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# Reaction between dialkyl acetylenedicarboxylates and six-membered 1,3-diketones in the presence of trialkylamines: a convenient synthesis of alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates

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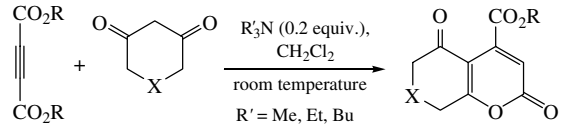
**The reaction of dialkyl acetylenedicarboxylates with six-membered cyclic 1,3-diketones such as 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in the presence of a catalytic amount of trimethylamine, triethylamine or tributylamine in $CH_2Cl_2$ leads to alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates in good yields.**

The synthesis of chromenes and their derivatives is of considerable interest because a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals[1] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers.[2] They have varied bioactivities, such as, inhibitory of platelet aggregation,[3] antibacterial,[4] anticancer,[5] inhibitory of steroid 5α-reductase[6] and inhibitory of HIV-1 protease.[7] Several strategies for the synthesis of chromenes were already developed.[8] However, the synthesis of alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates received little attention. The reported methods for the synthesis of these compounds suffer from harsh reaction conditions and exhibit low chemical yields.[9] We previously reported[10] the synthesis of 7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate from the reaction of dimethyl acetylenedicarboxylate with 5,5-dimethyl-1,3-cyclohexanedione in the presence of triphenylphosphine. Here we report a facile one-pot synthesis of alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates **3**. Thus, the reaction of dialkyl acetylenedicarboxylates **1** with cyclic 1,3-diketones **2** in the presence of a catalytic amount of trimethylamine, triethylamine or tributylamine leads to corresponding alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylates **3a–d** in good yields (Scheme 1).† The results show that the used amines had no considerable effect on the reaction product yields.

The structures of compounds **3a–d** were deduced from their elemental analyses and IR, $^1$H and $^{13}$C NMR spectra.† The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values. The $^1$H NMR spectrum of **3a** exhibited two singlets (δ 3.97 and 6.23 ppm) identified as OMe and olefinic protons along with a multiplet (δ 2.21 ppm) and two triplets (δ 2.61 and 2.92 ppm, $^3J_{HH}$ 6.3 Hz) for methylene protons of carbocyclic residue. The $^1$H decoupled $^{13}$C NMR spectrum of **3a** showed 11 distinct resonances in agreement with the proposed structure. Although the mechanism of the reaction between **1** and **2** in the presence of trialkylamines is unknown, a possible explanation is proposed in Scheme 2. It is reasonable to assume that **3** results from the initial addition of trialkylamine to the electron-deficient acetylenic esters and subsequent protonation of the 1,3-dipolar[11] intermediate **4**, by **2**. Then, the resulting positively charged ion **5** could be attacked




**1a** R = Me **2a** X = $CH_2$
**1b** R = Et **2b** X = $CMe_2$

**3a** R = Me, X = $CH_2$ (95%)
**3b** R = Me, X = $CMe_2$ (93%)
**3c** R = Et, X = $CH_2$ (72%)
**3d** R = Et, X = $CMe_2$ (70%)

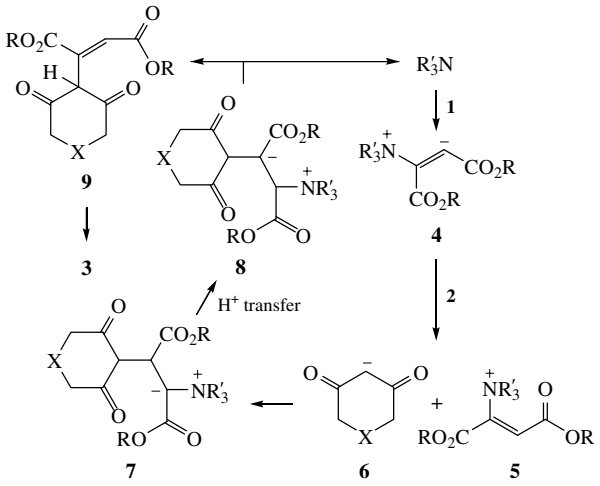
**Scheme 1**

† Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed with the calculated values. The IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for $^1$H and 62.9 MHz for $^{13}$C) with $CDCl_3$ as a solvent. Chemical shifts are given relative to TMS as an internal standard. Mass spectra were recorded with a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

*Typical experimental procedure for the preparation of methyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate* **3a**. Trimethylamine solution (0.03 g, 45% in water, 0.2 mmol) was added to a stirred solution of dimethyl acetylenedicarboxylate **1a** (0.28 g, 2 mmol) and 1,3-cyclohexanedione **2a** (0.22 g, 2 mmol) in 10 ml of $CH_2Cl_2$ at room temperature. The reaction mixture was then stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck 230-400 mesh) column chromatography using *n*-hexane–EtOAc as an eluent. Product **3a** was obtained as colourless oil; yield, 0.42 g (95%). IR (KBr, ν/cm$^{-1}$): 1738 and 1680 (C=O), 1553 (C=C). $^1$H NMR, δ: 2.21 (m, 2H, $CH_2$), 2.61 (t, 2H, $CH_2$, $^3J_{HH}$ 6.3 Hz), 2.92 (t, 2H, $CH_2$, $^3J_{HH}$ 6.3 Hz), 3.97 (s, 3H, OMe), 6.23 (s, 1H, CH). $^{13}$C NMR, δ: 19.8, 28.5 and 36.5 (3$CH_2$), 53.2 (OMe), 112.1 (CH), 112.4 (O–C=*C*), 145.9 (*C*–$CO_2$Me), 158.7 (O–*C*=C), 165.9 (C=O, ester), 175.5 (C=O, lactone), 192.4 (C=O). MS, *m*/*z* (%): 222 (M$^+$, 15), 165 (100), 65 (70). Found (%): C, 59.5; H, 4.4. Calc. for $C_{11}H_{10}O_5$ (222.2) (%): C, 59.46; H, 4.54.

*Methyl 7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate* **3b**: colourless crystals; yield, 0.47 g (93%), mp 97–98 °C. IR (KBr, ν/cm$^{-1}$): 1750 and 1685 (C=O), 1546 (C=C). $^1$H NMR, δ: 1.20 (s, 6H, 2Me), 2.40 and 2.60 (2s, 4H, 2$CH_2$), 3.90 (s, 3H, OMe), 6.20 (s, 1H, CH). $^{13}$C NMR, δ: 28.1 (C*Me*$_2$), 32.5 (*C*Me$_2$), 42.0 and 50.5 (2$CH_2$), 53.1 (OMe), 111.3 (O–C=*C*), 111.8 (CH), 145.6 (*C*–$CO_2$Me), 159.0 (O–*C*=C), 165.8 (C=O, ester), 174.0 (C=O, lactone), 192.4 (C=O). MS, *m*/*z* (%): 250 (M$^+$, 20), 194 (100), 93 (77). Found (%): C, 62.3; H, 5.7. Calc. for $C_{13}H_{14}O_5$ (250.3) (%): C, 62.40; H, 5.64.

by the enolate anion of CH acid **6** to produce nitrogen ylide **7**, which undergoes a proton-transfer reaction to produce **8**. 1,3-Dipolar ion **8** is converted to **9** by elimination of trialkylamine.[12] Product **3** is then formed by intramolecular lactonization of **9** (Scheme 2).




**Scheme 2**

When the size of the alkyl group in the acetylenic esters increased, the yield of the products reduced (see Scheme 1) and, when R is a bulky group such as *tert*-butyl, the reaction cannot proceed. It seems that increasing the alkyl group size in acetylenic esters inhibits from the attack of enolate anion of the CH acid to positively charged ion and subsequently addition product **9** is not formed.

The above reactions of dialkyl acetylenedicarboxylates with six-membered 1,3-diketones in the presence of catalytic amounts of trialkylamines provide a simple entry into the synthesis of alkyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate derivatives of potential synthetic interest.

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*Ethyl 2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate* **3c**: colourless oil; yield, 0.34 g (72%). IR (KBr, $\nu$/cm$^{-1}$): 1760 and 1686 (C=O), 1557 (C=C). $^1$H NMR, $\delta$: 1.37 (t, 3H, Me, $^3J_{HH}$ 7.3 Hz), 2.18 (m, 2H, $CH_2$), 2.59 (t, 2H, $CH_2$, $^3J_{HH}$ 6.3 Hz), 2.89 (t, 2H, $CH_2$, $^3J_{HH}$ 6.3 Hz), 4.40 (q, 2H, $OCH_2$, $^3J_{HH}$ 7.3 Hz), 6.17 (s, 1H, CH). $^{13}$C NMR, $\delta$: 13.8 (Me), 19.8, 28.5 and 36.5 ($3CH_2$), 62.5 ($OCH_2$), 111.9 (CH), 112.4 (O–C=*C*), 146.3 (*C*–$CO_2$Me), 158.8 (O–*C*=C), 165.4 (C=O, ester), 175.4 (C=O, lactone), 192.4 (C=O). MS, *m*/*z* (%): 236 ($M^+$, 18), 179 (100), 79 (60). Found (%): C, 61.1; H, 5.0. Calc. for $C_{12}H_{12}O_5$ (236.2) (%): C, 61.02; H, 5.12.

*Ethyl 7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2*H*-chromene-4-carboxylate* **3d**: colourless crystals; yield, 0.37 g (70%), mp 136–138 °C. IR (KBr, $\nu$/cm$^{-1}$): 1753 and 1677 (C=O), 1559 (C=C). $^1$H NMR, $\delta$: 1.21 (s, 6H, 2Me), 1.41 (t, 3H, Me, $^3J_{HH}$ 7.3 Hz), 2.49 and 2.79 (2s, 4H, $2CH_2$), 4.44 (q, 2H, $OCH_2$, $^3J_{HH}$ 7.3 Hz), 6.23 (s, 1H, CH). $^{13}$C NMR, $\delta$: 13.9 (Me), 28.2 (C*Me*$_2$), 32.5 (*C*Me$_2$), 42.2 and 50.7 ($2CH_2$), 62.6 ($OCH_2$), 111.5 (O–C=*C*), 111.8 (CH), 146.1 (*C*–$CO_2$Me), 159.1 (O–*C*=C), 165.4 (C=O, ester), 173.9 (C=O, lactone), 192.3 (C=O). MS, *m*/*z* (%): 264 ($M^+$, 16), 207 (100), 107 (70). Found (%): C, 63.5; H, 6.2. Calc. for $C_{14}H_{16}O_5$ (264.3) (%): C, 63.63; H, 6.10.