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Solvent-free synthesis of chromene derivatives

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Abstract: We report the reaction between dialkyl acetylenedicarboxylates and enolic systems such as 4-hydroxy coumarin, 5,5-dimethyl-1,3-cyclohexanedione, 1,3-cyclohexanedione and 1,3-cyclopentanedione in the presence of isoquinoline under solvent-free conditions which leads to chromene derivatives.

Keywords: One-pot reactions, 4-Hydroxy coumarin, Acetylenic compounds, Solvent-free, Isoquinoline.

Introduction

Chromenes have attracted considerable attention due to their biological activity and their presence in a variety of significant natural products [1]. Pyrano [3,2-c]chromene derivatives are a class of important heterocycles with a wide range of biological properties [2] such as spasmolytic, diuretic, anticoagulant, anti-cancer, and anti-anaphylactic activity [3]. Moreover they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [4]. Consequently, a number of synthetic strategies have been reported for the construction pyrano[3,2-c]chromene derivatives have been reported [5]. Some of the reported procedures require long reaction times, multi-step reactions and complex synthetic pathways, afford products with only modest yields [6-13]. Therefore, the development of more effective methods for their preparation is still necessary. We wish to report herein the results of our studies on the reaction of O-H acidic compounds **1** with activated acetylenic compounds **2** in the presence of isoquinoline **3** under solvent-free conditions at 70 ^{o}C (Scheme **1**).

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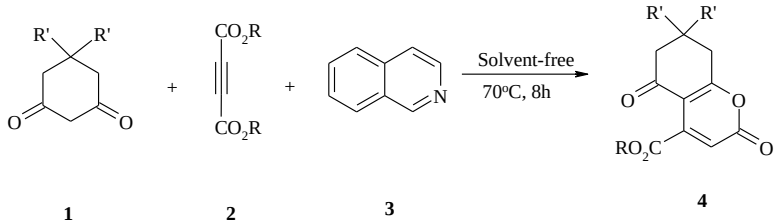
Results and discussion

The reaction of dimedone **1** with dialkyl acetylenedicarboxylates **2** in the presence of isoquinoline **3** under solvent-free conditions at 70^{o}C afforded 2*H*-chromene-4-carboxylate (**4**) in excellent yield (Scheme **1**). The procedure was simple and easy to handle. Structures of compounds **4a–4d** were assigned by IR, ^{1}HNMR, ^{13}CNMR and mass spectral data. The ^{1}HNMR spectrum of **4a** exhibited one singlet at δ = 1.22 for methyl protons, two singlet at δ = 2.45 and 2.85 for the CH_2 protons, one singlet at δ = 3.87 for methoxy group and one singlet at 6.27 for methin proton. The carbonyl group resonances in ^{13}CNMR spectra of **4a** appear at 165.8, 174.2 and 192.5 ppm. The mass spectra of **4a** displayed the molecular ion peaks at 250.

To explain the result of these reactions we suggest the mechanism of these reactions is driven from the initial formation of a 1:1 zwitterionic intermediate [14-19] **5** between isoquinoline and activated acetylenes. This intermediate is protonated by enolic system and then attacked by the conjugate base of the CH-acid. Cyclization of this intermediate leads to the compound **4** (Scheme **2**).

Under similar conditions, the reaction of isoquinoline with dialkyl acetylenedicarboxylates and 4-hydroxycoumarin **11** led to methyl 2,5-dihydro-2,5-

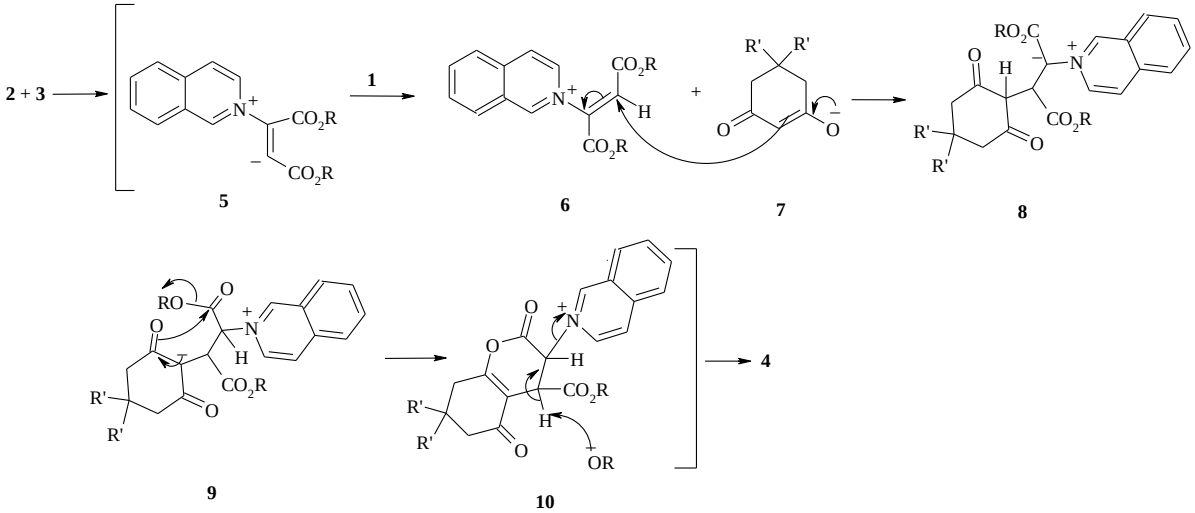
dioxopyrano[3,2-c]chromene-4-carboxylate **12** in 92% yield (Scheme **3**).



1 **2** **3** **4**

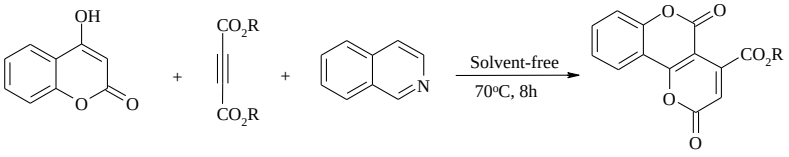
1, 2, 4	R	R'	Yield/ % of **4**
a	Me	Me	95
b	Et	Me	92
c	Me	H	87
d	Et	H	90

Scheme 1: Three-component reactions of enolic systems activated acetylenic compounds and isoquinoline.



5 **6** **7** **8** **9** **10**

Scheme 2: Possible mechanism for the formation of products **4**.



11 **2** **3** **12**

2, 11	R	Yield/ % of **12**
a	Me	87
b	Et	85

Scheme 3: Three-component reactions of 4-hydroxycoumarine, acetylenic compounds and isoquinoline.

In the ^{1}H NMR spectrum of compound 12a methoxy group was observed at σ 3.98 ppm as a single signal. A singlet was observed at σ 6.42 for the olefinic proton. The aromatic protons appeared at σ 7.45-8.18 ppm. In the ^{13}C NMR spectrum fourteen distinct signals were observed, which is consistent with the proposed structure.

Conclusion

In summary, the reaction of enolic system and activated acetylenic compounds in the presence of

isoquinoline under solvent-free conditions which afforded chromene derivatives in excellent yields. The advantages of our work are as follows: (1) the reaction is performed under solvent-free conditions. (2) No catalyst is required for this reaction. (3) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches**.**

Experimental

All chemicals were obtained from commercial sources. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

General procedure for preparation of compounds 4a-d and 12a-b:

A mixture of enolic system **1** or **11** (2 mmol) and dialkyl acetylenedicarboxylate **2** (2 mmol) was warmed at about 70 °C for 30 min. Then, isoquinoline **3** (0.26 g, 2 mmol) was added slowly. The reaction mixture was stirred for 8 h at 70 °C, and then poured into 15 mL of water. The resulting precipitate was separated by filtration and using Et_2O to afford the pure title compounds.

Methyl 5,6,7,8-tetrahydro-7,7-dimethyl-2,5-dioxo-2H-chromene-4-carboxylate (4a):

White powder; yield 0.47 g (95%), mp 97-99 °C; IR (KBr) ν_{max}/cm^{-1}: 1740, 1675, 1548, 1323 and 1254 cm^{-1}. ^{1}H NMR: σ 1.22 (6 H, s, 2 Me), 2.45(2 H, s, CH_2), 2.85 (2 H, s, CH_2), 3.87 (3 H, s, MeO), 6.27 (1 H, s, CH) ppm. ^{13}C NMR: σ 28.1 (2 Me), 32.4 (C), 41.9 (CH_2), 50.4 (CH_2), 52.7 (MeO), 111.3 (CH), 111.7 (C), 145.7 (C), 159.1 (C), 165.8 (C=O), 174.2 (C=O), 192.5 (C=O) ppm. MS (*m/z*, %): 250 (M^+, 10), 219 (86), 31 (100). Anal.Calc. for $C_{13}H_{14}O_5$ (250.25): C, 62.40; H, 5.64%. Found: C, 62.48; H, 5.75%.

Ethyl 5,6,7,8-tetrahydro-7,7-dimethyl-2,5-dioxo-2H-chromene-4-carboxylate (4b):

White powder; yield 0.49 g (92%), mp 100-102 °C; IR (KBr) ν_{max}/cm^{-1}: 1762, 1735, 1548, 1487, 1334 and 1264 cm^{-1}. ^{1}H NMR: σ 1.15 (6 H, s, 2 Me), 1.37 (3 H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 2.42 (2 H, s, CH_2), 2.74 (2 H, s, CH_2), 4.42 (2 H, q, $^3J_{HH}$ 7.2 Hz, OCH_2), 6.15 (1 H, s, CH) ppm. ^{13}C NMR: σ 14.2 (Me), 28.5 (2 Me), 33.2 (C), 42.6 (CH_2), 51.3 (CH_2) 62.9 (OCH_2), 112.2 (CH), 112.5 (C), 146.5 (C), 159.7 (C), 165.8 (C=O), 174.5 (C=O), 192.8 (C=O) ppm. Anal.Calc. for $C_{14}H_{16}O_5$ (264.28): C, 63.63; H, 6.10%. Found: C, 63.80; H, 6.18%.

Methyl 5,6,7,8-tetrahydro-2,5-dioxo-2H-chromene-4-carboxylate (4c):

Pale yellow powder; yield 0.39 g (87%). IR (KBr) ν_{max}/cm^{-1}: 1740, 1673, 1587, 1425, 1325 and 1290 cm^{-1}. ^{1}H NMR: σ 2.25 (2 H, m, CH_2), 2.62 (2 H, t, CH_2, $^3J_{HH}$ 6.5 Hz), 2.93 (2 H, t, CH_2, $^3J_{HH}$ 6.5 Hz), 3.95 (3 H, s, MeO), 6.25 (1 H, s, CH) ppm. ^{13}C NMR: σ 19.9 (CH_2), 28.6 (CH_2), 36.5 (CH_2), 53.4 (MeO), 112.2 (CH), 112.5 (C), 146.0 (C), 158.8 (C), 166.0 (C=O), 175.6 (C=O), 192.4 (C=O) ppm. Anal.Calc. for $C_{11}H_{10}O_5$ (222.19): C, 59.46; H, 4.54%. Found: C, 59.52; H, 4.41%.

Ethyl 5,6,7,8-tetrahydro-2,5-dioxo-2H-chromene-4-carboxylate (4d):

White powder; yield 0.42 g (90%). IR (KBr) ν_{max}/cm^{-1}: 1760, 1686, 1587, 1463. 1352 and 1278. ^{1}H NMR: σ 1.35 (3 H, t, $^3J_{HH}$ 7.5 Hz, Me), 2.22 (2 H, m, CH_2), 2.63 (2 H, t, CH_2, $^3J_{HH}$ 6.4 Hz), 2.92 (2 H, t, $^3J_{HH}$ 6.3 Hz, CH_2), 4.42 (2 H,q, $^3J_{HH}$ 7.2 Hz, OCH_2), 6.17 (1 H, s, CH) ppm. ^{13}C NMR: σ 13.9 (Me), 19.9 (CH_2), 28.5 (CH_2), 36.5 (CH_2), 62.6 (OCH_2), 112.0 (CH), 112.4(C), 146.3 (C), 158.9 (C), 165.4 (C=O), 175.5 (C=O), 192.4 (C=O) ppm. Anal.Calc. for $C_{12}H_{12}O_5$ (236.22): C, 61.01; H, 5.12%. Found: C, 61.12; H, 5.25%.

References

[1] Cagniant, P.; Cagniant, D. *In Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J.; Eds.; Academic Press: New York, **1975**, *18*, 337. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao. G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.

[2] Green, G. R; Evans, J. M.; Vong., A. K. *in Comprehensive Heterocyclic Chemistry II*: Katritzky, A. R.; Rees, C. W.; Scriven, E. F.; Eds.; Pergamon Press, Oxford, **1995**, *5*, 469.

[3] Foye, W.O. *Principi Di Chemico Frmaceutica, Piccin, Padova, Italy*, **1991**.

[4] Konkoy, C. S.; Fick, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W. *Chem. Abstr*. **2001**, *134*, 29313a.

[5] (a) Pastine, S. J.; Youn, S. W.; Sames, D. *org. Lett.* **2003**, *5*, 1055; (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Tetrahedron* **2003**, *59*, 8859; (c) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435

(d) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.*, **1983**, *48*, 3894.
[6] Kuwada, T.; Harada, K.; Nobuhiro, J.; Choshi, T. *Heterocycles* **2002**, *57*, 2081.
[7] Wang, Q., Finn, M. G. *Org. Lett.* **2000**, *2*, 4063-4065
[8] Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095.
[9] Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993.
[10] Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2006**, 435
[11] Lacova, M.; Stankovicova, H.; Boha, A.; Kotzianova, B. *Tetrahedron* **2008**, *64*, 9646.
[12] Ahluwalia, V. K.; Kumar, R.; Khurana, A.; Bhatla, R. *Tetrahedron* **1990**, *46*, 3953.
[13] (a) Johnson, A. W.; Tebby, J. C.; *J. Chem. Soc*. **1961**, 2126; (b) Tebby, J. C.; Wilson, I. F.; Griffiths, D. V. *J. Chem. Soc. Perkin. Trans. 1* **1979**, 2133; (c) Butterfield, P. J.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc. Perkin. Trans. 1* **1979**, 1189.
[14] Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 423.
[15] (a) Johnson, A. W.; Tebby, J. C.; *J. Chem. Soc*. 1961, 2126; (b) Tebby, J. C.; Wilson, I. F.; Griffiths, D. V. *J. Chem. Soc. Perkin. Trans. 1* **1979**, 2133; (c) Butterfield, P. J.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc. Perkin. Trans. 1* **1979**, 1189.
[16] (a) Diels, O.; Alder, K. *Liebigs Ann Chem* **1932**, *498*, 16; (b) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125; (c) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.*, **1964**, 2676.
[17] (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952; (b) Winterfeldt, E.; Dillinger, H. *J. Chem. Ber*., **1966**, *99*, 1558.
[18] Winterfeldt, E., Schumann, D.; Dillinger, H. *J. Chem. Ber.* **1969**, *102*, 1656.
[19] Maghsoodlou, M.; Nassiri, M.; Heydari, R.; Hazeri, N.; Habibi-Khorassani S. M.; Jalili Milani, F. *Arkivoc* **2010,** 61.