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NOTE

A Facile One-Pot Synthesis of Chromen-2-one Derivatives Fused with Five Membered Heterocycles

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A facile one-pot synthesis of 3-benzoxazol-2-yl-chromen-2-ones (**4**) by the condensation of chromen-2-one-3-carboxylates (**1**) with *o*-hydroxy aniline (**3**) is being reported in this paper. Alternatively 3-benzoxazol-2-yl-chromen-2-ones are prepared from chromen-2-one-3-carboxylic acids (**2**). The structures of all the products have been established by their spectral and analytical data.

Key Words: Chromen-2-one-3-carboxylates, Chromen-2-one-3-carboxylic acid, *o*-Hydroxy aniline, Polyphosphoric acid.

During the investigation of the literature we found that heterocycles containing imidazoles, oxadiazoles and oxazoles have been reported to exhibit broad spectrum of biological activities, which include antibacterial[1], anticonvulsant[2,3], anti-inflammatory[4], CNS stimulant[5], antihypertensive[6], anticancer[7] and antimicrobial[8] activities.

Chromen-2-ones are important compounds found widely in nature[9] and have numerous applications in medicine (*e.g.* anticlotting)[10] and perfumery[11], as dyes in laser technology[12a] and as fluorescent indicators[12b]. Chomen-2-one derivatives condensed with the ring system containing nitrogen and oxygen hetero-elements have been reported to exhibit significant biological activities such as an antitumor[13] and chemotherapy[14]. Keeping this in view, the present paper deals with the synthesis of chromen-2-ones containing oxadiazole moieties.

General conditions: Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR was recorded on VARIAN 400 MHz instrument and mass spectra were recorded on Agilent-LC-MS instrument.

Preaparation of 3-benzoxazol-2-yl-chromen-2-ones (4) from 1: A mixture of **1** (6.32 g, 0.1 mol) and **3** (5.66 g, 0.1 mol) was heated in polyphosphoric acid, for a period of 6 h. The completion of reaction was confirmed by thin layer chromatography. After that the complete disappearance of the substrate spot on thin layer chromatography, the reaction mixture was cooled to room temperature and poured in ice-cold water. The separated solid was filtered washed and dried to obtain crude 3-benzoxazol-2-yl-chromen-2-ones (**4**). The crude residual product was purified by column chromatography using ethylacetate and hexane (15:85) to give pure compound **4**.

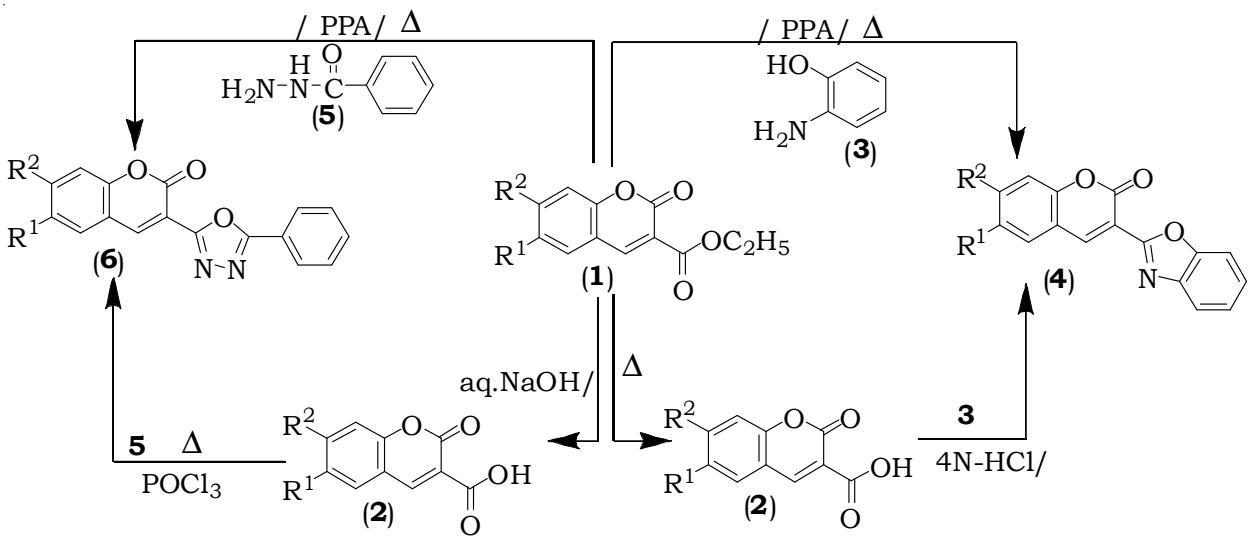
4a. Colourless solid; yield 1.9 g (90 %); m.p. 191-92 ºC; spectral data is described under results & discussion.

4b. Colourless solid; yield 0.8 g (87 %); m.p. 246-47 ºC; IR (KBr): 3220 cm^{-1} (medium, broad, -OH stretching), 1730 (strong, sharp, carbonyl group of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 7.08-8.90 (m, complex, 8 H aryl protons) and 10.89 (s, 1H, hydroxyl proton); mass: *m/z* 280 (M^{+}+1).

4c. Colourless solid; yield 1.4 g (88 %); m.p. 224-26 ºC; IR (KBr): 1743 (strong, sharp, carbonyl group of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): 4.08 (S, 3H, methoxy protons) and 7.12-8.92 (m, complex, 8H aryl protons); mass: *m/z* 294 (M^{+}+1).

4d. Colourless solid yield 1.9 g (87 %); m.p. 237-39 ºC; IR (KBr): 1739 cm^{-1} (strong, sharp, carbonyl group of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): 7.09-8.90 (m, complex, 7 H aryl protons); mass: *m/z* 330 (M^{+}+1).

Alternative general procedure for the preparation of 4 from 2: A mixture of **2** (4.5 g, 0.1 mol) and **3** (3.86 g, 0.1 mol) was refluxed in 4N-HCl, for 7 h, under Philips condition, resulted in a product homogeneous on TLC and different from the starting material. At the end, the reaction mixture was poured in ice-cold water (50 mL). The separated solid was filtered washed with water and dried well to obtain the crude **4**. The crude residue was purified on dissolving in ethyl acetate and water. Finally, the organic layer was dried and concentrated under reduced pressure to obtain pure compound **4**.



Scheme-I

Treatment of chromen-2-one-3-carboxylate[15] (**1a** *i.e.*, **1**, R^1=R^2=H), with *o*-hydroxy aniline (**3**) in polyphosphoric acid (PPA) for 6 h gave a product 3-benzoxazol-2-yl-chromen-2-one (**4a**, *i.e.* **4**, R^1=R^2=H) homogenous on TLC and different from the starting material. The structure of this compound was supported by spectral and analytical data. Thus, its IR (KBr), spectrum showed characteristic peak at 1745 cm^{-1} due to lactone C=O group. Its ^{1}H NMR (DMSO-d_6/TMS) spectrum, showed signals at δ 6.94-8.96 (complex m, 9 H, aryl protons). Its mass spectrum when recorded in CI method showed a molecular ion peak at *m/z* (*i.e.*, M^++1) 263 (base peak) corresponding to a molecular mass of 262.

Above reaction was found to be general one, by adopting the same above procedure, other compounds namely, 3-(1H-benzoxazol-2-yl)-6-hydroxy-chromen-2-one (**4b**, *i.e.*, **4**, R^1 = OH, R^2 = H), 3-(1H-benzoxazol-2-yl)-6-methoxy-chromen-2-one (**4c**, *i.e.*, **4**, R^1 = OCH_3, R^2 = H) and 3-(1H-benzoxazol-2-yl)-6,7-dichloro-chromen-2-one (**4d**, *i.e.*, **4**, R^1 = R^2 = Cl) synthesized. All the compounds have been characterized by spectral and analytical data. The yields, melting points and spectral data are given in experimental section.

In an alternative procedure, chromen-2-one-3-carboxylic acid (**2a** *i.e.*, **2**, R^1 = R^2 = H), when subjected to Philips condition[15,16], *i.e.*, when refluxed with **3** in 4N-HCl for a period of 7 h afforded a solid **4a** (*i.e.*, R^1 = R^2 = H) which was found to be identical in all respects like mp, mmp and co-tlc with the compound which obtained from **1a** (*i.e.*, **1**, R^1 = R^2 = H), with compound **3** (**Scheme-I**).

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