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Synthesis of 3-(2-(4,5-Dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one Derivatives via Multicomponent Approach

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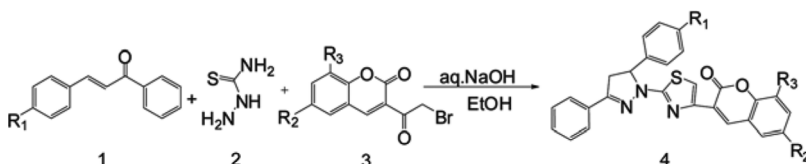
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SYNTHESIS OF 3-(2-(4,5-DIHYDRO-3,5-DIPHENYLPYRAZOL-1-YL)THIAZOL-4-YL)-2H-CHROMEN-2-ONE DERIVATIVES VIA MULTICOMPONENT APPROACH

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 Andhra Pradesh, India

GRAPHICAL ABSTRACT



Abstract An efficient synthesis of 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one derivatives by a simple, atom-economical, and multicomponent reaction of chalcones, thiosemicarbazide, and 3-(2-bromoacetyl) coumarins in the presence of aqueous sodium hydroxide in refluxing ethanol is reported. The structures of newly prepared compounds have been confirmed by their analytical and spectral (IR, ¹HNMR, ¹³CNMR and mass) data.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Chalcone; coumarin; multicomponent; pyrazole; thiazole

INTRODUCTION

Thiazole ring-containing compounds show pharmacological activities such as antimicrobial,^[1] antiinflammatory,^[2] antitubercular,^[3] antitumor,^[4] cardiotonic,^[5] analgesic,^[6] anti-HIV,^[7] and anti-allergenic^[8] activities. These are used in drug development for the curing of allergies,^[9] schizophrenia,^[10] and as hypnotics,^[11] and the different substituents of pyrazolines show various pharmacological activities such as antinociceptive,^[12] anticancer,^[13] antidepressant,^[14] and antidiabetic^[15] activities.

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Chalcones have good pharmacological properties such as nitric oxide inhibition,^[16] and antioxidant,^[17] antimalarial,^[18] analgesic,^[19] antiviral,^[20] and antitubercular^[21] activity.

Coumarin-containing compounds show a broad range of biological activities such as anthelmintic insecticide,^[22] antifungal,^[23] and herbicidal^[24] activities. Its derivatives show various pharmacological and physiological activities such as anticoagulant,^[25] antiviral,^[26] bactericidal,^[27] and anti-inflammatory^[28] activity.

Recently multicomponent reactions have been widely used in organic synthesis because of their advantages such as high efficiency, atom economy, convergence, exploratory power, and greater yield, leading to the straightforward synthesis of new structures.^[29]

In continuation of our earlier work^[30,31] on the synthesis of a heterocyclic system derived from coumarin, we report here in the facile one-pot synthesis of 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2*H*-chromen-2-one derivatives.

RESULTS AND DISCUSSION

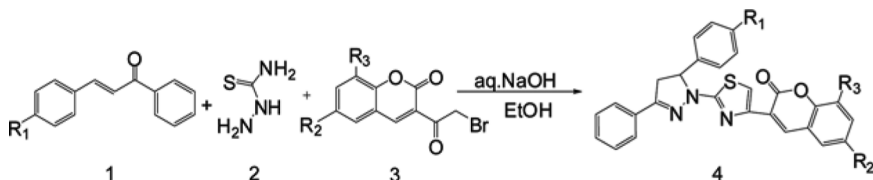
Synthesis of 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2*H*-chromen-2-ones (**4**) if has been achieved in one pot by using different substituted chalcones (**1**), thiosemicarbazide (**2**), and different substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**3**) in ethanol containing aqueous NaOH. These compounds are obtained in good yields.

Method 1

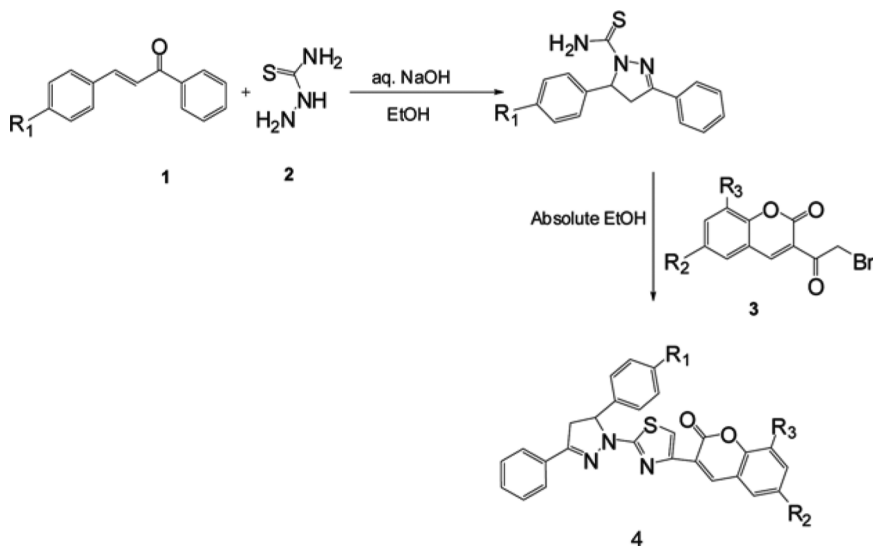
The structures (**4**) of newly prepared compounds were confirmed by unambiguous synthesis. In this method chalcones were reacted with thiosemicarbazide to give a thioamide intermediate. These compounds were reacted with various 3-(2-bromoacetyl) coumarins in absolute ethanol to yield the compounds **4**. This is a stepwise and unambiguous process. The products (**4**) obtained by both methods were found to be identical by their mixed melting points and thin-layer chromatographic (TLC) and infrared (IR) spectra (Scheme 1).

Method 2

The structures of the title compounds have been identified by analytical and spectral data (Scheme 2). In the IR spectrum the compound **4a** showed lactone C=O stretching vibration at 1719 cm⁻¹ and C=N stretching vibration at 1545 cm⁻¹.



Scheme 1. Synthesis of 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2*H*-chromen-2-one derivatives via multicomponent approach.



Scheme 2. Unambiguous synthesis of 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one.

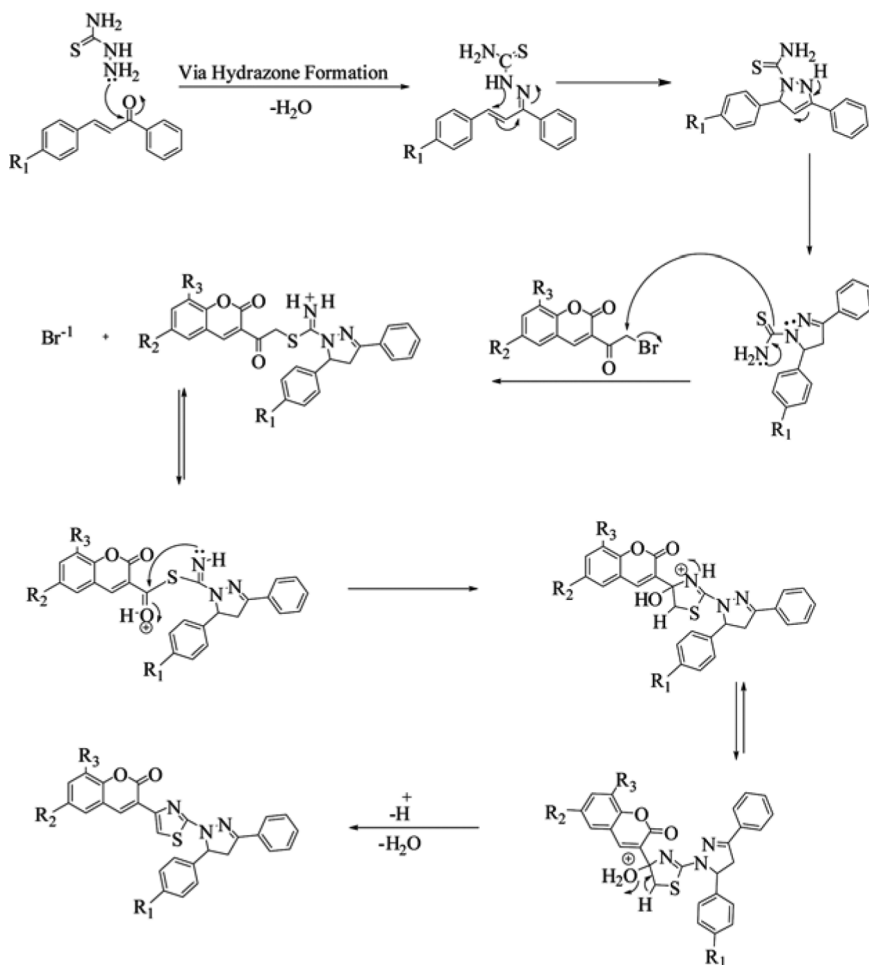
The ^1H NMR spectrum of 4a showed three double doublets (ABX pattern) at δ 3.36, 3.93, and 5.64, integrating for one proton each, and assigned to H_A , H_B , H_X proton of pyrazolone^[32] ring respectively. Aromatic protons appeared at δ 7.25–7.80 and C-4 of coumarin proton appeared at δ 8.17. The ^{13}C NMR spectrum of 4a shows aliphatic carbons at δ 43.4, 64.2 and the lactone carbonyl carbon appeared at 151.5. In the mass spectrum (ESI-MS) compound 4a showed quasi-molecular-ion peak at m/z 450. See Scheme 3 and Table 1.

CONCLUSION

In summary we have synthesized 3-(2-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-ones via multicomponent reaction of different chalcones, thiosemicarbazide, and substituted 3-(2-bromoacetyl)-2H-chromen-2-ones in ethanol containing aqueous NaOH in a one-pot reaction. It is a more efficient synthesis because of short reaction time, few steps, and high yields.

EXPERIMENTAL

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-coumarins^[34] were prepared by the literature procedure. Melting points were determined in open capillaries with a Stuart melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). IR spectra (KBr) were recorded on a Perkin-Elmer spectrum 100S. ^1H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ parts



Scheme 3. Mechanism^[33] for the formation of product **4**.

Table 1. Times and yields of compounds prepared

Entry	4	R ₁	R ₂	R ₃	Time (h)	Yield (%)
1	4a	H	H	H	4	85
2	4b	H	H	Br	4	80
3	4c	H	Br	Br	6	82
4	4d	H	H	Cl	4	80
5	4e	H	Cl	Cl	6	84
6	4f	H	H	NO ₂	5	78
7	4g	H	H	OCH ₃	4	80
8	4h	Br	H	H	4	85
9	4i	Br	H	Br	4	82
10	4j	Br	Br	Br	6	80
11	4k	Br	H	Cl	4	76
12	4l	Br	Cl	Cl	6	85

per million (ppm) using tetramethylsilane (TMS) as the standard. Electrospray ionization mass spectra (ESI-MS) were determined on Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

A mixture of 1,3-diphenyl-propenone (1 mmol), thiosemicarbazide (1 mmol), 3-(2-bromoacetyl)-2*H*-chromen-2-ones (1 mmol), and aqueous NaOH (0.08 in 1 ml of water) in ethanol (10 ml) was refluxed for 4 h and cooled, and the solid separated was filtered and recrystallized from methanol. Yellow solid, mp 261–263 °C. ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 3.36 (dd, *J* = 17.4 Hz, 7.4 Hz, 1H, H_A), 3.93 (dd, *J* = 17.4 Hz, 11.8 Hz, 1H, H_B), 5.64 (dd, *J* = 11.8 Hz, 7.4 Hz, 1H, H_X), 7.25–7.46 (m, 13H, ArH), 7.76–7.80 (m, 2H, ArH), 8.17 (s, 1H, C-4 of coumarin); ¹³C NMR (DMSO-*d*₆, δ ppm): 43.0, 64.4, 111.0, 115.8, 119.0, 120.4, 124.7, 126.4, 127.0, 127.6, 128.5, 128.8, 130.0, 130.8, 131.6, 138.2, 141.5, 143.7, 152.2, 153.3, 158.5, 163.5; IR (KBr, ν, cm^{−1}): 1719 (lactone carbonyl), 1545 (C=N); ESI-MS: *m/z* = 450 (*M* + 1) Anal. calcd. for C₂₇H₁₉N₃O₂S: C, 72.14; H, 4.26; N, 9.35. Found: C, 71.18; H, 4.22; N, 9.32.

Spectral and analytical data for other synthesized compounds are available in the online supplemental section.

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