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Reaction between alkyl isocyanides and dimethyl acetylenedicarboxylate in the presence of polyhydroxybenzenes. Synthesis of 4*H*-chromene derivatives

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Abstract—The reactive intermediate generated by the addition of alkyl isocyanides to dimethyl acetylenedicarboxylate was trapped by phenols such as resorcinol, catechol, hydroquinone, pyrogallol, 2,4-dihydroxybenzaldehyde, or 8-hydroxyquinoline to produce highly functionalized 4*H*-chromenes in fairly good yields.

1. Introduction

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] The key bicyclic ring system of chromenes has inspired a number of different synthetic approaches.[3,4] Substituted 4*H*-chromenes are a new class of anti-cancer compounds.[5] Many studies have been reported on the synthesis of the chromene ring system.[6,7] 2-Amino-4*H*-chromenes have been of interest because of their biological activity[8] and a few methods have been reported for their synthesis.[9] As part of our current studies[10–13] on the development of new routes to heterocyclic systems, we now report an efficient synthetic route to 2-amino-4*H*-chromenes using alkyl isocyanides and dimethyl acetylenedicarboxylate in the presence of phenols such as resorcinol, catechol, hydroquinone, pyrogallol, 2,4-dihydroxybenzaldehyde, or 8-hydroxyquinoline.

2. Results and discussion

The reaction of dimethyl acetylenedicarboxylate (DMAD) with cyclohexyl isocyanide in the presence of resorcinol proceeded spontaneously at room temperature in dichloromethane, and produced dimethyl 2-cyclohexylamino-5-hydroxy-4*H*-chromene-3,4-dicarboxylate (**4a**) (Scheme 1). The structure of **4a** was determined on the basis of its elemental analyses, mass spectrum (MS), ^{1}H and ^{13}C NMR and IR spectroscopic data. The ^{1}H NMR spectrum of **4a** exhibited four singlets identified as methoxy (δ=3.66 and 3.69), methine (δ=4.62), and hydroxy (δ=8.07) protons along with multiplets (δ=6.51–7.27) for aromatic protons. The NH proton resonance at δ=8.67 disappeared after addition of D_2O to the $CDCl_3$ solution of **4a**. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances in agreement with the proposed structure. 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 apears at δ=160.40, while and the β-carbon at δ=70.80. Similar chemical shifts have been observed for the polarized carbon–carbon double bonds in 2-alkylamino-4*H*-benzo[*h*]chromene derivatives.[13] The carbonyl groups of **4a** appear at δ=170.02 and 175.18.

Using DMAD with other hydroxy acids, such as catechol, hydroquinone, pyrogallol, or 2,4-dihydroxybenzaldehyde, in the presence of alkyl isocyanides, produced compounds **4b**–**4f** (Scheme 1).

The reaction of *tert*-butyl isocyanide with DMAD in the presence of 8-hydroxyquinoline afforded the isomeric dimethyl 2-(*tert*-butylamino)-4*H*-pyrano[3,2,*h*]-quinoline-3,4-dicarboxylate (**7**) and dimethyl 2-[(*tert*-butylimino)-methylene]-3-(8-hydroxy-7-quinolyl)succinate (**8**) in nearly 3:1 ratio and good yield (Scheme 2). The structures of **7** and **8** were deduced from their ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{13}C NMR spectra of **7** are similar to those for **4a** except for the aromatic moiety, which is replaced by the quinoline residue. The ^{1}H NMR spectrum of **8** exhibited four singlets identified as *tert*-butyl (δ=1.06), methoxy (δ=3.74 and 3.75), and methine (δ=5.26) protons. The proton-decoupled ^{13}C NMR spectrum of **8** showed 18 distinct resonances in

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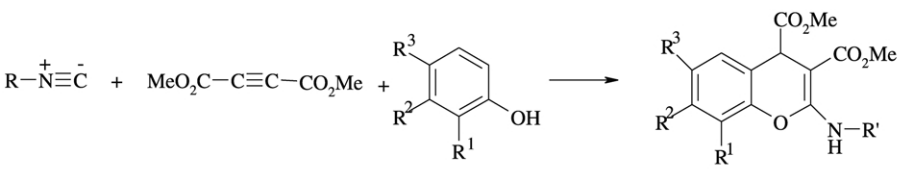
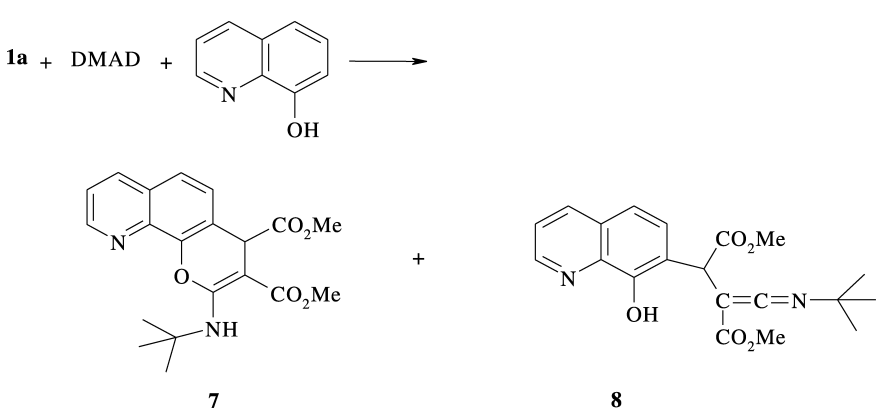


1	R
a	*t*-Bu
b	*c*-Hexyl

2 **3**

4	R^1	R^2	R^3	R	Yield %
a	H	OH	H	*c*-Hexyl	90
b	OH	H	H	t-Bu	85
c	H	H	OH	*c*-Hexyl	80
d	OH	OH	H	*c*-Hexyl	80
e	H	H	CHO	*t*-Bu	90
f	H	H	CHO	*c*-Hexyl	95

Scheme 1.



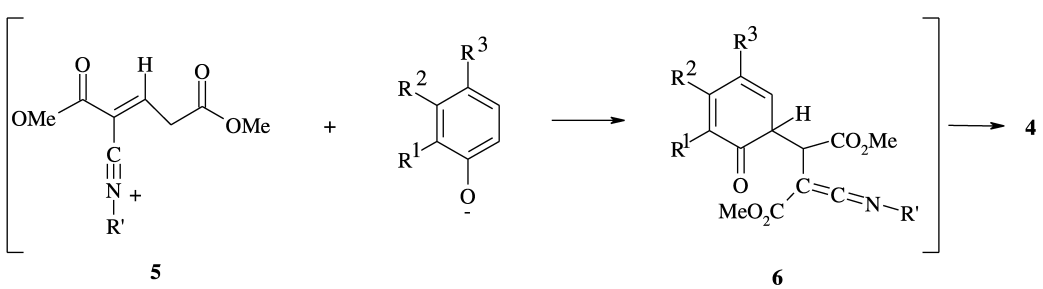
7 **8**

Scheme 2.

agreement with the proposed structure. Partial assignments of these resonances are given in Section 3. The structural assignment of compound **8** made on the basis of its NMR spectra was supported by its IR spectrum. Of special interest is the strong ketenimine absorption band at about 2050 cm^{-1} in **8**.

Although we have not yet established the mechanism of the reaction between alkyl isocyanides and DMAD in the presence of polyhydroxybenzenes in an experimental manner, a possible explanation is proposed in Scheme 3. On the basis of the well established chemistry of isocyanides[14–18] 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**. Similar mechanistic scheme can be considered for formation of compounds **4b**–**4f**, **7**, and **8** (Scheme 3).

In summary, we have found an efficient synthetic method for the preparation of some 4*H*-chromenes. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting



5 **6**

Scheme 3.

materials and reagents can be mixed without any activation or modification.

3. 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-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides, DMAD, resorcinol, catechol, hydroquinone, pyrogallol, 2,4-dihydroxybenzaldehyde, and 8-hydroxyquinoline were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

3.1. General procedure

To a magnetically stirred solution of resorcinol (0.22 g, 2 mmol) and DMAD (0.28 g, 2 mmol) in 10 mL CH_2Cl_2 was added dropwise at −10 °C over 10 min cyclohexyl isocyanide (0.21 g, 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 separated by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–ethyl acetate as eluent.

3.1.1. Dimethyl 2-(cyclohexylamino)-5-hydroxy-4*H*-chromene-3,4-dicarboxylate (4a). Yellow powder, yield 0.65 g, 90%, mp 120–122 °C. IR (KBr) (ν_{max}/cm^{-1}): 3255 (NH), 1727 and 1661 (C=O). MS, *m*/*z* (%): 361 (M$^+$, 2), 304 (8), 303 (38), 189 (24), 188 (100). Anal. calcd for $C_{19}H_{23}NO_6$ (361.4): C, 63.15; H, 6.41; N, 3.88; Found: C, 63.1; H, 6.4; N, 3.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1.25–1.97 (10H, m, $5CH_2$), 3.66 and 3.69 (6H, 2s, $2OCH_3$), 3.73 (1H, m, CHN), 4.62 (1H, s, CH), 6.51–7.27 (3H, m, 3CH), 8.07 (1H, s, OH), 8.67 (1H, broad, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=24.4, 24.5, 25.5, 33.4, and 33.8 ($5CH_2$), 40.6 (CH), 49.7 (CHN), 51.0 and 52.5 ($2OCH_3$), 70.8 (*C*=C–N), 103.4, 112.4, and 129.3 (3CH), 110.8, 149.7, and 156.9 (3C), 160.4 (C=*C*–N), 170.0 and 175.2 (2C=O, ester).

3.1.2. Dimethyl 2-(*tert*-butylamino)-8-hydroxy-4*H*-chromene-3,4-dicarboxylate (4b). Yellow powder, yield 0.56 g, 85%, mp 74–76 °C. IR (KBr) (ν_{max}/cm^{-1}): 3245 (NH), 1729 and 1664 (C=O). MS, *m*/*z* (%): 335 (M$^+$, 4), 277 (26), 219 (100), 188 (90). Anal. calcd for $C_{17}H_{21}NO_6$ (335.3): C, 60.89; H, 6.31; N, 4.18; Found: C, 60.9; H, 6.3; N, 4.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1.50 (9 H, s, *t*-Bu), 3.66 and 3.70 (6H, 2s, $2OCH_3$), 4.71 (1H, s, CH), 5.71 (1H, s, OH), 6.85–6.97 (3H, m, 3CH), 8.88 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=30.6 ($3CH_3$), 41.1 (CH), 51.1 and 52.5 ($2OCH_3$), 60.5 (*C*Me$_3$), 71.9 (*C*=C–N), 115.4, 119.9, and 124.5 (3CH), 120.8, 137.4, and 144.0 (3C), 161.3 (C=*C*–N), 169.9 and 174.0 (2C=O, ester).

3.1.3. Dimethyl 2-(cyclohexylamino)-6-hydroxy-4*H*-chromene-3,4-dicarboxylate (4c). Yellow powder, yield 0.58 g, 80%, mp 89–91 °C. IR (KBr) (ν_{max}/cm^{-1}): 3250 (NH), 1730 and 1658 (C=O). MS, *m*/*z* (%): 361 (M$^+$, 2), 303 (42), 220 (30), 188 (30), 110 (100), 88 (60). Anal. calcd for $C_{19}H_{23}NO_6$ (361.4): C, 63.15; H, 6.41; N, 3.88; Found: C, 63.1; H, 6.4; N, 3.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1.25–1.76 (10H, m, $5CH_2$), 3.66 and 3.68 (6H, 2s, $2OCH_3$), 3.77 (1H, m, CHN), 4.64 (1H, s, CH), 6.01 (1H, s, OH), 6.74–6.91 (3H, m, 3CH), 8.67 (1H, broad, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=24.5, 24.6, 25.5, 33.5, and 33.9 ($5CH_2$), 41.6 (CH), 49.6 (CHN), 50.9 and 52.6 ($2OCH_3$), 70.1 (*C*=C–N), 114.6, 116.1, and 117.3 (3CH), 120.2, 143.0, and 152.6 (3C), 160.5 (C=*C*–N), 169.8 and 174.5 (2C=O, ester).

3.1.4. Dimethyl 2-(cyclohexylamino)-6,7-hydroxy-4*H*-chromene-3,4-dicarboxylate (4d). Red powder, yield 0.60 g, 80%, mp 160–162 °C. IR (KBr) (ν_{max}/cm^{-1}): 3235 (NH), 1713 and 1651 (C=O). MS, *m*/*z* (%): 377 (M$^+$, 3), 319 (82), 236 (40), 204 (100), 52 (70). Anal. calcd for $C_{19}H_{23}NO_7$ (377.4): C, 60.47; H, 6.14; N, 3.71; Found: C, 60.5; H, 6.1; N, 3.7%. ^{1}H NMR (500.1 MHz, CD_3OD): δ=1.31–1.77 (10H, m, $5CH_2$), 3.64 and 3.68 (6H, 2s, $2OCH_3$), 3.75 (1H, m, CHN), 4.61 (1H, s, CH), 6.61 and 6.73 (2H, d, $^3J_{HH}$=8.2Hz, 2CH), 7.42 (1H, broad, NH). ^{13}C NMR (125.7 MHz, CD_3OD): δ=24.0, 24.1, 25.2, 33.1, and 33.4 ($5CH_2$), 40.6 (CH), 49.0 (CHN), 50.5 and 52.0 ($2OCH_3$), 70.6 (*C*=C–N), 111.0, and 118.1 (2CH), 111.0, 132.6, 138.2, and 148.2 (4C), 160.2 (C=*C*–N), 169.8 and 175.1 (2C=O, ester).

3.1.5. Dimethyl 2-(*tert*-butylamino)-6-formyl-5-hydroxy-4*H*-chromene-3,4-dicarboxylate (4e). Yellow powder, yield 0.65 g, 90%, mp 142–144 °C. IR (KBr) (ν_{max}/cm^{-1}): 3247 (NH), 1724 and 1660 (C=O). MS, *m*/*z* (%): 363 (M$^+$, 2), 304 (18), 248 (90), 216 (100). Anal. calcd for $C_{18}H_{21}NO_7$ (363.4): C, 59.50; H, 5.82; N, 3.85; Found: C, 59.5; H, 5.8; N, 3.8%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1.50 (9 H, s, *t*-Bu), 3.66 and 3.70 (6H, 2s, $2OCH_3$), 4.98 (1H, s, CH), 6.75 and 7.50 (2H, d, $^3J_{HH}$=8.4Hz, 2CH), 8.88 (1H, s, NH), 9.80 (1H, s, CHO), 11.75 (1H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=30.4 ($3CH_3$), 34.9 (CH), 50.9 and 52.2 ($2OCH_3$), 52.6 (*C*Me$_3$), 72.1 (*C*=C–N), 110.1 and 133.7 (2CH), 108.3, 117.2, 155.5, and 160.4 (4C), 161.2 (C=*C*–N), 169.4 and 172.7 (2C=O, ester), 194.9 (CHO).

3.1.6. Dimethyl 2-(cyclohexylamino)-6-formyl-5-hydroxy-4*H*-chromene-3,4-dicarboxylate (4f). White powder, yield 0.73 g, 95%, mp 188–190 °C. IR (KBr) (ν_{max}/cm^{-1}): 3270 (NH), 1718 and 1663 (C=O). MS, *m*/*z* (%): 389 (M$^+$, 2), (331, 76), (248, 38), (216 90), (52, 100). Anal. calcd for $C_{20}H_{23}NO_7$ (389.4): C, 61.69; H, 5.95; N, 3.60; Found: C, 61.7; H, 6.0; N, 3.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ =1.28–1.91 (10H, m, $5CH_2$), 3.65 and 3.72 (6H, 2s, $2OCH_3$), 3.80 (1H, m, CHN), 4.96 (1H, s, CH), 6.73 and 7.49 (1H, d, $^3J_{HH}$=8.4Hz, 2CH), 8.66 (1H, d, $^3J_{HH}$=6.1Hz, NH), 9.80 (1H, s, CHO), 11.74 (1H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=24.4, 24.4, 25.4, 33.4, and 33.8 ($5CH_2$), 35.2 (CH), 49.9 (CHN), 50.9 and 52.4 ($2OCH_3$), 71.2 (*C*=C–N), 108.6 and 133.7 (2CH), 110.0, 117.1, 155.7, and 159.8 (4C),

160.5 (C═*C*–N), 169.4 and 173.2 (2C═O, ester), 195.0 (CHO).

3.1.7. Dimethyl 2-(*tert*-butylamino)-4*H*-pyrano[3,2-*h*]quinoline-3,4-dicarboxylate (7). Yellow powder, yield 0.44 g, 60%, mp 153–155 °C. IR (KBr) (ν_{max}/cm^{-1}): 3235 (NH), 1731 and 1664 (C═O). MS, *m*/*z* (%): 370 (M^+, 2), 312 (28), 255 (100), 223 (60), 195 (80), 54 (100), 35 (88). Anal. calcd for $C_{20}H_{22}N_2O_5$ (370.4): C, 64.85; H, 5.99; N, 7.56; Found: C, 64.8; H, 6.0; N, 7.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1.65 (9 H, s, *t*-Bu), 3.65 and 3.73 (6H, 2s, 2OCH_3), 4.86 (1H, s, CH), 7.39 (1H, dd, $^3J_{HH}$=7.6 and 4.1Hz, CH), 7.50 (1H, d, $^3J_{HH}$=8.5Hz, CH), 8.07 (1H, d, $^3J_{HH}$=7.6Hz, CH), 8.92 (1H, d, $^3J_{HH}$=4.1Hz, CH), 8.91 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=30.3 (3CH_3), 41.9 (CH), 50.9 and 53.0 (2OCH_3), 52.4 (*C*Me_3), 71.1 (*C*═C–N), 118.3, 128.5, 138.8, and 150.5 (4C), 121.7, 123.2, 126.3, 135.3, and 150.5 (5CH), 161.6 (C═*C*–N), 169.8 and 173.7 (2C═O, ester).

3.1.8. Dimethyl 2-[(*tert*-butylimino)methylene]-3-(8-hydroxy-7-quinolyl)succinate (8). Yellow powder, yield 0.28 g, 38%, mp 110–112 °C. IR (KBr) (ν_{max}/cm^{-1}): 2030 (C═C═N), 1733 and 1674 (C═O). MS, *m*/*z* (%): 370 (M^+, 2), 314 (28), 255 (100), 223 (90), 195 (30), 145 (90), 54 (100), 35 (88)%. Anal. calcd for $C_{20}H_{22}N_2O_5$ (370.4): C, 64.85; H, 5.99; N, 7.56; Found: C, 64.8; H, 6.0; N, 7.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ=1. 06 (9 H, s, *t*-Bu), 3.74 and 3.75 (6H, 2s, 2OCH_3), 5.26 (1H, s, CH), 7.15 (1H, d, $^3J_{HH}$=7.9 Hz, CH), 7.37 (1H, d, $^3J_{HH}$=7.9 Hz, CH), 7.50 (1H, dd, $^3J_{HH}$=7.9 and 4.8Hz, CH), 8.43 (1H, d, $^3J_{HH}$=8.1Hz, CH), 8.79 (1H, d, $^4J_{HH}$=3.43Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=29.9 (3CH_3), 43.2 (CH), 51.7 and 52.6 (2OCH_3), 61.7 (*C*Me_3), 66.8 (*C*═C–N), 109.2, 122.2, 126.6, 132.7, and 147.7 (5CH), 123.9, 126.8, 138.5, and 152.1 (4C), 169.0 (C═*C*–N), 170.0 and 173.0 (2C═O, ester).

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