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## Unprecedented reaction of ninhydrin with ethyl cyanoacetate and diethyl malonate on ultrasonic irradiation

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### ABSTRACT

Ultrasonic-assisted, catalyst-free reactions of ninhydrin with ethyl cyanoacetate and diethyl malonate led to the unprecedented formation of an indenopyran and a spiroindenofuran *viz.* diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** and diethyl 3*a*',8*b*'-dihydroxy-1,3,4'-trioxo-1,3,3*a*',4'-tetrahydrospiro[indene-2,2'-indeno[1,2-*b*]furan]-3',3'(8*b*'*H*)-dicarboxylate **3**, respectively. In addition to these unprecedented results, reactions of ninhydrin with dimedone, ethyl acetoacetate and ethyl nitroacetate yielded 4*b*,9*b*-dihydroxy-7,7-dimethyl-7,8-dihydro-4*bH*-indeno[1,2-*b*]benzofuran-9,10(6*H*,9*bH*)-dione **5**, ethyl 3*a*,8*b*-dihydroxy-2-methyl-4-oxo-4,8*b*-dihydro-3*aH*-indeno[1,2-*b*]furan-3-carboxylate **6** and 2-hydroxy-2-(nitromethyl)-1*H*-indene-1,3(2*H*)-dione **7**, respectively. The structures of **1**, **3**, **5**, **6** and **7** were determined by X-ray crystallography and attempts have been made to propose the mechanism of their formation.

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## 1. Introduction

Ninhydrin (Indane-1,2,3-trione), traditionally used for the analysis of amino acids,<sup>1</sup> is known to participate in a number of chemical reactions giving rise to the formation of many structurally functionalized molecules such as aldols,<sup>2</sup> Knoevenagel condensates,<sup>2</sup> phthiocol via 2-hydroxy-2-(1-nitroethyl)-1*H*-indene-1,3(2*H*)-dione,<sup>3</sup> O-containing heterocycles such as indenofurans,<sup>2</sup> indenopyrans<sup>4</sup> and spiroheterocycles.<sup>5</sup> Fused heterocyclic systems are present in a large variety of natural products and drugs.<sup>6</sup> Indenopyrans are used for the development of many pharmaceutical agents<sup>7</sup> and are known to possess *anti*-ulcer, *anti*-depressant and *anti*-allergenic activities<sup>8</sup> whilst indenofurans constitute part-structure of many natural products and are known to exhibit *anti*-microbial and free radical scavenging properties<sup>9</sup> (see Figs. 1 and 2). Molecules with spirocyclic structures possess activities as hypertensive, analgesic, muscle relaxant, *anti*-inflammatory and *anti*-microbial agents.<sup>10</sup> The spiro functionality is also present in

phytochemicals such as alkaloids and terpenoids.<sup>11</sup> Further, indene derivatives are also known to be potent therapeutic agents and possess *anti*-bacterial activities.<sup>12</sup>

## 2. Genesis

Ninhydrin on reaction with 1 equiv of active methylene yields aldols **A** and Knoevenagel condensates **B**. Some aldols are further known to produce intramolecular cyclisation products such as indenofurans **C** (Scheme 1).<sup>2,13</sup> These aldols and Knoevenagel condensates are highly functionalized and are capable of undergoing further reactions with active methylenes and reactive carbonyl compounds (e.g., ninhydrin), respectively. Knoevenagel product **B**, in particular has attracted our attention since the nature of EWG<sub>1</sub> and EWG<sub>2</sub> can influence the attack of second active methylene molecule. This may lead to the formation of Michael products **D** and **E**. Further intramolecular reactions of **D** and **E** may lead to respective cyclic products. We wished to probe into the reaction of aldols and Knoevenagel condensates with active methylene compounds in a quest to obtain newer heterocyclic products (path **a** and **b**) (Scheme 2). Aldol **A** may capture another molecule of ninhydrin leading to the formation of spiroindenofuran derivatives of type **F** (path **c**) (Scheme 2).

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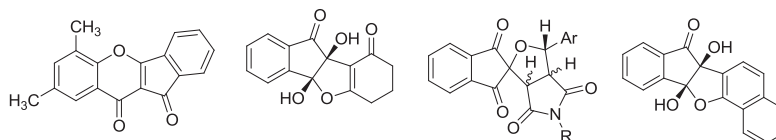


Fig. 1. Some biologically important indenopyran and indenofuran derivatives.<sup>7d,9b–d,10e</sup>

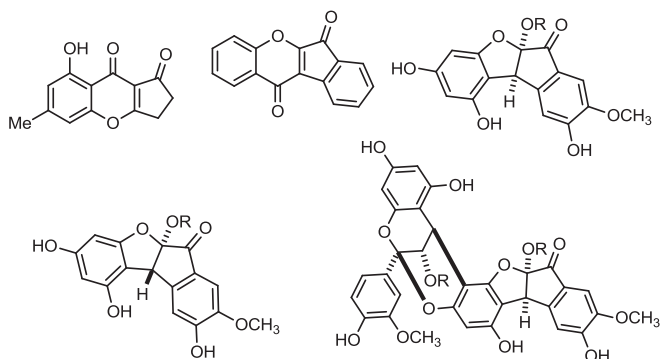
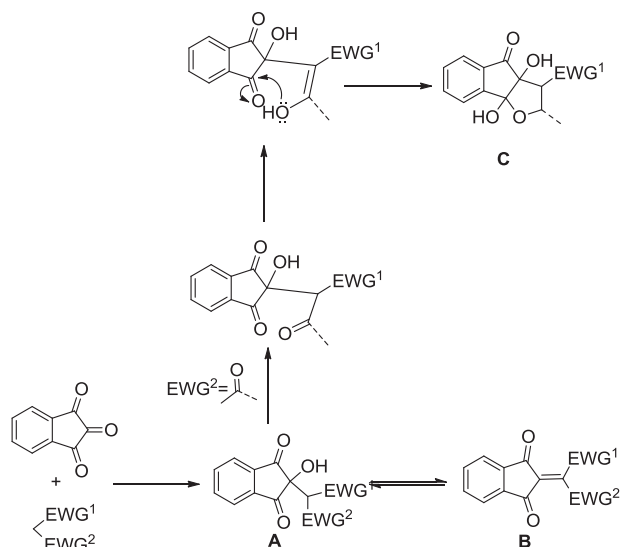


Fig. 2. Some natural products containing indenopyran<sup>7d</sup> and indenofuran substructures.<sup>9a</sup>



Scheme 1. Products of the reaction of ninhydrin with 1 equiv of active methylene.

### 3. Results and discussion

When ninhydrin is reacted with ethyl cyanoacetate (ECA) in water, reported<sup>2</sup> aldol product of type **A** separates out as white solid. We thought of using ethanol instead of water with a hope that the aldol product does not precipitate out and undergoes further reaction as proposed in genesis leading to the formation of newer products. With this perspective in mind, 1:1 mixture of ninhydrin and ethyl cyanoacetate was stirred at room temperature using ethanol as solvent and the progress of the reaction was monitored using TLC. After 7 h of stirring, formation of two new products was observed. The two products were isolated as crystalline solids

and characterized, respectively as diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** (32%) and diethyl 2,2'-(1,3-dioxo-2,3-dihydro-1*H*-indene-2,2-diyl)bis(2-cyanoacetate) **2** (15%). Further corroboration of structures **1** and **2** was arrived at by X-ray crystallographic studies (Fig. 3). To improve the yields, attempts such as (i) performing above reaction in refluxing ethanol, microwave irradiation, ultrasonic-irradiation (entries **1–3**) and (ii) replacing ethanol with other organic solvents (entries **4–11**) were made (Table 1).

It was found that use of ethanol as solvent on ultrasonic-irradiation gave best results (entry **3**). Slight improvement in yields of products **1** (from 54% to 61%) and **2** (from 20% to 24%) was observed in a reaction of ninhydrin with 2 equiv of ethyl cyanoacetate (Scheme 3).

The plausible mechanism for the formation of diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** and diethyl 2,2'-(1,3-dioxo-2,3-dihydro-1*H*-indene-2,2-diyl)bis(2-cyanoacetate) **2** is shown in Scheme 4.

Ultrasonication of ethanolic solution of 1:1 mixture of ninhydrin and diethyl malonate (DEM) yielded diethyl 3*a*',8*b*'-dihydroxy-1,3,4'-trioxo-1,3,3*a*',4'-tetrahydrospiro[indene-2,2'-indeno[1,2-*b*]furan]-3',3'(8*b*'*H*)-dicarboxylate **3** and previously reported<sup>2</sup> aldol product diethyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)malonate **4** in 53 and 24% yields, respectively. However, when the reaction was carried out with 2:1 mixture of ninhydrin and diethyl malonate, improvement in yield of the spiro product **3** (64%) was noticed (Scheme 5). Mechanistically, this is in resonance with that proposed by Holzer et al. for the reaction of ninhydrin with methyl(di)azines having methyl group in  $\alpha$ -position to the ring nitrogen atom.<sup>5c</sup>

Plausible mechanism for the formation of **3** is shown in Scheme 6. Diethyl malonate captures two molecules of ninhydrin in a stepwise manner to produce **G**, which cyclizes intramolecularly to produce **3**.

In addition to above unprecedented results the reaction of ninhydrin with dimedone, ethyl acetoacetate (EAA) and ethyl nitroacetate (ENA) gave expected products. The reaction of ninhydrin with dimedone has been reported<sup>13</sup> to yield the aldol product of type **A**. To our delight similar reaction on ultrasonic-irradiation in ethanol led to the formation of the cyclized indenofuran derivative 4*b*,9*b*-dihydroxy-7,7-dimethyl-7,8-dihydro-4*bH*-indeno[1,2-*b*]benzofuran-9,10(6*H*,9*bH*)-dione **5** in 96% yield. A product resembling with **5** has been reported by Mehdi et al.<sup>9b</sup> by the reaction of ninhydrin with cyclohexane-1,3-dione on refluxing using acetic acid as solvent. Being eco-friendly and convenient, our method is advantageous over this reported method. The reaction of ninhydrin with ethyl acetoacetate (EAA) yielded reported product<sup>2,12</sup> ethyl 3*a*,8*b*-dihydroxy-2-methyl-4-oxo-4,8*b*-dihydro-3*aH*-indeno[1,2-*b*]furan-3-carboxylate **6** in 95% yield. Ethyl nitroacetate (ENA) upon reaction with ninhydrin under similar conditions yielded 1*H*-indene derivative 2-hydroxy-2-(nitromethyl)-1*H*-indene-1,3(2*H*)-dione **7** (78%) after de-ethyldecarboxylation of the aldol product (Scheme 7, Fig. 3).

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