

# Green, Two Components Highly Efficient Reaction of Ninhydrin with Aromatic Amines, and Malononitrile Using Ball-Milling Technique

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**Abstract** Ninhydrin (1) underwent several reactions with benzidine (2), o-phenylene diamine (4), p-toluidine (6) and malononitrile (9) for the purpose of producing novel indanedione derivatives of expected biological activity.

**Keywords** Green Chemistry, Ninhydrin, Aromatic Amines, Condensation Reactions

## 1. Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. We report herein an efficient, solid-state synthesis of highly functionalized indan-1,3-diones via the reaction of ninhydrin with a variety of reagents as an extension to our previous work on the benign synthesis of these compounds [1a,b].

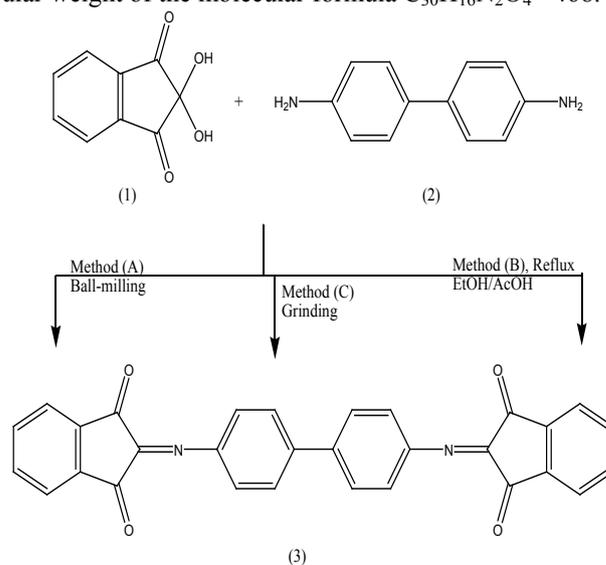
## 2. Results and Discussions

The easy access of a hydroxyl group of ninhydrin (1) to its substitution and the presence of carbonyl groups makes this highly reactive compound an interesting start point for cascade reactions with amino compounds[2].

Benzidine 2 condensed quantitatively with ninhydrin 1 at room temperature (molar ratio 1:1) in the solid state (ball milling) to give bis-azomethine 3 in 100% yield. The potential of the ball milling can be achieved by comparing the yield % of the same product 3 obtained when the reaction was carried out in solution (EtOH – AcOH, ratio 7:3) or by grinding. The yield % in both cases reached to 60%

The ball milling reaction of ninhydrin 1 with benzidine 2 at room temperature afforded only the corresponding bis-azomethine 3 in a quantitative yield. The water of reaction was easily removed by heating to 80°C in a vacuum. The chemical structure of 3 was established on the basis of spectral data. The IR spectrum confirmed the presence of -C=N and C=O stretching absorption bands at 1608, and 1718 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum revealed the ArH at

7.3-8 ppm. The mass spectrum showed a molecular ion peak (M<sup>+</sup>) at m/z = 469.04 (M<sup>+</sup>+1), corresponding to the molecular weight of the molecular formula C<sub>30</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>= 468.46.



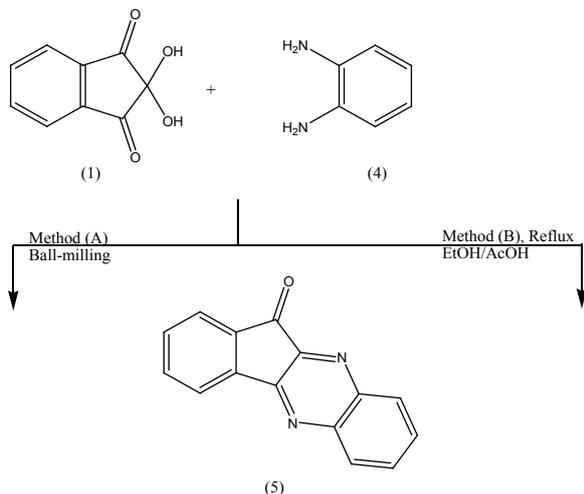
Reaction of ninhydrin 1 with an equimolar amount of benzidine 2 in EtOH/AcOH, (ratio 7:3) afforded the corresponding bis-azomethine 3 in 60% yield. The spectral data of azomethine 3 were in consistent with the structure. By analogy, grinding 1 and 2 in a mortar at room temperature for two hours resulted in the formation of 3 as inferred from its correct analytical and spectral data. In all three methods of synthesis, the m.p is the same.

The technique of waste-free solid-state reaction could be applied to prepare the intramolecular bis-azomethine 5. It has been reported that stoichiometric runs by the ball milling of ninhydrin 1 with o-phenylene diamine 4 afforded the corresponding pyrazine derivative 5 with 100% yield without the aid of any catalysts or solvents.

The 4-cascades of 1 with o-phenylenediamine 4, reported by Kauppp[2] are fully regiospecific and also quantitative

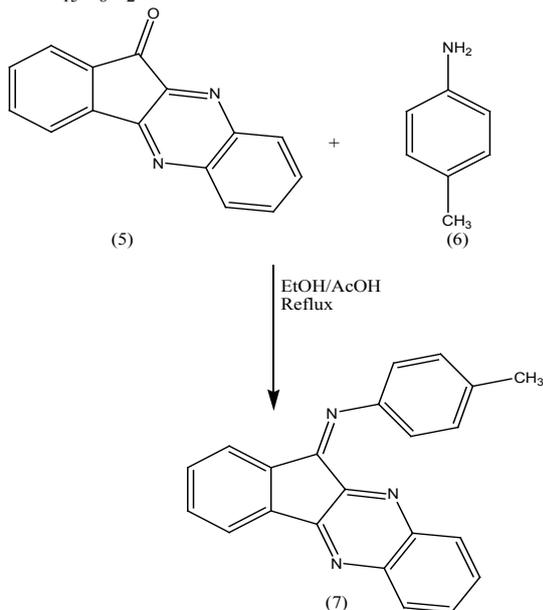
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upon milling at  $-5^{\circ}\text{C}$  and drying at  $80^{\circ}\text{C}$  in vacuum. Our method is an easy access to 5 with well-defined substitution at room temperature. A reasonable sequence of events is addition to  $\text{C}=\text{O}$ , substitution of  $\text{OH}$  and two eliminations of water



Further evidence for the formation of 5 was gained from its synthesis in (EtOH/AcOH, ratio 7:3) in 60% yield, mp and mixed mp. The formation of 5 finds support from the correct analytical and spectral data.

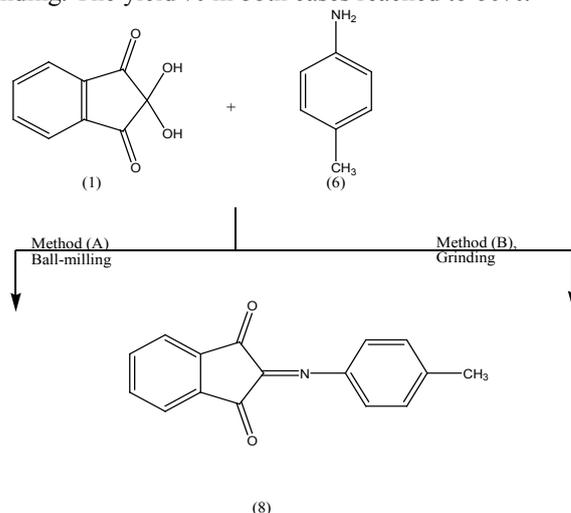
The IR spectrum confirmed the presence of  $\text{-C}=\text{N}$  and  $\text{C}=\text{O}$  absorption bands at  $1604, 1727\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum revealed the ArH at  $\delta\ 7.2\text{-}8.1\text{ ppm}$ . The mass spectrum showed a molecular ion peak ( $\text{M}^+$ ) at  $m/z = 232.33$  corresponding to the molecular weight of the molecular formula  $\text{C}_{15}\text{H}_8\text{N}_2\text{O} = 232.24$ .



As a further extension for the above successful reactions, it seemed of interest to react the pyrazine 5 with p-tolidine 6 by refluxing in EtOH/AcOH (ratio 7:3) to give compound 7. The formation of 7 finds support from the correct analytical and spectral data. The IR spectrum confirmed the presence of  $\text{-C}=\text{N}$  absorption band at  $1614\text{ cm}^{-1}$ . The mass spectrum showed a molecular ion peak ( $\text{M}^+$ ) at  $m/z = 321.43$  (100%)

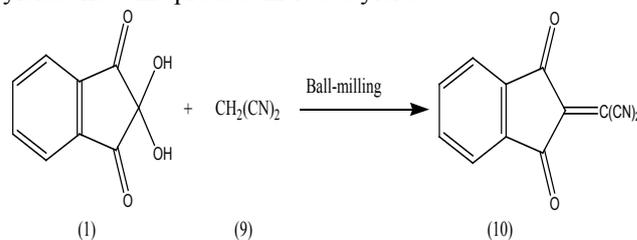
corresponding to the molecular weight of the molecular formula  $\text{C}_{22}\text{H}_{15}\text{N}_3 = 321.37$ .

p-Toulidine 6 condensed quantitatively with ninhydrin 1 at room temperature (molar ratio 1:1) in the solid state (ball milling) to give the azomethine 8 in 100% yield. The potential of the ball milling can be achieved by comparing the yield % of the same product 3 obtained when the reaction was carried out in solution (EtOH – AcOH, ratio 7:3) or by grinding. The yield % in both cases reached to 60%.



The ball milling reaction of ninhydrin 1 with p-tolidine 6 at room temperature afforded only the corresponding azomethine 8 in a quantitative yield. The water of reaction was easily removed by heating to  $80^{\circ}\text{C}$  in a vacuum. The chemical structure of 8 was established on the basis of spectral data. The IR spectrum confirmed the presence of  $\text{-C}=\text{N}$  and  $\text{C}=\text{O}$  stretching absorption bands at  $1592, 1710\text{ cm}^{-1}$ . The mass spectrum showed a molecular ion peak ( $\text{M}^+$ ) at  $m/z = 249.18$  (75.2%) ( $\text{M}^+$ ), corresponding to the molecular weight of the molecular formula  $\text{C}_{16}\text{H}_{11}\text{NO}_2 = 249.18$ .

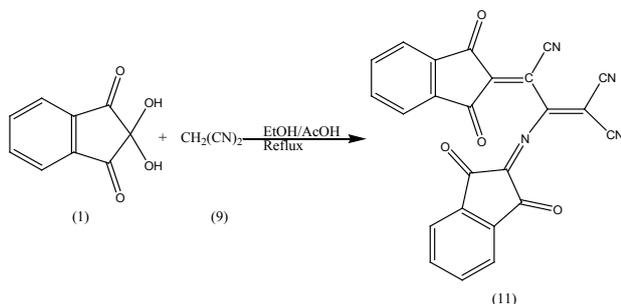
It has been reported[3,4] that reaction between ninhydrin (1) and malononitrile (9) in clay or  $\text{H}_2\text{O}$  yield compound (10) in 80% yield, and we found that reaction between (1) and (9) without the aid of any catalyst and by using ball-milling yields the same product in 100% yield.



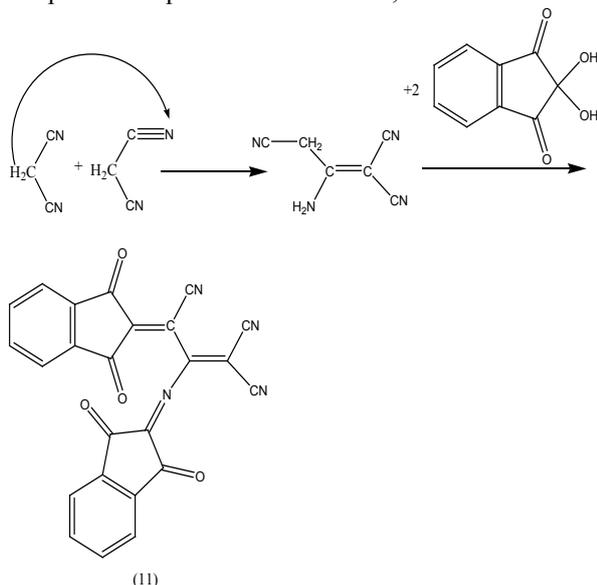
The formation of (10) finds support from its analytical and spectral data; the IR spectrum showed absorption band at ( $1707$  and  $2200\text{ cm}^{-1}$ ) for  $\text{C}=\text{O}$  and  $\text{C}\equiv\text{N}$ .

The  $^1\text{HNMR}$  spectrum showed bands at  $\delta\ 7.4\text{-}8.4\text{ ppm}$  for Ar-H and the mass spectrum exhibited the molecular ion peak at  $m/z = 208.74$  [ $\text{M}^+$ ] corresponding to the molecular weight of the molecular formula  $\text{C}_{12}\text{H}_4\text{O}_2\text{N}_2 = 208.17$

By repeating the above reaction in (EtOH/AcOH ratio 7:3) it gives compound (11).



We provide a plausible mechanism;



The formation of (11) finds support from its analytical and spectral data; the IR spectrum showed absorption bands at (1706 and 2196 cm<sup>-1</sup>) for C=O and C≡N.

The <sup>1</sup>H NMR spectrum showed bands at δ 7.5-8.3 ppm for Ar-H and the mass spectrum exhibited the molecular ion peak at m/z = 416.38 [M<sup>+</sup>] corresponding to the molecular weight of the molecular formula C<sub>24</sub>H<sub>8</sub>O<sub>4</sub>N<sub>4</sub> = 416.38.

### 3. Experimental

Melting points are uncorrected and were determined with a Fisher-Johns melting point apparatus. Elemental analyses were carried out at Microanalytical Unit of the Faculty of Science, Mansoura University; the results were in satisfactory agreement with the calculated values. IR spectra (KBr) were recorded with 5000 FTIR spectrometer (not all frequencies are reported). The <sup>1</sup>H-NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz (<sup>1</sup>H) or 75.5 MHz (<sup>13</sup>C) in broad band mode. Mass spectra were obtained at a Finnigan MAT 212 instrument by electron impact at 70 eV. The ball-mill was a Retsch MM 2000 swing mill with a 10 cm<sup>3</sup> stainless steel, double-walled beaker with fittings for circulating coolants. Two stainless steel balls of 12 mm diameter were used. Ball-milling was performed at 20225 Hz frequency, usually at room temperature (without circulating liquid and the temperature did not rise above 30 °C).

Reaction of ninhydrin 1 with benzidine 2: Formation of 3  
Method (A); Ball-milling

A mixture of 356 mg of ninhydrin 1 (2.00 mmol) and 184 mg of benzidine 2 (1.00 mmol) was ball-milled at room temperature for 1 h. The material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 3 with 100% yield and did not require purifying workup.

Method (B); Using Solvent

A mixture of 356 mg of ninhydrin 1 (2.00 mmol) and 184 mg of benzidine 2 (1.00 mmol) was refluxed in 10 ml absolute EtOH and 2 ml glacial AcOH for 10 hrs, left to cool. The ppt. formed filtered off and left to dry, recrystallize from EtOH, to give pure 3 with 60% yield.

Method (C); By Grinding

A mixture of 178 mg of ninhydrin 1 (1.00 mmol) and 184 mg of benzidine 2 (1.00 mmol) was grinded in a mortar at room temperature for 30 min, material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 3 with 60% yield and did not require purifying workup.

The product 3

Brownish powder mp 300°C; IR (KBr):  $\bar{\nu}$  1718 (C=O), 1608 (C=N) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, [D<sub>6</sub>] DMSO, 25°C, TMS) δ = 7.50-8.00 (m, 7H, ArH) ppm. MS (EI, 70 eV): m/z (%) = 469.04 [M<sup>+</sup>]. C<sub>30</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (468.46): calcd. C 76.92 H 3.44 N 5.98 O 13.66; found C 67.93 H 3.40 N 5.95 O 13.72.

Reaction of ninhydrin 1 with o-phenylenediamine 4, formation of 5

Method (A); Ball-milling

A mixture of 178 mg of ninhydrin 1 (1.00 mmol) and 108 mg of o-phenylenediamine 4 (1.00 mmol) was ball-milled at room temperature for 1 h. The material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 5 with 100% yield and did not require purifying workup.

Method (B); Using Solvent

A mixture of 356 mg of ninhydrin 1 (2.00 mmol) and 216 mg of o-phenylenediamine 4 (2.00 mmol) was refluxed in 10 ml absolute EtOH and 2 ml glacial AcOH for 5 hrs, left to cool. The ppt. formed filtered off and left to dry, recrystallize from EtOH, to give pure 5 with 60% yield.

The product 5

Green powder mp 227-229°C; IR (KBr):  $\bar{\nu}$  1727 (C=O), 1650 (C=N) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, 25°C, TMS) δ = 7.50-8.50 (m, 8H, ArH) ppm. MS (EI, 70 eV): m/z (%) = 232.33 [M<sup>+</sup>]. C<sub>15</sub>H<sub>8</sub>N<sub>2</sub>O (232.24): calcd. C 77.58 H 3.47 N 12.06 O 6.89; found C 78.01 H 3.42 N 12.03 O 7.00.

Reaction of product 5 with p-toulidine 6: formation of 7

A mixture of 696 mg of product 5 (3.00 mmol) and 321 mg of p-toulidine 6 (3.00 mmol) was refluxed in 10 ml absolute EtOH and 2 ml glacial AcOH for 3 hours, left to cool. The ppt. formed filtered off and left to dry, recrystallize from EtOH, to give pure 7.

The product 7

Reddish orange powder mp 195°C; IR (KBr):  $\bar{\nu}$  1650 (C=N) cm<sup>-1</sup>. MS (EI, 70 eV): m/z (%) = 321.43(100%) [M<sup>+</sup>]. C<sub>15</sub>H<sub>8</sub>N<sub>2</sub>O (321.37): calcd. C 82.22 H 4.70 N 13.08; found C 82.25 H 4.74 N 13.13.

Reaction of ninhydrin 1 with p-toulidine 6: Formation of 8  
Method (A); Ball-milling

A mixture of 356 mg of ninhydrin 1 (2.00 mmol) and 214 mg of p-toulidine 6 (2.00 mmol) was ball-milled at room temperature for 1 h. The material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 8 with 100% yield and did not require purifying workup.

Method (B); By Grinding

A mixture of 356 mg of ninhydrin 1 (2.00 mmol) and 214 mg of p-toulidine 6 (2.00 mmol) was grinded in a mortar at room temperature for 30 min, material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 8 with 60% yield and did not require purifying workup.

The product 8

Brownish powder mp 85-90°C; IR (KBr):  $\bar{\nu}$  1710 (C=O), 1590 (C=N)  $\text{cm}^{-1}$ . MS (EI, 70 eV): m/z (%) = 249.07 (61.7%) $[\text{M}^+]$ .  $\text{C}_{16}\text{H}_{11}\text{NO}_2$  (249.26): calcd. C 77.10 H 4.45 N 5.62 O 12.84; found C 77.12 H 4.50 N 5.64 O 12.81.

Reaction of ninhydrin 1 with malononitrile 9: Formation of 10

Method (A); Ball-milling

A mixture of 534 mg of ninhydrin 1 (3.00 mmol) and 198 mg of malononitrile 9 (3.00 mmol) was ball-milled at room temperature for 1 h. The material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 10 with 100% yield and did not require purifying workup.

Method (C); By Grinding

A mixture of 534 mg of ninhydrin 1 (3.00 mmol) and 198 mg of malononitrile 6 (3.00 mmol) was grinded in a mortar at room temperature for 30 min, material obtained was dried at 0.01 bar at 80 °C in vacuum to give pure 10 with 60% yield and did not require purifying workup.

The product 10

Green powder mp 210-213°C; IR (KBr):  $\bar{\nu}$  1707 (C=O),

2229, 2200 (C $\equiv$ N)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ , 25°C, TMS)  $\delta$  = 7.50-8.50 (m, 8H, ArH) ppm. MS (EI, 70 eV): m/z (%) = 208.74  $[\text{M}^+]$ .  $\text{C}_{12}\text{H}_4\text{N}_2\text{O}_2$  (208.17): calcd. C 69.24 H 1.94 N 13.46 O 15.37; found C 69.26 H 1.93 N 13.51 O 15.40.

Method (B); Using Solvent

A mixture of 891 mg of ninhydrin 1 (5.00 mmol) and 990 mg of malononitrile 6 (5.00 mmol) was refluxed in 10 ml absolute EtOH and 2 ml glacial AcOH for 8 hrs, left to cool. The ppt. formed filtered off and left to dry, recrystallize from EtOH, to give pure 11 with 60% yield.

The product 11

Greenish powder mp 243-245°C; IR (KBr):  $\bar{\nu}$  1633 (C=N), 1672, 1706, 1745, 1767 (C=O), 2196, 2217 (C $\equiv$ N) $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ , 25°C, TMS)  $\delta$  = 7.50-8.50 (m, 8H, ArH) ppm. MS (EI, 70 eV): m/z (%) = 416.38  $[\text{M}^+]$ .  $\text{C}_{24}\text{H}_8\text{N}_4\text{O}_4$  (416.34): calcd. C 69.24 H 1.94 N 13.46 O 15.37; found

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