Synthesis of 4,5-dihydropyrazolyl-2*H*-indenediones by aldol condensation of ninhydrin with 1*H*-pyrazol-5-ol

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A simple and efficient procedure for the synthesis of 2-hydroxy-2-(5-hydroxy-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione derivatives, proceeding *via* aldol condensation between ninhydrin and various 3-alkyl-1*H*-pyrazol-5-ols is described. The syntheses were carried out in ethanol at room temperature and proceeded with short reaction times to give the products with high yields.

Keywords: ninhydrin, pyrazolone, indandione, aldol condensation

Ninhydrin (indane-1,2,3-trione), traditionally used for the analysis of amino acids,[1] is known to participate in a number of chemical reactions, such as aldol and Knoevenagel condensations, giving rise to the formation of many 1,3-indenediones.[2] The 1,3-indanedione grouping is present in a large variety of natural products and drugs.[3] In addition, these compounds also have a range of biological activities, such as anticoagulant, antioxidant, antiplatelet aggregation, antithrombosis, antiangina, antimicrobial, antifungal, antiproliferative and antiinflammatory activities.[4-6]

Among the wide variety of heterocycles that have been explored for developing potential pharmacologically active compounds, pyrazolones fused with different heterocycles are known to possess various chemotherapeutic effects and have found use as antimicrobial,[7,8] antifungal[9] and antiviral agents.[10] In addition, some fused pyrazolone derivatives have been reported to induce various antileukemic,[11] antitumor[12,13] and antiproliferative[14,15] activities. Development of new methods for the synthesis of pyrazolone derivatives, which will yield subsets of heterocycles with the potential to serve as templates for new biologically active molecules, is of great importance.

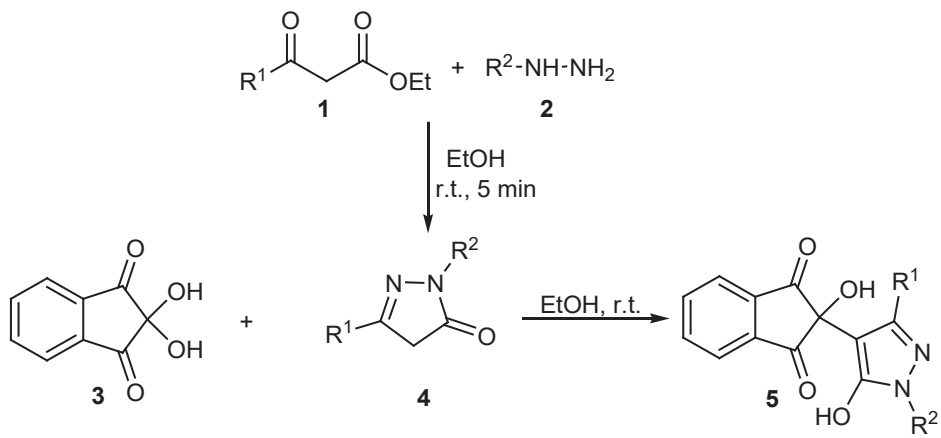
Results and discussion

In continuation of our interest in the synthesis of heterocyclic[16–19] and pyrazolone compounds,[20,21] we report the development herein of the synthesis of 4,5-dihydropyrazolyl-2*H*-indenediones *via* an aldol condensation of ninhydrin **3** and 1*H*-pyrazol-5-ol **4** in ethanol at room temperature in high yield (Scheme 1). It should be noted that the pyrazolones **4** were available by the condensation of β-keto esters **1** and hydrazine **2** in ethanol for 5 min (Scheme 1).[22]

As a model reaction, we first investigated the condensation of ninhydrin **3** and 3-methyl-1*H*-pyrazol-5-ol (**4**; R^1 = Me, R^2 = H) under various conditions. We first investigated the model reaction rate in different solvents by measuring the isolated yield using identical amounts of reactants for a fixed reaction time of 5 h at room temperature. The desired product was obtained in polar solvents such as water, ethanol, methanol, ethyl acetate and acetonitrile, but ethanol afforded the product in the highest yield. The desired product was not obtained in a non-polar solvent, such as dichloromethane, toluene and benzene. This result can be explained by a simple acid-catalysis mechanism facilitated by the strong hydrogen bond interaction at the organic–ethanol interface, which stabilises the reaction intermediate. In addition, it was found that addition of water to the ethanol solution did not improve the reaction outcome and, interestingly, when the reaction was performed in pure ethanol, the corresponding product was obtained in high yield. Next, we studied the model reaction in ethanol at different temperatures. The reaction rate did not change as the temperature was increased. At room temperature, the maximum yield was obtained in a reaction time of 5 h.

With optimised conditions established, we then applied the process to six variously substituted pyrazolones and the results are summarised in Table 1. In all cases, good yields were obtained. The structures of the products were established by spectroscopic methods.

Although we have not experimentally established the reaction mechanism, a possible explanation is proposed (Scheme 2). Mechanistically, the active methylene of pyrazolone **4** is converted into the enolate form in the presence of ethanol,



Scheme 1

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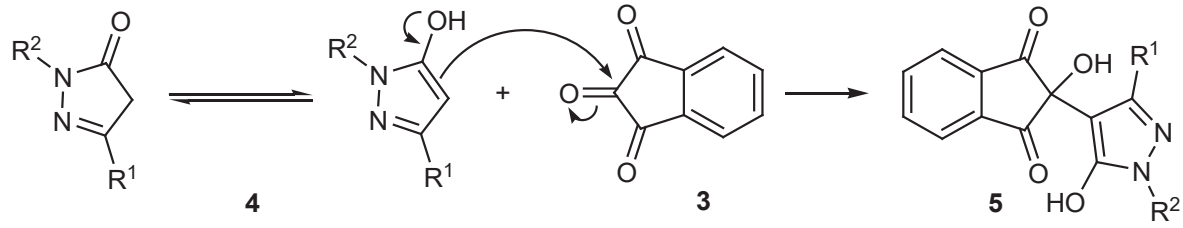

Scheme 2

Table 1 Yields of variously substituted pyrazolyl indandiones **5** prepared from ninhydrin **3** and variously substituted pyrazolones **4** (Scheme 1)[a]

Entry	R^1	R^2	Products	Yield/%[b]
1	Me	H	**5a**	91
2	Pr	H	**5b**	90
3	Me	Ph	**5c**	89
4	CO_2Me	H	**5d**	85
5	^{i}Pr	H	**5e**	81
6	Me	2,4-NO_2–Ph	**5f**	70

[a]Reaction conditions: a solution containing ninhydrin **3** (1.0 mmol) and pyrazolone **4** (1.0 mmol) in ethanol (10 mL) was stirred at room temperature for 5 h.
[b]Isolated yield.

which then reacts with ninhydrin in an aldol-type addition reaction to give the product **5** (Scheme 2).

Conclusion

In conclusion, we have developed a new and efficient approach for the synthesis of a wide range of pyrazolyl indandione derivatives from the reaction of ninhydrin and pyrazolone in ethanol at room temperature in high yield. The reaction has been shown to display good functional group tolerance and is high yielding, and product isolation is very straightforward.

Experimental

All chemicals were purchased from Fluka, Merck or Aldrich, and were used without further purification. Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Ray Leigh Wqf-510 Fourier Transform Infrared (FTIR) spectrometer, respectively. The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker-400 Avance instrument using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard at 400 and 100 MHz, respectively. The mass spectra were recorded on a Finnigan-MAT 8430 instrument.

Synthesis of pyrazolyl indandione derivatives (**5a**–**f**)*; general procedure*

A solution containing ninhydrin (1.0 mmol) and a pyrazolone **4** (1.0 mmol) in ethanol (10 mL) was stirred at room temperature for 5 h. Then the solution was diluted with ethanol (10 mL) and stirred in an ice bath for 30 min. The resultant solid was filtered off, washed with cool ethanol (10 mL) and recrystallised from ethanol to give pure pyrazolyl indandiones.

*2-Hydroxy-2-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione* (**5a**): White powder; m.p. 210–212 °C; yield 0.23 g (91%); IR (KBr) (ν_{max} cm^{-1}): 3550, 3450, 3050, 1650, 1600, 1475; MS *m/z*: 258 (M$^+$), 343, 173, 161, 97, 85; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (3H, s, CH_3), 3.54 (2H, brs, OH and NH), 6.42 (1H, s, *C*=C–OH), 7.97 (4H, m, H–Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.0 (CH_3), 76.0 (*C*–OH), 98.0 (*C*=C–OH), 123.9 (C–ninhydrin), 136.8 (C–ninhydrin), 140.5 (C–ninhydrin), 141.0 (C=*C*–OH), 158.2 (C=N), 199.4 (C=O). Anal. calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85; found: C, 60.44; H, 3.91; N, 10.80%.

*2-Hydroxy-2-(5-hydroxy-3-propyl-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione* (**5b**): White powder; m.p. 211–213 °C; yield 0.26 g (90%); IR (KBr) (ν_{max} cm^{-1}): 3450, 3350, 3030, 1770, 1700, 1600, 1550; MS *m/z*: 286 (M$^+$), 257, 243, 202, 144, 125, 85, 43; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (3H, t, $^3J_{HH}$ = 8.0 Hz, CH_3), 1.66–1.68 (2H, m, CH_2), 2.77 (2H, t, $^3J_{HH}$ = 8.0 Hz, CH_3), 6.33 (1H, s, *C*=C–OH), 7.95–7.98 (4H, m, H–Ar), 9.50 (1H, s, OH), 11.30 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.0 (CH_3–propyl), 22.1 (CH_2–propyl), 27.4 (CH_2–propyl), 75.6 (*C*–OH), 97.0 (*C*=C–OH), 123.3 (C–ninhydrin), 136.2 (C–ninhydrin), 140.1 (C–ninhydrin), 142.0 (C=*C*–OH), 158.5 (C=N), 199.0 (C=O). Anal. calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; found: C, 62.89; H, 4.92; N, 9.76%.

*2-Hydroxy-2-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione* (**5c**): White powder; m.p. 210–212 °C; yield 0.29 g, (89%); IR (KBr) (ν_{max} cm^{-1}): 3450, 3200, 3100, 1750, 1700, 1600, 1475; MS *m/z*: 334 (M$^+$), 319, 257, 229, 173, 161, 132, 85; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (3H, s, CH_3), 6.60 (1H, s, *C*=C–OH), 7.10–7.98 (9H, m, H–Ar), 11.70 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.8 (CH_3), 75.2 (*C*–OH), 118.5 (*C*=C–OH), 123.3 (C–ninhydrin), 124.7 (C–Ph), 128.8 (C–Ph), 136.2 (C–ninhydrin), 140.0 (C–ninhydrin), 140.2 (C=*C*–OH), 152.1 (C–Ph), 160.0 (C=N), 199.0 (C=O). Anal. calcd for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38; found: C, 68.23; H, 4.22; N, 8.36%.

*Methyl 4-(2,3-dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-5-hydroxy-1*H*-pyrazole-3-carboxylate* (**5d**): White powder; m.p. 214–216 °C; yield 0.25 g (85%); IR (KBr) (ν_{max} cm^{-1}): 3450, 3400, 1750, 1700, 1600, 1480; MS *m/z*: 302 (M$^+$), 273, 271, 202, 161, 144, 85; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (3H, s, CH_3), 6.38 (1H, s, *C*=C–OH), 7.94–8.00 (4H, m, H–Ar), 9.70 (1H, s, OH), 11.70 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.7 (OCH_3), 75.2 (*C*–OH), 98.0 (*C*=C–OH), 123.4 (C–ninhydrin), 136.3 (C–ninhydrin), 140.0 (C–ninhydrin), 141.2 (C=*C*–OH), 160.0 (C=N), 161.0 (C=O), 198.7 (C=O). Anal. calcd for $C_{14}H_{10}N_2O_6$: C, 55.63; H, 3.33; N, 9.27; found: C, 55.61; H, 3.32; N, 9.30%.

*2-Hydroxy-2-(5-hydroxy-3-isopropyl-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione* (**5e**): White powder; m.p. 215–217 °C; yield 0.23 g (81%); IR (KBr) (ν_{max} cm^{-1}): 3550, 3450, 3200, 1750, 1700, 1600, 1500; MS *m/z*: 286 (M$^+$), 257, 243, 202, 161, 85, 43; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (6H, d, $^3J_{HH}$ = 8.0 Hz, CH_3), 3.76 (2H, quin, $^3J_{HH}$ = 8.0 Hz, CH), 6.34 (1H, s, *C*=C–OH), 7.96–7.97 (4H, m, H–Ar), 9.70 (1H, s, OH), 11.50 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.18 (CH_3–isopropyl), 24.70 (CH–isopropyl), 75.7 (*C*–OH), 98.0 (*C*=C–OH), 123.3 (C–ninhydrin), 136.1 (C–ninhydrin), 140.10 (C=*C*–OH), 152.0 (C–ninhydrin), 158.0 (C=N), 198.9 (C=O). Anal. calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; found: C, 62.95; H, 4.90; N, 9.77%.

*2-Hydroxy-2-(5-hydroxy-3-methyl-1-(2,4-dinitrophenyl)-1*H*-pyrazol-4-yl)-2*H*-indene-1,3-dione* (**5f**): White powder; m.p. 219–221 °C; yield 0.29 g (70%); IR (KBr) (ν_{max} cm^{-1}): 3550, 3350, 1750, 1600, 1490; MS *m/z*: 424 (M$^+$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (3H, s, CH_3), 6.12 (1H, s, *C*=C–OH), 7.02 (1H, s, H–Ar), 7.65–8.00 (6H, m, H–Ar), 10.20 (1H, s, OH), 10.80 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.1 (CH_3), 83.0 (*C*–OH), 115.0 (*C*=C–OH), 122.9 (C–Ph), 123.1 (C–ninhydrin), 126.0 (C–Ph), 126.1 (C–Ph), 129.4 (C–Ph), 129.6 (C–Ph), 130.2 (C–Ph), 130.4 (C–ninhydrin), 135.5 (C–ninhydrin), 149.5 (C=*C*–OH), 160.9, (C=N), 199.0 (C=O). Anal. calcd for $C_{19}H_{12}N_4O_8$: C, 53.78; H, 2.85; N, 13.20; found: C, 53.79; H, 2.86; N, 13.21%.

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