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Synthesis of 3-(2-oxo-*2H*-chromen-3-yl)-1-phenyl-*1H*-pyrazole-4-carbaldehydes

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ABSTRACT

*3-acetylchromen-2-ones (**1**) when treated with phenylhydrazine in acetic acid gave 3-(1-(2-phenylhydrazono)ethyl)-2H-chromen-2-ones (**2**) which on Vilsmeier-Haack reaction gave the title compounds 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes (**3**).*

Keywords: 3-acetylchromen-2-ones, phenylhydrazine, pyrazoles, Vilsmeier-Haack reaction.

INTRODUCTION

The synthesis of coumarins and their derivatives have attracted the attention of chemists for a long time because a large number of natural [1-2] and synthetic products [3-4] contain this nucleus. Coumarin derivatives have been reported to exhibit excellent biological activities such as anti-cancer [5], anti-oxidant [6], anti-microbial [7], anti-bacterial [8] etc.

Pyrazole derivatives, too, have attracted increasing attention due to their numerous biological activities, such as antimicrobial [9], analgesic [10], anti-fungal [11], anti-inflammatory [12] etc.

Keeping in view the importance of coumarins & pyrazoles and in continuation of our earlier work [13-15] on synthesis of oxygen containing heterocycles of potential biological interest, we now wish to describe our work on synthesis of heterocycles containing both the coumarin and pyrazole moieties.

MATERIALS AND METHODS

Melting points are uncorrected and were determined in open capillaries in sulfuric acid bath and are uncorrected. IR Spectra were recorded with Jasca FT-IR 5300. ^{1}H NMR and spectra were recorded in $CDCl_3$ / DMSO-d_6 using Varian 400-MHz instrument. Mass spectra were recorded on an Agilent LC-MS instrument giving only M^+ values in Q+1 mode. Thin-layer chromatography (TLC) analyses were carried out on glass plates coated with silica gel GF-254 and visualization was achieved using iodine vapors or UV lamp.

Preparation of 2 from 1 (General procedure): A mixture of **1** (10 mmol), phenylhydrazine (10 mmol) and acetic acid (20 mL) was stirred at RT for 10-15 min. The reaction was checked by TLC. After completion of reaction, the

mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 x 20 mL) and dried. The crude product was recrystallized from a suitable solvent to obtain pure **2**. (Please also see Table 1).

2a: IR (KBr): 3315-3418 cm^{-1} (-NH group), 1744 cm^{-1} (-CO of coumarin ring); ^{1}H NMR DMSO-d_6/TMS): δ 9.42 (s, 1H, -N**H**), 8.29 (s, 1H, -C=C**H** of coumarin ring), 6.77-7.85 (m, 8H, Ar-**H**), 2.22 (s, 3H, -C**H**$_3$); LCMS (CI): m/z 279 [M.$^+$+1].

2b: IR (KBr): 3309-3405 cm^{-1} (broad, medium, -NH group), 1721 cm^{-1} (strong, sharp, -CO of coumarin ring); ^{1}H NMR (DMSO-d_6/TMS): δ 9.04 (s, 1H, -N**H**), 8.37 (s, 1H, -C=C**H** of coumarin ring), 7.18-7.94 (m, 8H, Ar-**H**), 2.34 (s, 3H, -C**H**$_3$); LCMS (CI): m/z 313 [M.$^+$+1].

2c: IR (KBr): 3335-3438 cm^{-1} (broad, medium, -NH group), 1726 cm^{-1} (strong, sharp, -CO of coumarin ring); ^{1}H NMR (DMSO-d_6/TMS): δ 9.38 (s, 1H, -N**H**), 8.09 (s, 1H, -C=C**H** of coumarin ring), 7.20-7.89 (m, 8H, Ar-**H**), 2.28 (s, 3H, -C**H**$_3$); LCMS (CI): m/z 358 [M.$^+$+1].

2d: IR (KBr): 3298-3402 cm^{-1} (broad, medium, -NH group), 1732 cm^{-1} (strong, sharp, -CO of coumarin ring); ^{1}H NMR (DMSO-d_6/TMS): δ 9.11 (s, 1H, -N**H**), 8.82 (s, 1H, -C=C**H** of coumarin ring), 7.20-8.25 (m, 8H, Ar-**H**), 2.08 (s, 3H, -C**H**$_3$); LCMS (CI): m/z 324 [M.$^+$+1].

2e: IR (KBr): 3330-3420 cm^{-1} (broad, medium, -NH group), 1714 cm^{-1} (strong, sharp, -CO of coumarin ring); ^{1}H NMR (DMSO-d_6/TMS): δ 9.44 (s, 1H, -N**H**), 8.17 (s, 1H, -C=C**H** of coumarin ring), 6.77-7.40 (m, 8H, Ar-**H**), 3.92 (s, 3H, -OC**H**$_3$), 2.22 (s, 3H, -C**H**$_3$); LCMS (CI): m/z 309 [M.$^+$+1].

General procedure for synthesis of 3 from 2: To a cold solution of DMF (10 mL) and $POCl_3$ (2 mL) in an ice bath, was added (3-(1-(2-phenylhydrazono)ethyl)-2H-chromen-2-ones **(2)** (5 mmol). The reaction mixture was stirred at RT for 2-3 h. After the completion of reaction, as indicated by the disappearance of starting materials in TLC, the mixture was poured into ice-cold water (30 mL). The separated solid was filtered, washed with water and dried to obtain crude **3.** Recrystallization of crude **3** from a suitable solvent gave pure **3.** (Please also see Table 1).

3a: IR (KBr): 1764 cm^{-1} (-CO of coumarin ring), 1722 cm^{-1} (-CO of aldehyde group); ^{1}H NMR (DMSO-d_6/TMS): δ 9.97 (s, 1H, -C**H**O), 9.27 (s, 1H, -C=C**H** of pyrazole ring), 8.46 (s, 1H, -C=C**H** of coumarin ring) and 7.41-8.00 (m, 8H, Ar-**H**); LCMS (CI): m/z 317 [M.$^+$+1].

3b: IR (KBr): 1786 cm^{-1} (strong, sharp, -CO of coumarin ring), 1740 cm^{-1} (strong, sharp, -CO of aldehyde group); ^{1}H NMR (DMSO-d_6/TMS): δ 9.93 (s, 1H, -C**H**O), 9.29 (s, 1H, -C=C**H** of pyrazole ring), 8.42 (s, 1H, -C=C**H** of coumarin ring) and 7.43-8.00 (m, 8H, Ar-**H**); LCMS (CI): m/z 351 [M.$^+$+1].

3c: IR (KBr): 1764 cm^{-1} (strong, sharp, -CO of coumarin ring), 1729 cm^{-1} (strong, sharp, -CO of aldehyde group); ^{1}H NMR (DMSO-d_6/TMS): δ 9.74 (s, 1H, -C**H**O), 9.04 (s, 1H, -C=C**H** of pyrazole ring), 8.76 (s, 1H, -C=C**H** of coumarin ring) and 7.46-8.40 (m, 8H, Ar-**H**); LCMS (CI): m/z 396 [M.$^+$+1].

3d: IR (KBr): 1756 cm^{-1} (strong, sharp, -CO of coumarin ring), 1716 cm^{-1} (strong, sharp, -CO of aldehyde group); ^{1}H NMR (DMSO-d_6/TMS): δ 9.86 (s, 1H, -C**H**O), 9.12 (s, 1H, -C=C**H** of pyrazole ring), 8.20 (s, 1H, -C=C**H** of coumarin ring) and 7.31-7.64 (m, 8H, Ar-**H**); LCMS (CI): m/z 362 [M.$^+$+1].

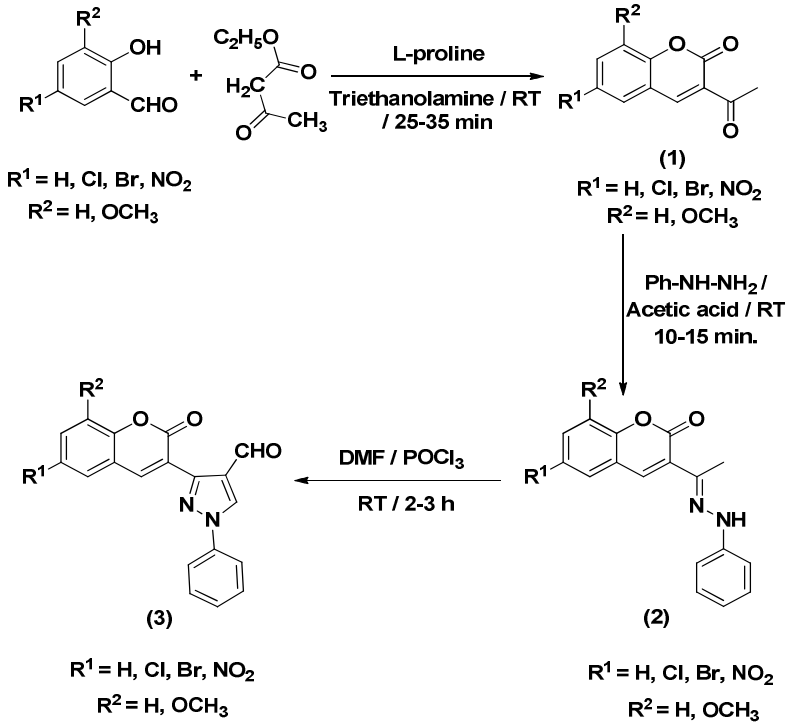
3e: IR (KBr): 1744 cm^{-1} (strong, sharp, -CO of coumarin ring), 1711 cm^{-1} (strong, sharp, -CO of aldehyde group); ^{1}H NMR (DMSO-d_6/TMS): δ 9.92 (s, 1H, -C**H**O), 9.28 (s, 1H, -C=C**H** of pyrazole ring), 8.44 (s, 1H, -C=C**H** of coumarin ring), 7.34-8.00 (m, 8H, Ar-**H**), 3.94 (s, 1H, -OC**H**$_3$); LCMS (CI): m/z 347 [M.$^+$+1].

Table 1: Reaction time, yield & physical data of compounds 2(a-e), 3(a-e)

Entry	Starting material used	Product obtained	Time	Yield (%)	Melting point °C (Solvent)
1	**1a**: R^1 = H, R^2 = H	**2a**: R^1 = H, R^2 = H	10 min	93	186-188 [lit[16] M.P 188 °C] (Ethanol)
2	**1b**: R^1 = Cl, R^2 = H	**2b**: R^1 = Cl, R^2 = H	15 min	85	132-134 (Methanol)
3	**1c**: R^1 = Br, R^2 = H	**2c**: R^1 = Br, R^2 = H	12 min	88	168-170 (Methanol)
4	**1d**: R^1 = NO_2, R^2 = H	**2d**: R^1 = NO_2, R^2 = H	10 min	86	180-182 (Acetic acid)
5	**1e**: R^1 = H, R^2 = OCH_3	**2e**: R^1 = H, R^2 = OCH_3	15 min	91	161-163 (Methanol)
6	**2a:** R^1 = H, R^2 = H	**3a**: R^1 = H, R^2 = H	2 h	87	212-214 [lit[16] M.P 215-216 °C] (Methanol)
7	**2b:** R^1 = Cl, R^2 = H	**3b**: R^1 = Cl, R^2 = H	2½ h	75	164-166 (Ethanol)
8	**2c:** R^1 = Br, R^2 = H	**3c**: R^1 = Br, R^2 = H	2 h	79	223-225 (Ethanol)
9	**2d:** R^1 = NO_2, R^2 = H	**3d**: R^1 = NO_2, R^2 = H	3 h	73	203-205 (Acetonitrile)
10	**2e**: R^1 = H, R^2 = OCH_3	**3e**: R^1 = H, R^2 = OCH_3	2½ h	72	238-240 (Chloroform)

RESULTS AND DISCUSSION

Commercially available salicylaldehydes were treated with ethyl acetoacetate in triethanolamine containing catalytic amount of L-proline at RT for 30 min to yield 3-acetylchromen-2-ones[15] (**1**). These, on treatment with phenylhydrazine in acetic acid at RT for 10 min resulted in the formation of the corresponding phenylhydrazones, (3-(1-(2-phenylhydrazono)ethyl)-2H-chromen-2-one (**2**). The latter on Vilsmeier-Haack formylation gave the title compounds 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**3**) in very good yields and good purity without the need of column chromatography. Thus, Vilsmeier-Haack reaction of hydrazones provides an efficient route for the synthesis of coumarinyl-pyrazoles.



Scheme 1: Synthesis of 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes

All the compounds obtained in this present work have been well characterized by spectral methods.

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