ninhydrin with enaminones **D**, **E**, **F** that made of amine derivatives of 1,3-dicarbonyl compounds,[13] dialkyl acetylenedicarboxylates[14] and alkyl propiolates[15,16] has led to the corresponding indeno[1,2-*b*]pyrrole. Synthesis of tetracyclic quinazolinone derivatives *via* a multicomponent reaction from isatoic anhydride and amine with ninhydrin has been reported.[17]

Common feature of all these methods is cyclization by a 1,2 nucleophilic addition of enamines on ninhydrin. The reaction takes place with high regio- and diastereoselectivity. The *cis* configuration of two hydroxy groups is determined by NMR and X-ray analysis.[18] In all these cases, the regioselective addition of β-carbon of enamine to carbonyl group in position 2 of ninhydrin is followed by cyclization with nitrogen to an enantiomeric mixture of *cis* hemiaminal.[19]

Herein, we report an efficient synthesis of dihydroxy-1-methyl-3-nitro-2-(arylamino)-dihydroindeno[1,2-*b*]pyrrole-4-one by an one-pot three-component reaction between ninhydrin, various aromatic amines and *N*-methyl-1-(methylthio)-2-nitroethena-

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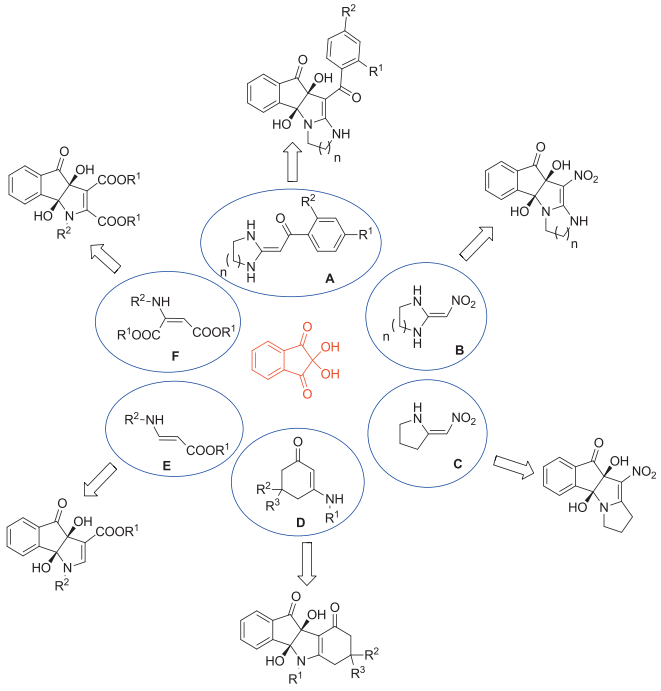
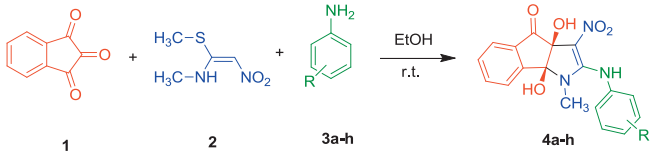


Fig. 1. Summary of previous studies of dihydroxyoxoindeno[1,2-*b*]pyrroles.

mine. According to our knowledge, these structures have not been synthesized so far.

Results and discussion

Inspired by the previous works (Fig. 1), herein we have developed a simple and efficient synthesis of dihydroxy-1-methyl-3-nitro-2-(arylamino)-1,8*b*-dihydroindeno[1,2-*b*]pyrrol-4-one derivatives **4** *via* a one-pot reaction under catalyst-free conditions in ethanol at room temperature. Initially, we used ninhydrin **1**, *N*-methyl-1-(methylthio)-2-nitroethenamine **2**, and 4-bromoaniline **3a** as model substrates to optimize the reaction



Scheme 1. Synthetic scheme for the generation of products **4**.

conditions with different solvents and temperatures (Table 1). The experimental results showed that the reaction proceeds with good yield to formation of **4a** when ethanol was used as the solvent without any catalyst at room temperature (entry 2, Table 1).

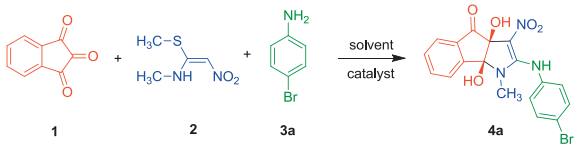
With information obtained from optimized table, we used ninhydrin **1**, *N*-methyl-1-(methylthio)-2-nitroethenamine **2** and various aromatic amines **3a–h** to synthesize the target compounds **4a–h** (Scheme 1).

The reactions were completed after 1–3 h to afford corresponding 2-arylamino-dihydroxyindenopyrroles **4a–h** in good yields (67–85%). The results are summarized in Table 2.

The reaction of various aromatic amines **3a–h** under similar conditions led to the formation of heterocyclic compounds **4a–h** with high efficiency and short reaction times (Table 2). The reaction with some others aromatic amines; 2-chloroaniline, 2-bromoaniline, 2-nitroaniline, 4-nitroaniline was carried out under the same conditions, but did not result in the desired products and the reaction mixture showed several spots on TLC. A reasonable explanation is that *ortho* substituted aniline derivatives exert steric hindrance between the substituent and the methyl group. When a series of nitroketene *N*,*S*-acetals **2** bearing *N*-ethyl, *N*-benzyl, *N*-isopropyl groups (like *N*-ethyl-1-(methylthio)-2-nitroethenamine, *N*-benzyl-1-(methylthio)-2-nitroethenamine, *N*-(1-(methylthio)-2-nitrovinyl)propane-2-amine) were applied in the same conditions, no reaction occurred, probably due to steric hindrance.

The structures of compounds **4a–h** were deduced from their Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data (see the Supporting information).

Table 1
Optimization of reaction conditions for the synthesis of **4a**.[a]



Entry	Solvent	Catalyst (mol%)	Time (h)	Temp (°C)	Yield[b] (%)
1	H_2O	–	3	25	nr[c]
2	**EtOH**	–	**2**	**25**	**85**
3	EtOH	*p*-TSA	5	78	40
4	EtOH	NEt_3	5	78	nr
5	H_2O/EtOH(1:1, v/v)	–	2	25	60
6	CH_3CN	–	2	25	75
7	Dioxane	–	3	25	nr
8	$CHCl_3$	–	3	25	nr

[a] The reaction was performed using **1**, **2**, **3a** (1 mmol), catalyst (0.02 mmol), and solvent (10 mL).
[b] Isolated yield based on **4a**.
[c] No reaction (the reaction is stopped at diol step without participation of amine).