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Reaction Between 7-Hydroxy Coumarin, Alkyl Isocyanides and Dialkyl Acetylenedicarboxylate: Synthesis of 4*H*-Chromenes and 1-Azabuta-1,3-dienes

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Abstract. The reactive intermediate generated by the addition of *tert*-butyl and 1,1,3,3-tetramethyl butyl isocyanide to dialkyl acetylenedicarboxylate was trapped by 7-hydroxycoumarin to produce highly functionalized 4*H*-chromenes in fairly good yields. When the reaction is performed with cyclohexyl isocyanide, 1-azabuta-1,3-dienes were obtained.
Key words: 7-hydroxycoumarin, dialkyl acetylenedicarboxylates, alkyl isocyanides, multicomponent reactions.

Resumen. Los intermediarios reactivos generados por la adición de isocianuros de t-butilo y 1,1,3,3-tetrametilbutilo a acetilendicarboxilatos de dialquilo fueron atrapados por 7-hidroxicumarina para producir 4H-cromenos altamente funcionalizados en buenos rendimientos. Cuando las reacciones se llevan a cabo con isocianuro de ciclohexilo, se obtuvieron 1-azabuta-1,3-dienos.
Palabras clave: 7-hidroxicumarina , acetilendicarboxilatos de dialquilo, isocianuros de alquilo, reacciones de multi-componentes.

Introduction

In recent years, isocyanide-based multicomponent condensation reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry [1, 2]. The fact that complex products can be formed in a single operation by simultaneous reactions of several reagents has caused IMCRs to be among the most powerful methods for the synthesis of organic molecules [3]. It has been shown that alkyl or aryl isocyanides add to dialkyl acetylenedicarboxylates to generate zwitterionic species, which serve as intermediates in many different reactions [4-9].

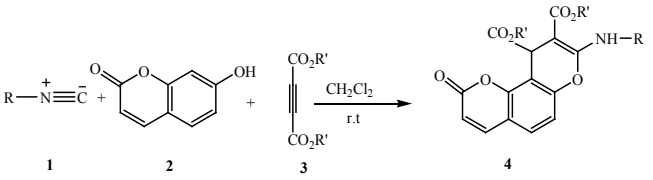
The reactions of 1-azadienes with various chiral dienophiles, leads to substituted pyridines [10], and substituted 4*H*-chromenes are a new class of anti-cancer compounds [11]. 2-Amino-4*H*-chromenes have been of interest because of their biological activity [12] and some methods have been reported for their synthesis [13-20]. As part of our current studies [21-26] on the development of new routes to heterocyclic systems, we now report an efficient synthetic route to 2-amino-4*H*-chromenes (**4**) using alkyl isocyanides (**1**), 7-hydroxycoumarin (**2**) and alkyl acetylenedicarboxylate (**3**) (Scheme 1). When the reaction was performed with cyclohexyl isocyanide, 1-azabuta-1,3-dienes (**5**) were obtained (Scheme 2).

Result and Discussion

The reaction proceeded spontaneously in CH_2Cl_2, and was completed within a few hours. The ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of **4** and **5**. The structures of compounds **4** and **5** were deduced from their elemental analyses and their IR, ^{1}H-NMR and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The NH proton resonance at δ = 8.76 disappeared after addition of D_2O to the $CDCl_3$ solution of **4a**. The proton decoupled ^{13}C NMR spectrum of **4a** showed the presence of oxo and amino groups at one end of the double bond leads to polarization of the olefinic system. The α-carbon atom of this polarized system appears at δ = 172.9 while and the β-carbon at δ = 72.1 ppm. Similar chemical shifts have been observed for the polarized carbon-carbon double bonds in 2-alkylamino-4*H*-benzo[h]chromene derivatives [13].

The ^{1}H NMR spectrum of **5a** exhibited three sharp lines for methoxy (δ = 3.72 and 3.86 ppm), and methine (δ = 6.17 ppm) protons. The cyclohexyl and coumarin moiety appeared at δ = 1.20-2.07 and δ = 6.63-7.80 ppm. The ^{13}C NMR spectrum of **5a** showed distinct resonances in agreement with the proposed structure.

NMR spectroscopy was employed to distinguish between (*Z*)-**5** or (*E*)-**5**. The *E* configuration of the olefinic double bond in **5a-b** is based on the chemical shift of the olefinic proton [27]. The ^{1}H NMR spectra of (*E*)-**5** showed the olefinic proton signal at 7.08-7.10 ppm.



1	R
a	*t*-Butyl
b	*1,1,3,3-tetra metyl* Butyl

3	R'
a	Me
b	Et

4	R	R'	yield %
a	*t*-Butyl	Me	84
b	*1,1,3,3-tetra metyl* Butyl	Me	79
c	*t*-Butyl	Et	94
d	*1,1,3,3-tetra metyl* Butyl	Et	91

Scheme 1.

On the basis of the well established chemistry of isocyanides [28-30] compound **4** result from nucleophilic addition of alkyl isocyanides to the acetylenic system and subsequent protonation of the 1:1 adduct by the OH-acid. Then, the positively charged ion **6** is attacked by the anion of the OH-acid to form ketenimine **7** (strong ketenimine absorption band at about ν = 2049 cm^{-1} was detected by IR spectroscopy during the reaction). Such an addition product may tautomerize to **8** and then cyclize, under the reaction conditions employed, to produce **4**. Direct addition to **6** leads to 1-aza-1,3-diene **5** (Scheme 3).

It seems that direct attack to *c*-hexyl isocyanide is more favorable due to weaker steric effect than *tert*-butyl and 1,1,3,3-tetramethyl butyl isocyanides.

Conclusion

In conclusion, we have found an efficient synthetic method for the preparation of some 4*H*-chromenes and 1-azabuta-1, 3-dienes. The present method carries the advantage that not only is the reaction performed under neutral conditions and without anhydrous conditions at room temperature, but also the starting materials and reagents can be mixed without any activation or modification.

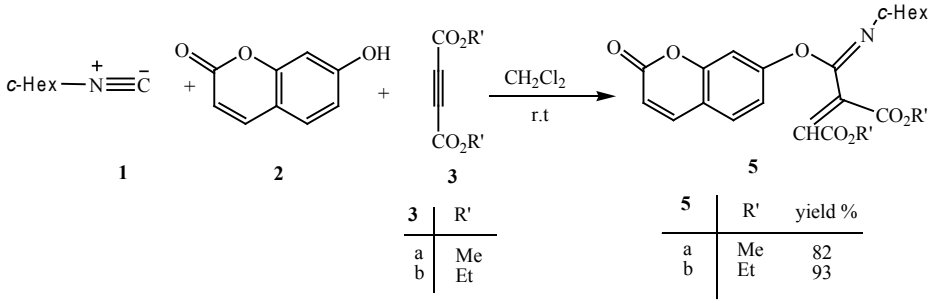
Experimental

Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 and 75.5 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides, alkyl acetylenedicarboxylates and 7-hydroxycoumarin were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

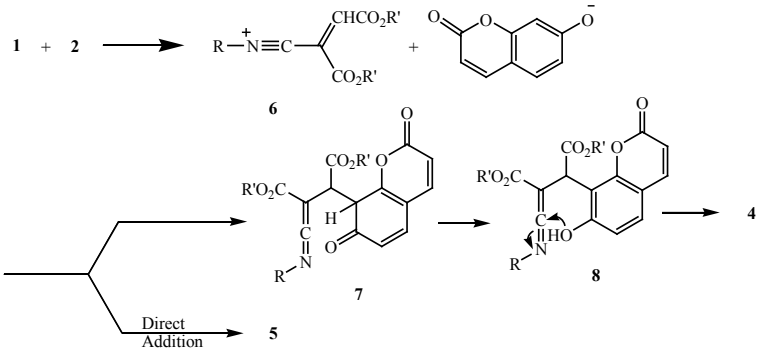
Typical procedure for preparation of compounds **4** *and* **5**

To a magnetically stirred solution of 7-hydroxycoumarin (2 mmol) and dimethyl acetylenedicarboxylate (2 mmol) in CH_2Cl_2 (10 mL) *tert*-butyl isocyanide (2 mmol) was added dropwise at –10 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (Merck 230-400 mesh) using (hexane: EtOAc, 5:1) as eluent.

Dimethyl 8-(tert-butylamino)-2-oxo-2H, 10H-pyrano[2,3-f]chromene-9,10-dicarboxylate **(4a)**. Yellow oil, yield: 0.65 g (84%). IR (KBr): 3466, 1735, 1671, 1621, 1439, 1243, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, br s, NH), 7.67 (1H, d, J = 9.6 Hz, CH), 7.40 (1H, d, J = 8.5 Hz, CH), 7.03 (1H, d, J = 8.5 Hz, CH), 6.36 (1H, d, J = 9.5 Hz, CH), 5.27 (1H, s, CH), 3.74 (3H, s, CH_3-O), 3.64 (3H, 3, CH_3-O), 1.46 (9H, s, $3CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9(C), 169.6 (C=O), 161.8 (C=O), 160.2 (C=O), 152.4 (C), 151.8 (C), 143.2 (CH), 127.6 (CH), 115.5 (C), 114.9 (CH), 112.7 (CH), 110.7 (C), 72.1 (C), 52.7 (C-N), 52.6 (CH_3-O), 51.0 (CH_3-O), 38.6



Scheme 2.



Scheme 3.

(CH), 31.2 ($3CH_3$). EI-MS *m/z* (rel.int.): 387 [M^+] (13), 238 (43), 272 (54), 161 (72), 142 (80), 83 (78), 57 (100). Anal. calcd. for **4a**, $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62; found: C, 62.04; H, 5.45; N, 3.60.

Dimethyl 8-(2,4,4-trimethylpentan-2-ylamino)-2-oxo-2H, 10H-pyrano[2,3-f]chromene-9,10-dicarboxylate **(4b)**. Yellow oil, yield: 0.70 g (79%). IR (KBr): 3450, 1738, 1668, 1623, 1427, 1224, 1072 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, br s, NH), 7.67 (1H, d, J = 9.6 Hz, CH), 7.41 (1H, d, J = 8.5 Hz, CH), 7.03 (1H, d, J = 8.5 Hz, CH), 6.37 (1H, d, J = 9.5 Hz, CH), 5.29 (1H, s, CH), 3.79 (3H, s, CH_3-O), 3.64 (3H, s, CH_3-O), 1.90 (2H, s, CH_2), 1.53 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.00 (9H, s, $3CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.7(C), 169.5 (C=O), 161.6 (C=O), 160.1 (C=O), 152.3 (C), 151.7 (C), 143.1 (CH), 127.6 (CH), 115.4 (C), 115.0 (CH), 112.6 (CH), 110.8 (C), 71.7 (C), 56.2 (C-N), 55.1 (CH_3-O), 53.4 (CH_2), 51.1 (CH_3-O), 34.9 (CH), 31.7 (CH_3), 31.6 (C), 31.4 ($3CH_3$), 31.1 (CH_3). EI-MS *m/z* (rel.int.): 443 [M^+] (8), 383 (35), 269 (100), 241 (24), 57 (73), 41 (59). Anal. calcd. for **4b**, $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16; found: C, 65.02; H, 6.58; N, 3.14.

Diethyl 8-(tert-butylamino)-2-oxo-2H, 10H-pyrano[2,3-f]chromene-9,10-dicarboxylate **(4c)**. Yellow oil, yield: 0.78 g (94%). IR (KBr): 3439, 1738, 1667, 1624, 1440, 1218, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, br s, NH), 7.67 (1H, d, J = 9.5 Hz, CH), 7.40 (1H, d, J = 8.5 Hz, CH), 7.03 (1H, d, J = 8.5 Hz, CH), 6.36 (1H, d, J = 9.5 Hz, CH), 5.24 (1H, s, CH), 4.28 (2H, m, CH_2-O), 4.10 (2H, m, CH_2-O), 1.47 (9H, s, $3CH_3$), 1.33 (3H, t, J = 7.1 Hz, CH_3), 1.21 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3(C), 168.9 (C=O), 161.1 (C=O), 159.8 (C=O), 151.9 (C), 151.5 (C), 142.8 (CH), 127.1 (CH), 114.9 (C), 114.5 (CH), 112.3 (CH), 110.3 (C), 71.7 (C), 60.8 (CH_2-O), 59.2 (CH_2-O), 52.2 (C-N), 38.3 (CH), 30.2 ($3CH_3$), 14.3 (CH_3), 13.7 (CH_3). EI-MS *m/z* (rel. int.): 415 [M^+] (12), 337 (100), 292 (43), 255 (66), 223 (84), 57 (96). Anal. calcd. for **4c**, $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37; O, 26.96; found: C, 63.62; H, 6.06; N, 3.35.

Diethyl 8-(2,4,4-trimethylpentan-2-ylamino)-2-oxo-2H, 10H-pyrano[2,3-f]chromene-9,10-dicarboxylate **(4d)**. Yellow oil, yield: 0.86 g (91%). IR (KBr): 3426, 1732, 1668, 1621, 1428, 1215, 1071 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, br s, NH), 7.68 (1H, d, J = 9.5 Hz, CH), 7.41 (1H, d, J = 8.5 Hz, CH), 7.02 (1H, d, J = 8.5 Hz, CH), 6.34 (1H, d, J = 9.5 Hz, CH), 5.24 (1H, s, CH), 4.15 (2H, m, CH_2-O), 4.07 (2H, m, CH_2-O), 1.80 (2H, s, CH_2), 1.51 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.31 (3H, t, J = 7.1 Hz, CH_3), 1.21 (3H, t, J = 7.1 Hz, CH_3), 0.98 (9H, s, $3CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6(C), 169.3 (C=O), 161.4 (C=O), 160.2 (C=O), 152.3 (C), 151.9 (C), 143.2 (CH), 127.6 (CH), 115.4 (C), 114.9 (CH), 112.6 (CH), 110.8 (C), 71.8 (C), 61.2 (CH_2-O), 59.5 (CH_2-O), 56.2 (C-N), 53.5 (CH_2), 35.3 (CH), 31.7 (CH_3), 31.6 (C), 31.4 ($3CH_3$), 31.2 (CH_3), 14.7 (CH_3), 14.1 (CH_3). EI-MS *m/z* (rel.int.): 471 [M^+] (7), 398 (39), 179 (60), 369 (46), 313 (53), 286 (100), 240 (61), 57 (96). Anal. calcd. for **4d**, $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97; found; C, 66.25; H, 7.04; N, 2.95.

Dimethyl 2-((1Z)-(2-oxo-2H-chromen-7-yloxy)(cyclohexyl imino)methyl)but-2-enedioate **(5a)**. Yellow oil, yield: 0.68 g (82%). IR (KBr): 1739, 1682, 1670, 1616, 1230, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 9.5 Hz, CH), 7.42 (1H, d, J = 8.5Hz, CH), 7.35 (1H, d, J = 2.0 Hz, CH), 7.20 (1H, dd, J = 8.5, 2.1 Hz, CH), 7.10 (1H, s, CH), 6.34 (1H, d, J = 9.5 Hz, CH), 3.91 (3H, s, CH_3-O), 3.82 (3H, s, CH_3-O), 2.99 (1H, m, CH), 1.18-1.66 (10H, m, $5CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4(C=O), 163.0 (C=O), 160.6 (C=O), 155.6 (C), 154.3 (C), 150.7 (C), 142.9 (CH), 136.3 (CH), 131.8 (CH), 127.6 (CH), 118.2 (CH), 115.2 (C), 114.6 (CH), 109.9 (C), 52.5 (CH_3-O), 51.1 (CH_3-O), 49.9 (CH), 38.3 (CH), 33.9 (CH_2) 33.6 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 24.5 (CH_2). EI-MS *m/z* (rel. int.): 413 [M^+] (21), 337 (100), 292 (23), 255 (66), 223 (84), 83 (74), 55 (27). Anal. calcd. for **5a**, $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39; found: C, 63.93; H, 5.62; N, 3.35.

Diethyl 2-(1Z)-(2-oxo-2H-chromen-7-yloxy)(cyclohexyli mino)methyl)but-2-enedioate **(5b)**. Yellow oil, yield: 0.92 g (93%). IR (KBr): 1729, 1682, 1655, 1613, 1255, 1118 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, d, J = 9.5 Hz, CH), 7.42 (1H, d, J = 8.5Hz, CH), 7.34 (1H, d, J = 2.0 Hz, CH), 7.19 (1H, dd, J = 8.4, 2.1 Hz, CH), 7.08 (1H, s, CH), 6.33 (1H, d, J = 9.5 Hz, CH), 4.34 (2H, q, J = 7.1 Hz, CH_2-O), 4.28 (2H, q, J = 7.1 Hz, CH_2-O), 3.00 (1H, m, CH), 11.34 (3H, t, J = 7.1 Hz, CH_3), 1.28 (3H, t, J = 7.1 Hz, CH_3), 17-1.85 (10H, m, $5CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4 (C=O), 163.0 (C=O), 161.6 (C=O), 155.6 (C), 154.3 (C), 150.3 (C), 142.9 (C), 136.3 (C), 131.4 (CH), 127.8 (CH), 118.2 (CH), 115.2 (CH), 114.6 (CH), 109.9 (CH), 71.3 (C), 61.1 (CH_2-O), 59.4 (CH_2-O), 49.9 (CH), 38.5 (CH), 33.9 (CH_2), 33.6 (CH_2), 25.5 (CH_2), 24.5 ($2CH_2$), 14.7 (CH_3), 14.1 (CH_3). EI-MS *m/z* (rel.int.): 441 [M^+] (17), 339 (85), 285 (14), 255 (66), 223 (84), 83 (100). Anal. calcd. for **5b**, $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17; found: C, 65.28; H, 6.17; N, 3.18.

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