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Synthesis of 4*H*-chromene derivatives by reaction between alkyl isocyanides and dialkyl acetylenedicarboxylate in the presence of 6-hydroxyquinoline

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Abstract

The reactive intermediate generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylate was trapped by 6-quinolinol to produce highlyfunctionalized 4*H*-chromenes in fairly good yields.

Keywords: 4*H*-Chromene; Alkyl isocyanides; Acetylenic ester; 6-Hydroxyquinoline

Chromenes constitute a major class of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents [1,2]. 2-Amino-4*H*-chromenes have been of interest because of their biological activity [3] and some methods have been reported for their synthesis [4]. The first amino-4*H*-chromenes synthesized via acetylenic esters and alkyl isocyanides was presented by Yavari *et al*. [5]. As part of our current studies [6,7] on the development of new routes to heterocyclic and carboxylic systems, we now report an efficient synthetic route to 2-amino-4*H*-chromenes using alkyl isocyanides and dialkyl acetylene-dicarboxylate in the presence of 6-quinolinol (Scheme 1).

1. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. 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. ^{1}H 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.

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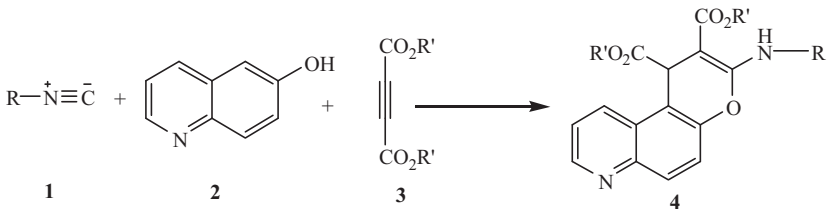


1	R
a	*t*-Butyl
b	*c*-Hexyl
c	1,1,3,3-*tetra*-Metylbutyl

3	R'
a	Me
b	Et

4	R	R'	Yeild %
a	*t*-Butyl	Me	88
b	*c*-Hexyl	Me	73
c	1,1,3,3-*tetra*-Metylbutyl	Me	94
d	*t*-Butyl	Et	80
e	*c*-Hexyl	Et	75
f	1,1,3,3-*tetra*-Metylbutyl	Et	90

Scheme 1.

1.1. Typical procedure

To a magnetically stirred solution of **2** (2 mmol) and dimethyl acetylenedicarboxylate (2 mmol) in 10 mL CH_2Cl_2 was added dropwise at −10 °C over 10 min *tert*-butyl isocyanide (2 mmol). 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 purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F254) 20 cm × 20 cm plates using *n*-hexane-AcOEt (3:1) as eluent.

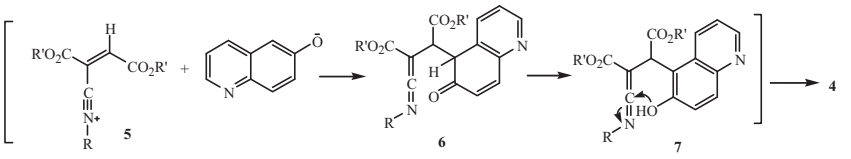
Dimethyl 3-(tert-butylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4a**): Yellow powder, yield 0.65 g (88%); mp: 87–91 °C. IR (neat) (ν_{max}/cm^{-1}): 3390 (NH), 1730 (C=O), 1668 (C=O). ^{1}H NMR: δ 1.55 (s, 3 CH_3), 3.60 (3, OCH_3), 3.79 (s, OCH_3), 5.35 (s, CH), 7.51–7.54 (m, 2 CH), 8.09 (d, ^3J = 9.1 Hz, CH), 8.70 (d, ^3J = 8.3 Hz, CH), 8.82 (brs, NH), 8.88 (d, ^3J = 4.2 Hz, CH). ^{13}C NMR: δ 31.0 (3 CH_3), 38.6 (CH), 51.5 (OCH_3), 52.8 (OCH_3), 53.0 (C), 72.4 (C), 114. 5 (CH), 120.6 (C), 122.2 (CH), 126.9 (CH), 131.3 (CH), 132.7 (C), 146.3 (C), 147.7 (CH), 149.6 (C), 162.4 (C=O), 170.0 (C=O), 173.4 (C). Anal. calcd. for $C_{20}H_{22}N_2O_5$ (370.4): C, 64.85; H, 5.99; N, 7.56%; Found: C, 64.66; H, 6.04; N, 7.51%.

Dimethyl 3-(cyclohexylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4b**): Yellow powder, yield 0.58 g (73%); mp: 102–105 °C. IR (neat) (ν_{max}/cm^{-1}): 3419 (NH), 1738 (C=O), 1675 (C=O). ^{1}H NMR δ 1.28–2.10 (m, 5 CH_2), 3.60 (s, CH_3), 3.78 (s, CH_3), 3.95 (m, CH), 5.33 (s, CH), 7.49–7.55 (m, 2 CH), 8.11 (d, ^3J = 9.2 Hz, CH), 8.63 (brs, NH), 8.72 (d, ^3J = 8.6 Hz, CH), 8.9 (d, ^3J = 4.2 Hz, CH). ^{13}C NMR δ 24.5 (CH_2), 24.6 (CH_2), 25.5 (CH_2), 33.6 (CH_2), 33.9 (CH_2) 38.3 (CH), 49.9 (CH), 51.1 (OCH_3), 52.5 (OCH_3), 71.1 (C), 114.0 (CH), 120.7 (C), 121.8 (CH) 126.6 (CH), 130.4 (CH), 132.8 (C), 145.6 (C), 147.6 (CH), 148.8 (C), 160.5 (C=O), 169.5 (C=O), 173.1(C). Anal. calcd. for $C_{22}H_{24}N_2O_5$ (396.44): C, 66.65; H, 6.10; N, 7.07%; Found: C, 66.69; H, 6.03; N, 7.10%.

Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4c**): Yellow powder, yield 0.80 g (94%); mp: 118–122 °C; IR (neat) (ν_{max}/cm^{-1}): 3408 (NH), 1739 (C=O), 1674 (C=O). ^{1}H NMR δ 1.02 (s, 3 CH_3), 1.56 (s, CH_3), 1.58 (s, CH_3), 1.85 (d, ^3J = 14.9 Hz, CH), 1.92 (d, ^3J = 14.9 Hz, CH), 3.56 (s, CH_3) 3.77 (s, CH_3), 5.34 (s, CH), 7.50–7.54 (m, 2 CH), 8.10 (d, ^3J = 9.1 Hz, CH), 8.71 (d, ^3J = 8.6 Hz, CH), 8.88 (brs, NH), 8.90 (d, ^3J = 4.1 Hz, CH). ^{13}C NMR δ 31.4 (3 CH_3), 31.5 (CH_3), 31.6 (CH_3), 31.7 (C), 38.2 (CH), 51.1 (OCH_3), 52.4 (OCH_3), 53.3 (CH_2), 56.2 (C), 71.7 (C), 114.2 (CH), 120.3 (C), 121.9 (CH), 126.6 (CH), 130.8 (CH), 132.6 (C), 145.7(C), 147.3 (CH), 149.1 (C), 161.8 (C=O), 169.6 (C=O), 173.0(C). Anal. calcd. for $C_{24}H_{30}N_2O_5$ (426.51): C, 67.59; H, 7.09; N, 6.57%; Found: C, 67.64; H, 6.92; N, 6.54%.

Diethyl 3-(tert-butylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4d**): Yellow powder, yield 0.64 g (80%); mp: 95–99 °C; IR (neat) (ν_{max}/cm^{-1}): 3390 (NH), 1730 (C=O), 1668 (C=O).^{1}H NMR δ 1.12 (t, ^3J = 7.1 Hz, CH_3), 1.32 (t, ^3J = 7.1 Hz, CH_3), 1.52 (s, 3 CH_3), 4.03 (m, OCH_2), 4.23 (m, OCH_2), 5.29 (s, CH), 7.42–7.51 (m, 2 CH), 8.03 (d, ^3J = 9.1 Hz, CH), 8.71 (d, ^3J = 8.4 Hz, CH), 8.82 (brs, NH), 8.88 (d, ^3J = 4.2 Hz, CH). ^{13}C NMR δ 14.1 (CH_3), 14.7 (CH_3), 30.6 (3 CH_3), 38.3 (CH), 52.6 (C), 59.5 (OCH_2), 61.1 (OCH_2), 72.1 (C), 114.0 (CH), 120.2 (C), 121.7 (CH), 126.6 (CH), 130.9 (CH), 132.3 (C), 146.0 (C), 147.2 (CH), 149.2 (C), 161.8 (C=O), 169.2 (C=O), 172.8 (C). Anal. calcd. for $C_{22}H_{26}N_2O_5$ (398.45); C, 66.32; H, 6.58; N, 7.03%; Found: C, 66.28; H, 6.65; N, 7.00%.

Diethyl 3-(cyclohexylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4e**): Yellow powder, yield 0.64 g (75%); m.p.: 107–110 °C; IR (neat) (ν_{max}/cm^{-1}): 3254 (NH), 1729 (C=O), 1671 (C=O). ^{1}H NMR δ 1.12 (t,



Scheme 2.

^3J = 7.1 Hz, CH_3), 1.33 (t, ^3J = 7.1 Hz, CH_3), 1.28–2.09 (m, 5 CH_2), 3.90 (m, CH), 4.05 (m, OCH_2), 4.25 (m, OCH_2), 5.30 (s, CH), 7.46–7.53 (m, 2 CH), 8.08 (d, ^3J = 9.1 Hz, CH) 8.68 (brs, NH), 8.75 (d, ^3J = 8.5 Hz, CH), 8.87 (d, ^3J = 4.0 Hz, CH). ^{13}C NMR δ 14.1 (CH_3), 14.7 (CH_3), 24.5 ($2CH_2$), 25.5 (CH_2), 33.6 (CH_2), 33.9 (CH_2), 38.5 (CH), 49.9 (CH), 59.4 (OCH_2), 61.1 (OCH_2), 71.3 (C), 114.0 (CH), 120.7 (C), 121.6 (CH), 126.6 (CH), 130.5 (CH), 132.8 (C), 145.7 (C), 147.5 (CH), 148.9 (C), 160.4 (C=O), 169.2 (C=O), 172.9(C). Anal. calcd. for $C_{24}H_{28}N_2O_5$ (424.49): C, 67.91; H, 6.65; N, 6.60%; Found: C, 67.94; H, 6.61; N, 6.64%.

Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-pyrano[3,2-f]quinoline-1,2-dicarboxylate (**4f**): Yellow powder, yield 0.82 g (90%); mp: 135–140 °C; IR (neat) (ν_{max}/cm^{-1}): 3445 (NH), 1732 (C=O), 1670 (C=O). ^{1}H NMR δ 1.02 (s, 3 CH_3), 1.11 (t, ^3J = 7.1 Hz, CH_3), 1.33 (t, ^3J = 7.1 Hz, CH_3), 1.55 (s, CH_3), 1.57 (s, CH_3), 1.84 (d, ^3J = 14.9 Hz, CH), 4.04 (m, OCH_2), 4.23 (m, OCH_2), 7.44–7.53 (m, 2 CH), 8.08 (d, ^3J = 9.1 Hz, CH), 8.75 (d, ^3J = 8.4 Hz, CH), 8.84 (brs, NH), 8.90 (d, ^3J = 4.2 Hz, CH). ^{13}C NMR δ 14.1 (CH_3), 14.7 (CH_3), 31.4 (3 CH_3), 31.5 (2 CH_3), 31.7 (C), 38.5 (CH), 53.3 (CH_2), 56.1 (C), 59.4 (OCH_2), 61.1 (OCH_2), 71.9 (C), 114.1 (CH), 120.2 (C), 121.7 (CH), 126.6 (CH), 130.8 (CH), 132.6 (C), 145.8 (C), 147.2 (CH), 149.1 (C), 161.6 (C=O), 169.2 (C=O), 172.7 (C). Anal. calcd. for $C_{26}H_{34}N_2O_5$ (454.56): C, 68.70; H, 7.54; N, 6.16%; Found: C, 68.73; H, 7.50; N, 6.18%.

2. Result and discussion

The structure of **4a** was determined on the basis of its elemental analyses, ^{1}H and ^{13}C NMR and IR spectroscopic data. The ^{1}H NMR spectrum of **4a** exhibited four singlets identified as *tert*-butyl (δ 1.55), methoxy (δ 3.60 and 3.79) and methine (δ 5.35), quinolinol moiety appeared at (δ 7.51–8.88). The NH proton resonance at δ 8.85 disappeared after addition of D_2O to the $CDCl_3$ solution of **4a**. The ^{13}C NMR spectrum of **4a** showed 18 distinct resonances in agreement with the proposed structure. The α-carbon atom of this polarized system appears at δ 173.4, while and the β-carbon at δ 72.4. Partial assignment of these resonances is given in the experimental.

A possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides [8–11] it is reasonable to assume that compounds **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 **5** is attacked by the anion of the OH-acid to form ketenimine **6**. Such an addition product may tautomerize and then cyclize, under the reaction conditions employed, to produce **4**.

3. Conclusion

The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

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