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ONE-POT SYNTHESIS OF TRISUBSTITUTED PYRAZOLES *VIA* MULTICOMPONENT APPROACH

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An efficient one-pot multicomponent reaction for the synthesis of 1-aryl- or 1-heteryl-substituted 3,5-dimethylpyrazoles with excellent yields has been described. Reaction of 3-(2-bromoacetyl)coumarins or phenacyl bromides with acetylacetone and hydrazine hydrate in ethanol afforded the corresponding 3,5-dimethylpyrazoles in good yields. All the synthesized compounds were characterized by their analytical and spectral data.

Keywords: acetylacetone, 3-(2-bromoacetyl)coumarins, hydrazine hydrate, phenacyl bromides, pyrazole, one-pot, multicomponent reactions.

A multicomponent reaction, offering a straightforward route to generate complexity and diversity in a single operation, is an extremely powerful tool in combinatorial chemistry and drug discovery. Multicomponent reactions play an important role in modern organic chemistry because they generally exhibit higher atom economy and selectivity, as well as produce fewer by-products compared to classical multistep synthesis. In many cases, multicomponent reactions are easy to perform, inexpensive, and quick, consume less energy, and involve simple experimental procedures [1].

Pyrazoles are well-known and important nitrogen-containing heterocyclic compounds, and various methods have been developed for their synthesis [2]. Due to the interesting biological activity of substituted pyrazoles, considerable attention has been focused on this class of compounds.

Pyrazole derivatives have been found to possess antimicrobial [3], analgesic [4], immunosuppressive [5], anticancer [6], antidiabetic [7], and anti-inflammatory [8] activity. On the other hand, coumarin and its derivatives are biologically active compounds widely occurring in nature and are known to possess anti-inflammatory activity [9].

In view of the various biological activities of coumarins and pyrazoles, we became interested in new synthetic routes to pyrazoles incorporating the coumarin moiety.

As a part of our continuing work on the synthesis of novel heterocyclic systems [10–12], we have developed a novel one-pot reaction for the synthesis of 3-[2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-2H-chromen-2-one and 2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone derivatives *via* a three-component reaction.

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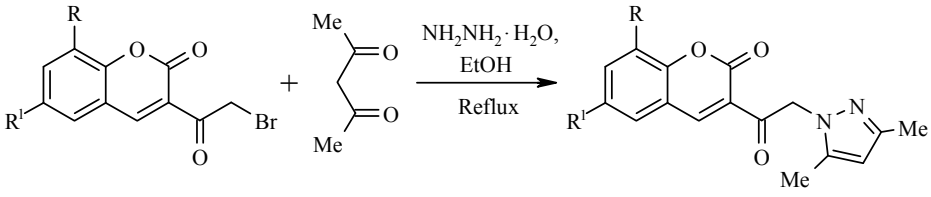
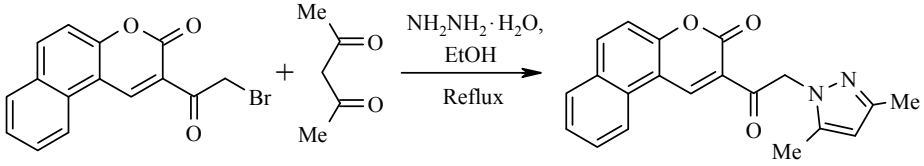
Scheme 1



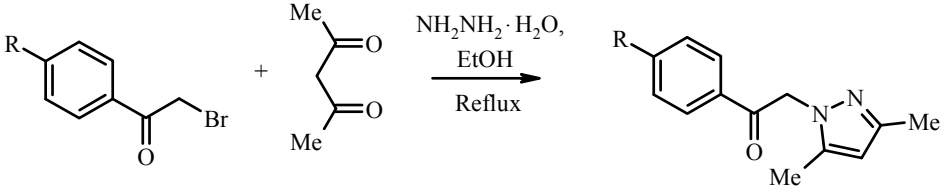
1a–f



1g

1 a R = R^1 = H; **b** R = Br, R^1 = H; **c** R = R^1 = Br; **d** R = Cl, R^1 = H; **e** R = R^1 = Cl; **f** R = H, R^1 = OMe

Scheme 2



2a–e

2 a R = H; **b** R = Cl; **c** R = Br; **d** R = OMe; **e** R = NO_2

TABLE 1. Analytical Data of Compounds **1a–g, 2a–e**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{16}H_{14}N_2O_3$	67.12 / 68.07	4.91 / 5.00	9.67 / 9.92	295	87
1b	$C_{16}H_{13}BrN_2O_3$	53.15 / 53.21	3.56 / 3.63	7.67 / 7.76	274	85
1c	$C_{16}H_{12}Br_2N_2O_3$	43.60 / 43.67	2.68 / 2.75	6.39 / 6.37	252	81
1d	$C_{16}H_{13}ClN_2O_3$	60.61 / 60.67	4.10 / 4.14	8.81 / 8.84	270	79
1e	$C_{16}H_{12}Cl_2N_2O_3$	54.74 / 54.72	3.38 / 3.44	7.91 / 7.98	265	76
1f	$C_{17}H_{16}N_2O_4$	68.31 / 65.38	5.10 / 5.16	8.91 / 8.97	210	85
1g	$C_{20}H_{16}N_2O_3$	72.21 / 72.28	4.80 / 4.85	8.38 / 8.43	288	82
2a	$C_{13}H_{14}N_2O$	72.81 / 72.87	6.51 / 6.59	12.96 / 13.07	274	76
2b	$C_{13}H_{13}ClN_2O$	62.71 / 62.78	5.21 / 5.27	14.12 / 14.25	291	81
2c	$C_{13}H_{13}BrN_2O$	53.21 / 53.26	4.41 / 4.47	9.51 / 9.56	270	85
2d	$C_{14}H_{16}N_2O_2$	68.80 / 68.83	6.56 / 6.60	11.41 / 11.47	186	81
2e	$C_{13}H_{13}N_3O_3$	60.18 / 60.22	4.97 / 5.05	16.16 / 16.21	186	78

TABLE 2. ^{1}H and ^{13}C* NMR Spectra of Compounds **1a–g, 2a–e**

Compound	Chemical shift ($CDCl_3$) δ, ppm (*J*, Hz)
1a	2.30 (3H, s, CH_3); 2.39 (3H, s, CH_3); 4.75 (2H, s, CH_2); 6.20 (1H, s, H pyrazole); 7.60 (1H, d, *J* = 8.0, H Ar); 7.65–7.78 (2H, m, H Ar); 7.79 (1H, d, *J* = 8.0, H Ar); 8.65 (1H, s, H-4 coumarin)
1b	2.32 (3H, s, CH_3); 2.39 (3H, s, CH_3); 4.76 (2H, s, CH_2); 5.96 (1H, s, H pyrazole); 8.21–8.32 (1H, m, H Ar); 8.43–8.51 (2H, m, H Ar); 8.65 (1H, s, H-4 coumarin)
1c	2.28 (3H, s, CH_3); 2.36 (3H, s, CH_3); 4.71 (2H, s, CH_2); 5.90 (1H, s, H pyrazole); 7.98 (1H, d, *J* = 2.0, H Ar); 8.15 (1H, d, *J* = 2.0, H Ar); 8.48 (1H, s, H-4 coumarin)
1d	2.30 (3H, s, CH_3); 2.37 (3H, s, CH_3); 4.78 (2H, s, CH_2); 5.92 (1H, s, H pyrazole); 7.40–7.56 (2H, m, H Ar); 7.92–8.00 (1H, m, H Ar); 8.21 (1H, s, H-4 coumarin)
1e	2.30 (3H, s, CH_3); 2.37 (3H, s, CH_3); 4.75 (2H, s, CH_2); 5.92 (1H, s, H pyrazole); 7.92 (1H, d, *J* = 2.0, H Ar); 8.22 (1H, d, *J* = 2.0, H Ar); 8.68 (1H, s, H-4 coumarin)
1f	2.19 (3H, s, CH_3); 2.22 (3H, s, CH_3); 4.00 (3H, s, OCH_3); 5.56 (2H, s, CH_2); 5.90 (1H, s, H pyrazole); 7.22–7.30 (3H, m, H Ar); 8.57 (1H, s, H-4 coumarin)
1g	2.30 (3H, s, CH_3); 2.38 (3H, s, CH_3); 4.78 (2H, s, CH_2); 5.94 (1H, s, H pyrazole); 7.42–8.07 (5H, m, H Ar); 8.41–8.49 (1H, m, H Ar); 9.10 (1H, s, H-4 coumarin)
2a	2.16 (3H, s, CH_3); 2.24 (3H, s, CH_3); 5.47 (2H, s, CH_2); 5.92 (1H, s, H pyrazole); 7.49–7.53 (2H, m, H Ar); 7.61–7.65 (1H, m, H Ar); 7.97–7.99 (2H, m, H Ar)
2b	2.08 (3H, s, CH_3); 2.09 (3H, s, CH_3); 5.67 (2H, s, CH_2); 5.86 (1H, s, H pyrazole); 7.66 (2H, d, *J* = 8.0, H Ar); 8.05 (2H, d, *J* = 8.4, H Ar)
2c	2.16 (3H, s, CH_3); 2.23 (3H, s, CH_3); 5.42 (2H, s, CH_2); 5.91 (1H, s, H pyrazole); 7.64 (2H, d, *J* = 8.4, H Ar); 7.84 (2H, d, *J* = 8.4, H Ar)
2d	2.16 (3H, s, CH_3); 2.23 (3H, s, CH_3); 3.88 (3H, s, OCH_3); 5.40 (2H, s, CH_2); 5.91 (1H, s, H pyrazole); 6.96 (2H, d, *J* = 8.8, H Ar); 7.96 (2H, d, *J* = 8.8, H Ar)
2e	2.16 (3H, s, CH_3); 2.23 (3H, s, CH_3); 5.72 (2H, s, CH_2); 6.41 (1H, s, H pyrazole); 8.22 (2H, d, *J* = 8.8, H Ar); 8.29 (2H, d, *J* = 8.8, H Ar)

* ^{13}C NMR, δ, ppm: compound **1a** (in $CDCl_3$) – 10.8, 13.4, 103.7, 105.4, 116.1, 119.5, 120.9, 124.5, 128.1, 131.1, 136.7, 138.0, 139.1, 147.0, 152.6, 158.8; compound **2a** (in DMSO-d_6) – 10.5, 13.2, 55.1, 104.9, 128.1, 128.9, 133.9, 134.5, 140.1, 146.1, 193.9; compound **2b** (in DMSO-d_6) – 10.5, 13.3, 55.1, 105.0, 129.1, 130.1, 133.3, 138.9, 140.2, 146.4, 193.1.

TABLE 3. IR Spectra of Compounds **1a–g, 2a–e**

Compound	ν, cm^{-1}			
	C=C	CN	C=O	lactone C=O
1a*	1544	1598	1692	1741
1b	1546	1600	1687	1731
1c	1556	1603	1687	1713
1d	1558	1609	1679	1728
1e	1549	1603	1692	1733
1f	1566	1606	1691	1722
1g	1562	1612	1688	1726
2a	1582	1617	1690	
2b	1576	1602	1713	
2c	1587	1607	1691	
2d*	1563	1594	1690	
2e	1554	1602	1718	

* Mass spectrum, *m/z:* compound **1a** – $[M+H]^+$ 283; compound **2a** – $[M+H]^+$ 249.

Condensation of various 3-(2-bromoacetyl)coumarins and phenacyl bromides with hydrazine hydrate and acetylacetone resulted in the formation of the cyclic products **1** and **2**, respectively. We believe that in the formation of the title products hydrazine hydrate first reacts with an α-halo carbonyl compound to give a phenacyl hydrazine intermediate which further undergoes cyclocondensation with acetylacetone to close the pyrazole ring. The pyrazoles of both series were obtained in good yields, which were not influenced by substituents in coumarin or benzene rings. The structures of the newly prepared compounds have been established on the basis of elemental analysis (Table 1) and spectral data (Table 2 and 3).

EXPERIMENTAL

Melting points were determined in open capillaries with a Cintex melting point apparatus and were uncorrected. IR spectra (KBr) were recorded on a Thermo Nicolet Nexus 670 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer (400 and 100 MHz, respectively) using TMS as internal standard. Mass spectra (EI-MS) were recorded on a Perkin-Elmer (SCIEX API-2000) at 12.5 eV. Elemental analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked on TLC plates (E. Merck, Mumbai, India). All the reagents and solvents were purchased from commercial sources and used without further purification. 3-(2-Bromoacetyl)coumarins were prepared using literature procedure [13].

Synthesis of Compounds 1a–g and 2a–e (**General Method**). A solution containing an equimolar amount of the appropriate 3-(2-bromoacetyl)coumarin or phenacyl bromide (1 mmol), hydrazine hydrate (0.048 ml, 1 mmol), and acetyl acetone (0.1 ml, 1 mmol) in ethanol (10 ml) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction mixture was cooled to room temperature. The product was separated by filtration, washed with water, and recrystallized from ethanol (compounds **1a–g**) or methanol (compounds **2a–e**).

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