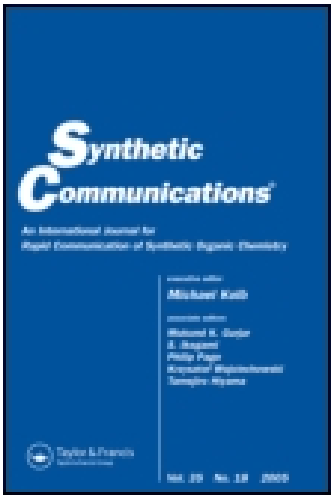

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Synthesis of 3-(3-Methyl-1-aryl-1H-pyrazol-5-yl)-2H-2-chromen-2-one Derivatives via a One-Pot, Three-Component Reaction

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SYNTHESIS OF 3-(3-METHYL-1-ARYL-1*H*-PYRAZOL-5-YL)-2*H*-2-CHROMEN-2-ONE DERIVATIVES VIA A ONE-POT, THREE-COMPONENT REACTION

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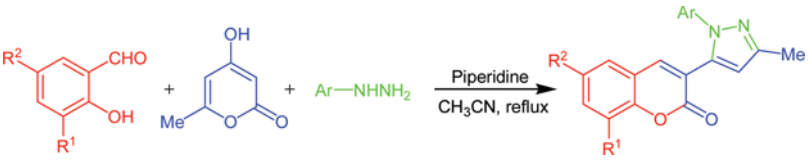
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of 3-(3-methyl-1-aryl-1*H*-pyrazol-5-yl)-2*H*-2-chromen-2-one derivatives by the reaction of salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and arylhydrazine in acetonitrile under reflux condition and in the presence of piperidine is reported. This three-component reaction has some advantages such as ease of handling, good yields, and easy purification. All structures were confirmed by infrared, mass, ^{1}H NMR, and ^{13}C NMR spectroscopy.*

Keywords Arylhydrazine; coumarin; 4-hydroxy-6-methyl-2*H*-pyran-2-one; pyrazole; salicylaldehyde

INTRODUCTION

Pyrazoles constitute a class of five-membered nitrogen-containing heterocyclic compounds. Because of their wide spectrum of biological activities, such as antifungal,[1] antiviral,[2] anticancer,[3] and anti-inflammatory[4] properties, they are widely used in the pharmaceutical industry and medicinal chemistry and they are also important core in natural products.[5,6] In addition, pyrazoles can act as kinase inhibitors for treatment of type 2 diabetes and obesity, thrombopiotin mimetics, and antiangiogenic agents.[7] Moreover, some pyrazoles are used in polymer and supramolecular chemistry, in the food industry, and as ultraviolet stabilizers and cosmetic colorings.[8–10] Accordingly, synthesis of new pyrazole derivatives and investigation of their biological activities have been considered by chemists.[11–13]

Coumarin moieties are a large group of oxygen-containing heterocycles that are widely distributed in plants such as grasses, legumes, and fruits.[14] Coumarins

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possess a wide range of biological activities including anticoagulant,[15] inhibition of HIV-1 protease,[16] hypnotic,[17] anti-inflammatory,[18] and antihelminthic.[19] Besides the biological applications, coumarins have been used in laser dyes, optical data storage devices, optical brightners, and solar cells.[20,21] Although many methods have been reported for the synthesis of coumarins, the development of novel strategies for synthesis of new coumarin derivatives is still required.[22–25]

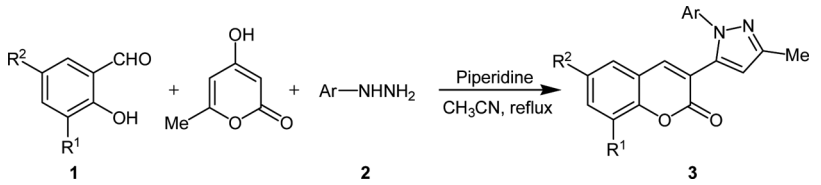
We are interested in examining the reaction of salicylaldehydes **1**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and arylhydrazines **2** to synthesize new coumarins containing pyrazole substitutions.

RESULTS AND DISCUSSION

In continuation of our studies on the synthesis of new heterocyclic compounds,[26–28] we decided to synthesize coumarin derivatives including pyrazole-substituted derivatives by the reaction of salicylaldehydes **1**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and arylhydrazines **2**. Our new synthetic route is shown in Scheme 1.

The reaction of salicylaldehydes **1**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and arylhydrazine **2** was performed in acetonitrile within 3 h in the presence of one drop of piperidine to produce 3-(3-methyl-1-aryl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-ones **3** in good yields (Table 1).

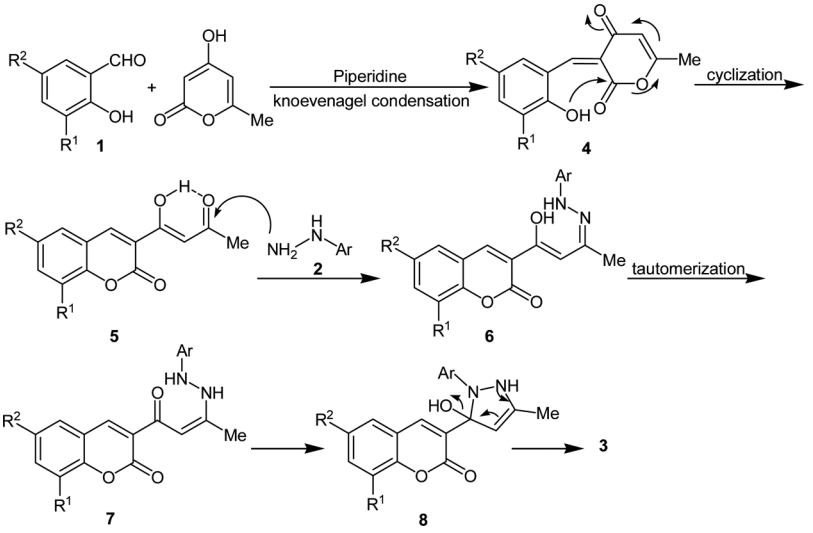
The structures of compounds **3a–f** were elucidated from their elemental analysis, infrared (IR), and high-field ^{1}H and ^{13}C NMR spectra. The IR spectrum of **3a** showed absorption bands due to the carbonyl group stretching frequency at 1724 cm^{-1} and absorption bands at 1602, 1497, 1464, and 1106 cm^{-1} assigned to the C=C and C-O groups, respectively. The mass spectrum of this compound displays the molecular ion peak at m/z 302 as a base peak, which is in agreement with the proposed structure. The ^{1}H NMR spectrum of **3a** showed three singlet signals for methyl, CH of the pyrazole ring, and CH of the coumarin ring groups (2.41, 6.63,



Scheme 1. Synthesis of 3-(3-methyl-1-aryl-1*H*-pyrazol-5-yl)-2*H*-2-chromen-2-one derivatives.

Table 1. 3-(3-Methyl-1-aryl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-ones **3**

Entry	R^1	R^2	Ar	Product	Yield (%)
1	H	H	Ph	**3a**	60
2	H	Br	Ph	**3b**	73
3	OCH_3	H	Ph	**3c**	69
4	Br	Br	Ph	**3d**	89
5	Br	Br	4-Me-C_6H_4	**3e**	84
6	Cl	Cl	Ph	**3f**	80



Scheme 2. Plausible mechanism for the formation of products **3a–f**.

and 7.48 ppm), and one doublet, two multiplets, and one triplet of doublet for aromatic hydrogens [7.28 ($^3J = 6.0$), 7.33–7.35, 7.40–7.42, and 7.55 ($^3J = 8.0$, $^4J = 1.6$)], respectively. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 17 distinct resonances in agreement with the suggested structure.

According to these results, a plausible mechanism for the sequential three-component reaction is proposed on the basis of known reactions[29,5] (Scheme 2).

The formation of product **3** can be explained by initial condensation between salicylaldehyde and 4-hydroxy-6-methyl-2*H*-pyran-2-one in the presence of piperidine to afford the desired 3-acetoacetylcoumarin **5**. Then the intermediate **5** can condense with an arylhydrazine and tautomerize to give intermediate **7**. Finally, intramolecular cyclization and dehydration of compound **7** give the product **3** in good yields. To evaluate the proposed mechanism, 3-acetoacetylcoumarin **5a** was synthesized separately and its structure has been confirmed by ^{1}H NMR and ^{13}C NMR spectroscopies. In another attempt, the reaction between compound **4a** and phenylhydrazine gave the desired product **3a**.

EXPERIMENTAL

The salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one and arylhydrazines, were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-400 Avance spectrometer at 400.13 and 100 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer and absorbencies are reported in centimeters^{-1}.

Typical Procedure for Preparation of 3-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-one (3a)

A solution of salicylaldeyde (**1a**, 0.122 g, 1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.126 g, 1 mmol) in acetonitrile (5 ml) and one drop of piperidine were magnetically stirred for 1 h at reflux. Then phenylhydrazine (**2a**, 0.108 g, 1 mmol) was added, and the solution was magnetically stirred for 2 h at reflux. After completion, the reaction was monitored by thin-layer chromatography (TLC), the solvent was evaporated, and the residue was purified by column chromatography over silica gel using *n*-hexane/ethyl acetate (9:1) as eluent to afford the pure product **3a**.

3-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-one (3a)

Yield: 181 mg (60%); white powder; mp = 126–127 °C. IR (KBr): 1724 (CO_2), 1602, 1497, and 1464 (Ar), 1106 (C-O) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): $\delta_H = 2.41$ (3H, s, CH_3), 6.63 (1H, s, CH of pyrazole), 7.28 (1H, d, $^3J_{HH} = 6.0$ Hz, CH_{para} of Ph), 7.33–7.35 (4H, m, CH of Ar), 7.40–7.42 (4H, m, CH of Ar), 7.48 (1H, s, CH^4 of chromene), 7.55 (1H, td, $^3J_{HH} = 8.0$ Hz, $^4J_{HH} = 1.6$ Hz, CH of Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta_C = 13.6$ (CH_3), 110.2 (CH^3 of pyrazole), 116.7 (CH^8 of chromene), 118.6 (C^3 of chromene), 118.9 (C^{4a} of chromene), 124.7 (CH^6 of chromene), 124.7 (2 CH_{ortho} of Ph), 127.7 (CH^5 of chromene), 128.2 (CH_{para} of Ph), 129.3 (2 CH_{meta} of Ph), 132.2 (CH^7 of chromene), 136.3 (C^5 of pyrazole), 140.2 (C_{ipso}-N of Ph), 142.2 (CH^4 of chromene), 149.6 (C^3 of pyrazole) 153.6 (C^{8a} of chromene), 159.0 (CO_2). MS (EI, 70 eV): m/z (%) = 302 (M^+, 100), 285 (19), 273 (62), 232 (21), 204 (34), 151 (25), 139 (28), 115 (33), 102 (28), 91 (34), 77 (77). Anal. Calcd. for $C_{19}H_{14}N_2O_2$ (302.33): C, 75.48; H, 4.67; N, 9.27%. Found: C, 75.37; H, 4.75; N, 9.20%.

CONCLUSION

In summary, we have disclosed a concise approach to the synthesis of 3-(3-methyl-1-aryl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-ones by a one-pot and sequential three-component reaction of salicylaldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and arylhydrazines. Good yields, inexpensive starting materials, and simple performance are the main aspect of the present method. Because of the importance of coumarins and pyrazoles, the present methods can be considered for biological evaluation in the near future.

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SUPPORTING INFORMATION

Full experimental details and ^1H and ^{13}C NMR spectra can be accessed on the publisher's website.

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