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One-Pot, Three-Component Synthesis of 3-(5-Amino-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones

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ONE-POT, THREE-COMPONENT SYNTHESIS OF 3-(5-AMINO-1*H*-PYRAZOL-4-YL)-3-(2-HYDROXY-4,4-DIMETHYL-6-OXOCYCLOHEX-1-ENYL)INDOLIN-2-ONES

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A clean, efficient, one-pot, three-component method for the synthesis of 3-(5-amino-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one derivatives by condensation reaction of dimedone, 1H-pyrazol-5-amines, and isatins in aqueous media is reported.

Keywords: Dimedone; isatin; oxindole; pyrazole

INTRODUCTION

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1,2] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

Isatin and its derivatives have proved to be versatile starting materials for the synthesis of heterocyclic, and noncyclic, natural products and analogs, as well as for the synthesis of potentially important compounds with biological activities.[3] Oxindoles are well known among these compounds (Fig. 1). Oxindoles are useful as antibacterial, anti-inflammatory, and laxative products.[4,5] Furthermore, these heterocyclic compounds were recently isolated from plants. For example, the marine alkaloid convolutamydine A, isolated from the marine bryozoan *Amathia convolute* was found to show potent activity in the differentiation of HL-60 human promyelocytic leukenie cell.[6]

The 3,3-substituted oxindoles have been shown to possess mechanism-specific antiproliferative, antibacterial, antiprotozoal, and anti-inflammatory activities.[7–10] Compounds **1** and **2** have been used as laxatives.[5] Therefore, recently, a few methods have been developed for the synthesis of 3,3-substituted oxindoles.[5,11–13]

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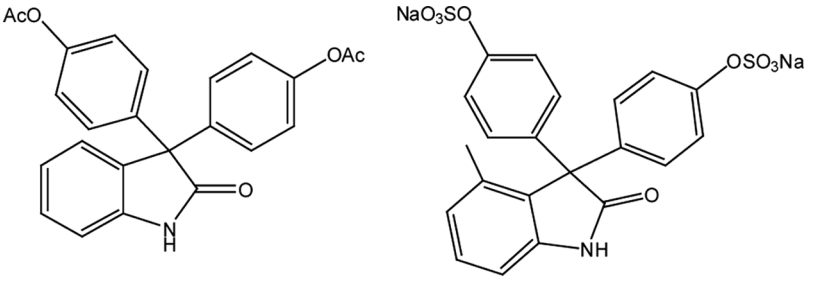

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Figure 1. Examples of biologically active oxindoles.

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds,[14–16] among them such prominent drug molecules as Celecoxib and Pyrazofurines. Recently, they have also emerged as potential atypical antipsychotics.[17]

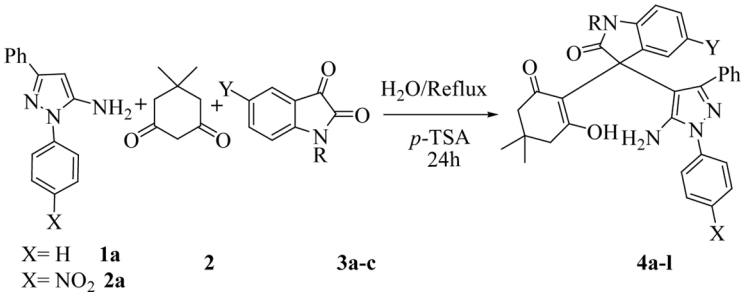
As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[18–24] we performed the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl) indolin-2-ones through a condensation reaction employing water as the reaction medium. In fact, as clearly stated by R. A. Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water."[25]

RESULTS AND DISCUSSION

To achieve suitable conditions for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones **4**, we tested the reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine **1a**, dimedone **2**, and isatin **3a** as a simple model substrate in various solvents and under solvent-free classical heating conditions in the presence of *p*-toluenesulfonic acid (*p*-TSA), an inexpensive and available catalyst (Scheme 1). In refluxing solvents or under solvent-free conditions, the yield of product was very poor. The results are shown in Table 1. It was found that water was the solvent of choice for the reaction, and the desired product was obtained in good yield in water (entry 2).

To explore the scope and limitations of this reaction, we extended the reaction of 1*H*-pyrazol-5-amines **1a**,**b** and dimedone **2** with a range of isatins **3a**–**h** under similar conditions (using H_2O/*p*-TSA) for 24 h, furnishing the respective 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones **4a**–**m** in good yields (Scheme 1). The optimized results are summarized in Table 2. The results were good in terms of yields and product purity in the presence of *p*-TSA, but without it the yields of products were poor (<30%), even after 60 h.

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z



Scheme 1. Synthesis of oxindoles **4**.

values. Compounds **4** are stable solids whose structures are fully supported by infrared (IR), ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry (MS), and elemental analysis.

We have not established an exact mechanism for the formation of oxindoles **4**, but two reasonable possibilities are indicated in Scheme 2. Addition of pyrazol-5-amine **1** to isatin **3** leads to highly reactive intermediate **5** via a standard nucleophilic addition.[26] Interception of **5** by dimedone **2**, possibly through its enol tautomer, produces product **4** (pathway A). Isatin **3** and dimedone **2** would react to produce

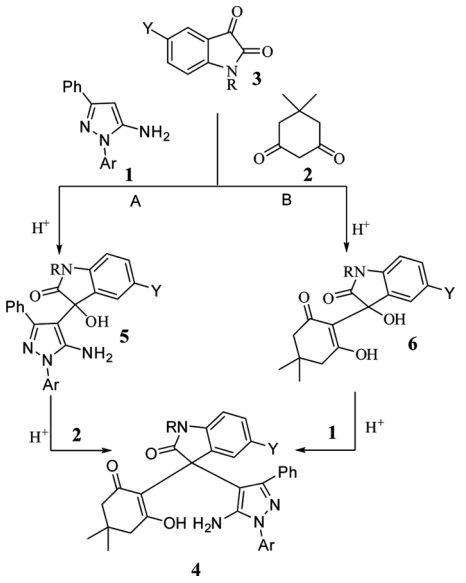
Table 1. Solvent effects on the reaction time and yield[a]

Entry	Conditions	Time (h)	Yield (%)
1	Solvent-free, 100°C	12	45
2	Water (reflux)	24	77
3	CH_3CN (reflux)	24	40
4	EtOH (reflux)	12	64
5	Dimethylformamide (reflux)	24	58

[a]Dimedone (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), isatin (1 mmol), and *p*-TSA (0.1 g).

Table 2. Synthesis of oxindoles **4**

Product **4**	R	X	Y	Yield (%)
a	H	H	H	77
b	H	H	Br	83
c	H	H	NO_2	81
d	Me	H	H	75
e	Me	H	Br	90
f	Et	H	H	73
g	H	H	Me	72
h	Et	H	Br	76
i	Et	H	NO_2	73
j	H	NO_2	H	80
k	Me	NO_2	H	70
l	Et	NO_2	H	72
m	H	NO_2	NO_2	77



Scheme 2. Proposed mechanism of the reaction.

highly reactive intermediate **6**,[27] followed by a nucleophilic addition with pyrazol-5-amine **1** to afford oxindol **4** (pathway 5).

EXPERIMENTAL

General

Melting points were measured on an Elecrtothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Fourier transform (FT)–IR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General Procedure for the Preparation of 3-(5-Amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl) indolin-2-one (4a)

A mixture of dimedone (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), isatine (1 mmol), and *p*-TSA (0.1 g) in refluxing water (5 ml) was stirred for 24 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, the reaction mixture was filtered, and the precipitate was washed with water. The residue was recrystallized from EtOH to afford the pure product **4a**. White powder (77%); mp 290°C dec. IR (KBr) (ν_{max}/cm^{-1}): 3305, 3070, 1706, 1608. MS (EI, 70 eV) m/z (%): 504 (M^+, 10), 489 (10), 402 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H(ppm) 0.93 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.96 and

2.08 (2H, AB system, $J = 16.1$ Hz, CH_2), 2.58 (2H, s, CH_2), 3.57 (1H, bs, OH exchanged with solvent), 6.48–7.60 (16H, m, H-Ar and NH_2), 9.79 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.3, 28.6, 32.4, 41.4, 49.4, 51.1, 101.9, 108.7, 109.1, 121.5, 123.6, 124.2, 127.6, 128.1, 128.2, 129.0, 129.9, 133.2, 137.4, 138.1, 138.6, 142.8, 149.8, 153.0, 179.9, 193.5. Anal. calcd for $C_{31}H_{28}N_4O_3$: C, 73.79; H, 5.59; N, 11.10%. Found: C, 73.74; H, 5.55; N, 11.17%.

Selected Characterization Data

3-(5-Amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-bromo-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one (4b). Cream powder (83%); mp 240°C dec. IR (KBr) (ν_{max}/cm^{-1}): 3219, 2957, 1714, 1616. MS (EI, 70 eV) m/z (%): 582 (M^+, 7), 564 (5), 482 (100), 402 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H(ppm) 0.98 (6H, s, $2CH_3$), 1.98 (2H, s, CH_2), 2.58 (2H, s, CH_2), 6.40–7.65 (15H, m, H-Ar and NH_2), 9.90 (1H, s, NH), 9.94 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.6, 28.2, 32.5, 41.3, 49.5, 50.8, 101.2, 108.1, 111.0, 113.0, 124.5, 126.3, 127.8, 128.2, 128.3, 128.9, 129.9, 130.4, 133.0, 137.4, 138.0, 140.7, 142.1, 149.8, 153.5, 179.6, 193.7. IR (KBr) cm^{-1}: 3219.4, 2957.49 and 2859.91, 1714.69, 1616.47. Anal. calcd. for $C_{31}H_{27}BrN_4O_3$: C, 63.81; H, 4.66; N, 9.60%. Found: C, 63.87; H, 4.61; N, 9.66%.

3-(5-Amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-nitroindolin-2-one (4c). Light brown powder (81%); mp 215°C dec. IR (KBr) (ν_{max}/cm^{-1}): 3224, 2952, 1735, 1617. MS (EI, 70 eV) m/z (%): 549 (M^+, 5), 529 (20), 419 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (6H, s, $2CH_3$), 2.05 (2H, s, CH_2), 2.51 and 2.65 (2H, AB system, $J = 24.7$ Hz, CH_2), 6.58–8.03 (15H, m, H-Ar and NH_2), 10.03 (1H, s, NH), 10.55 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.8, 28.0, 32.6, 41.2, 49.3, 50.7, 100.8, 107.6, 109.0, 118.8, 124.5, 125.4, 127.9, 128.2, 128.5, 129.0, 129.9, 132.8, 137.9, 139.1, 142.2, 149.4, 149.8, 154.2, 180.6, 193.9. Anal. calcd. for $C_{31}H_{27}N_5O_5$: C, 67.75; H, 4.95; N, 12.74%. Found: C, 67.70; H, 4.89; N, 12.68%.

3-(5-Amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-1-methylindolin-2-one (4d). Cream powder (75%); mp 294°C dec. IR (KBr) (ν_{max}/cm^{-1}): 3333, 3051, 2955, 1691, 1624. MS (EI, 70 eV) m/z (%): 500 (M^+-$H_2$0, 50), 416 (100), 426 (26), 387 (45).^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.97 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.93 and 2.06 (2H, AB system, $J = 24.3$ Hz, CH_2), 2.60 (2H, s, CH_2), 2.62 (3H, s, CH_3), 6.58–7.65 (16H, m, H-Ar and NH_2), 9.93 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 25.9, 27.3, 28.6, 32.5, 41.4, 48.8, 50.9, 102.0, 107.7, 108.2, 122.2, 123.8, 124.1, 127.6, 127.9, 128.0, 128.1, 128.9, 129.9, 133.0, 137.5, 138.1, 143.6, 149.7, 153.5, 178.2, 193.4 Anal. calcd. for $C_{32}H_{30}N_4O_3$: C, 74.11; H, 5.83; N, 10.80%. Found: C, 74.17; H, 5.77; N, 10.87%.

3-(5-Amino-1-(4-nitrophenyl)-3-phenyl-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-1-methylindolin-2-one (4k). Yellow powder (70%); mp > 320°C. IR (KBr) (ν_{max}/cm^{-1}): 3465, 3219, 1714, 1601. MS (EI, 70 eV) m/z (%): 563 (M^+, 10), 538 (M^+, 40), 368 (70), 57 (100). ^{1}H NMR

(300 MHz, DMSO-d_6): δ_H 0.99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.95 and 2.09 (2H, AB system, $J = 15.7$ Hz, CH_2), 2.61 (5H, s, CH_2 and CH_3), 6.58–7.27 (11H, m, H-Ar and NH_2), 7.94 (2H, d, $J = 8.8$ Hz, H-Ar), 8.43 (2H, d, $J = 8.9$ Hz, H-Ar), 10.01 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C 25.9, 27.4, 28.5, 32.6, 41.45, 48.7, 50.9, 103.0, 107.9, 108.7, 122.3, 123.4, 124.2, 125.5, 127.8, 128.1, 128.6, 128.8, 132.4, 137.2, 137.9, 143.1, 143.6, 146.1, 151.4, 153.2, 177.9, 193.8. Anal. calcd. for $C_{32}H_{29}N_5O_5$: C, 68.19; H, 5.19; N, 12.43%. Found: C, 68.13; H, 5.24; N, 12.49%.

CONCLUSION

In conclusion, we have described a clean, simple, one-pot, three-component method for the preparation of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one derivatives in condensation reaction of 1*H*-pyrazol-5-amines, dimedone, and isatins under reflux in water.

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