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Synthesis of highly functionalised 1*H*-furo[3,4-*b*]chromenes

Issa Yavari,* Hoorieh Djahaniani and Farough Nasiri

Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran.
Fax: +98 21 8006544; e-mail: isayavar@yahoo.com

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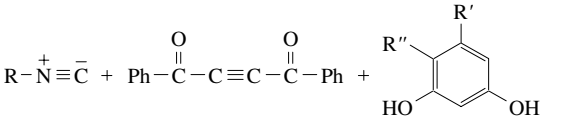
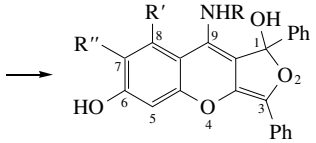
An effective route to 1*H*-furo[3,4-*b*]chromene-1,6-diols involves the reaction of alkyl isocyanides and dibenzoylacetylene in the presence of resorcinol derivatives.

The chromene (benzopyran) substructure is frequently found in naturally occurring heterocycles, many of which exhibit biological activity.[1,2] While a variety of synthetic methodologies for chromene have been developed,[3] data on one-pot cyclization methods based on a consecutive process are scarce. Most of these methods either suffer from harsh reaction conditions and poor substituent tolerance or exhibit low chemical yields.[4,5] In the context of the development of new routes to heterocyclic and carbocyclic systems,[6–9] we now report a reaction between alkyl isocyanides **1** and dibenzoylacetylene in the presence of resorcinol **2a**, 3,5-dihydroxytoluene **2b** or 2,4-dihydroxybenzaldehyde **2c**. Thus, the reaction of dibenzoylacetylene and alkyl isocyanides in the presence of **2a**, **2b** or **2c** leads to 1*H*-furo[3,4-*b*]chromene-1,6-diols **3** (Scheme 1).



1a R = Bu^t
1b R = Bn

2a R′ = H, R″ = H
2b R′ = Me, R″ = H
2c R′ = H, R″ = CHO



	R	R′	R″	Yield (%)
3a	Bu^t	H	H	88
3b	Bn	H	H	85
3c	Bu^t	Me	H	95
3d	Bn	Me	H	98
3e	Bu^t	H	CHO	98
3f	Bn	H	CHO	90

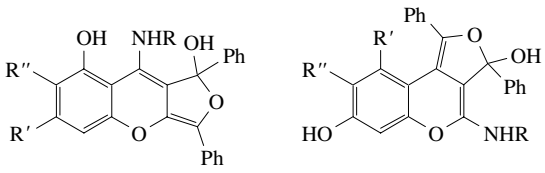
Scheme 1

The reaction of *tert*-butyl isocyanide and dibenzoylacetylene in the presence of resorcinol proceeded smoothly in CH_2Cl_2 at room temparature and completed within 24 h. The ^{1}H and ^{13}C NMR spectra of the crude reaction mixture clearly indicated the formation of 1*H*-furo[3,4-*b*]chromene-1,6-diol **3a**. The structure of **3a** was deduced from its elemental analysis and IR, ^{1}H NMR and ^{13}C NMR spectra.† The nature of this compound as a 1:1:1 adduct was apparent from its mass spectrum, which displayed a molecular ion peak at *m*/*z* 427.

The ^{1}H NMR spectrum of **3a** exhibited a single sharp line readily recognised as arising from *tert*-butyl (δ 1.14 ppm) and a fairly broad singlet (δ 5.59 ppm) for the NH group along with a singlet (δ 6.93 ppm) for the isolated CH group of the resorcinol residue. The vicinal CH groups of this residue together with the phenyl group give rise to a complex multiplet. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 22 distinct resonances, five of which appear above δ 150 ppm, in agreement with the proposed structure. The structure of **4** (Scheme 2) is ruled out because it should give rise to two 'doublets' and a 'triplet' for the resorcinol residue. The structure of **5** is also unlikely because it is expected to show only four ^{13}C resonances above δ 150 ppm.

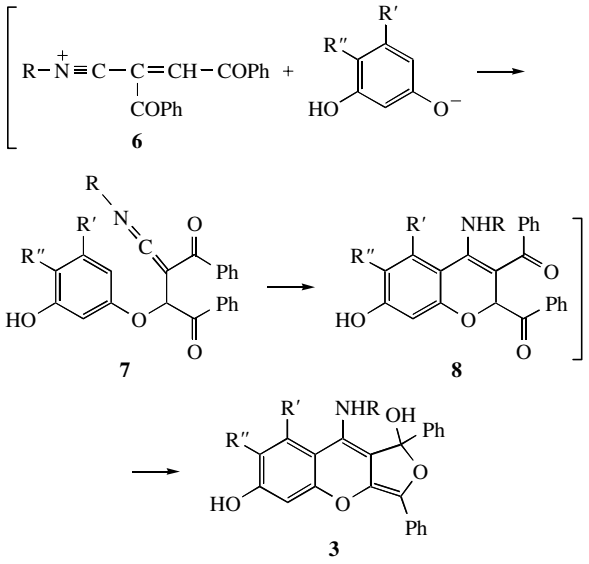
The ^{1}H and ^{13}C NMR spectra of **3b–f** are similar to those of **3a** except for the isocyanide and aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

The ^{1}H NMR spectra of **3e** and **3f** exhibited two single sharp lines at about δ 7.0 and 7.3 ppm arising from two aromatic CH protons. The signal at about δ 7.0 ppm is present in the ^{1}H NMR spectrum of all products.



4 **5**

Scheme 2



Scheme 3

Although we have not established the mechanism of the reaction between alkyl isocyanides and dibenzoylacetylene in the presence of **2** in an experimental manner, a possible explanation is proposed in Scheme 3. On the basis of the well-established chemistry of isocyanides,[10–14] it is reasonable to assume that compound **3** results from the nucleophilic addition of the isocyanide to the electron-deficient acetylenic ketone and subsequent protonation of the 1:1 adduct by **2**. Then, positively charged ion **6** is attacked by the conjugate base of the phenol to form intermediate **7**. Such an addition product can isomerise and cyclise under the reaction conditions employed to produce fused heterocyclic system **3**.

The above reaction of alkyl isocyanides with dibenzoylacetylene in the presence of resorcinol, 3,5-dihydroxytoluene or 2,4-dihydroxybenzaldehyde provides a simple one-pot synthesis of 1*H*-furo[3,4-*b*]chromen-1,6-diol derivatives of potential synthetic interest. The present method carries the advantage that not only the reaction is performed under neutral conditions, but also the starting materials and reagents can be mixed without activation or modification.

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† A typical procedure is described for the preparation of 9-(*tert*-butylamino)-1,3-diphenyl-1*H*-furo[3,4-*b*]chromene-1,6-diol **3a**. *tert*-Butyl isocyanide (0.16 g, 2 mmol) was added dropwise to a stirred solution of resorcinol (0.22 g, 2 mmol) and dibenzoylacetylene (0.47 g, 2 mmol) in 10 ml of CH_2Cl_2 at –10 °C for 10 min. The reaction mixture was 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–EtOAc as an eluent to give the product as a white powder; yield 0.41 g (95%), mp 157–159 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.14 (CMe_3), 5.60 (br. s, 1H, NH), 6.64 (d, 1H, CH, $^3J_{HH}$ 7.6 Hz), 6.93 (s, 1H, CH), 6.98–7.83 (m, 12H, 2Ph, CH and OH), 15.96 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.5 (C*Me*$_3$), 51.5 (*C*Me$_3$), 94.1 (HO–*C*–Ph), 98.1, 112.3 and 120.6 (3CH), 110.8 and 123.1 (2C), 125.6, 127.5, 127.6, 128.5, 128.9, 129.1 and 129.4 (10CH), 130.3 and 135.7 (2C$_{ipso}$), 151.2, 154.4 and 154.9 (3C), 171.1 and 171.4 (O–C=C–O). IR (KBr, ν_{max}/cm^{-1}): 3375 (OH), 3145 (NH), 1620 (C=C). MS, *m*/*z* (%): 427 (M$^+$, 10), 354 (50), 105 (100), 77 (60), 43 (50). Found (%): C, 76.01; H, 5.83; N, 3.30. Calc. for $C_{27}H_{25}NO_4$ (427.5) (%): C, 75.86; H, 5.89; N, 3.28.

For **3b**: yellow powder, yield 0.41 g (90%), mp 130–132 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 4.21 (dd, 1H, CH, $^3J_{HH}$ 5.2 Hz, $^2J_{HH}$ 15.2 Hz), 4.51 (dd, 1H, CH, $^3J_{HH}$ 5.2 Hz, $^2J_{HH}$ 15.2 Hz), 6.10 (t, 1H, NH, $^3J_{HH}$ 5.8 Hz), 6.91 (d, 1H, CH, $^4J_{HH}$ 1.8 Hz), 6.33–7.83 (m, 18H, 3Ph, 2CH and OH), 15.63 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 43.2 (CH_2), 93.5 (HO–*C*–Ph), 98.2, 112.7 and 120.3 (3CH), 107.7, 110.0, and 123.1 (3C), 125.6, 126.9, 127.2, 127.5, 127.7, 128.5, 128.5, 128.9, 129.7 and 130.2 (15CH), 135.2 and 137.5 (2C$_{ipso}$), 151.5, 154.9 and 154.9 (3C), 171.4 and 171.9 (O–C=C–O). IR (KBr, ν_{max}/cm^{-1}): 3375 (OH), 3130 (NH), 1613 (C=C). MS, *m*/*z* (%): 461 (M$^+$, 50), 354 (30), 105 (100), 91 (50), 77 (60). Found (%): C, 78.11; H, 5.08; N, 3.04. Calc. for $C_{30}H_{23}NO_4$ (461.5) (%): C, 78.08; H, 5.02; N, 3.03.

For **3c**: yellow crystals, yield 0.40 g (88%), mp 182–194 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.24 (CMe_3), 2.43 (Me), 5.60 (br. s, 1H, NH), 5.79 (br. s, 1H, OH), 6.52 and 6.83 (2s, 2H, 2CH), 7.02–7.76 (m, 10H, 2Ph), 15.89 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 18.3 (Me), 28.7 (CMe_3), 51.7 (CMe_3), 95.7 (HO–*C*–Ph), 95.9 and 114.1 (2CH), 110.4 and 121.6 (2C), 125.4, 127.5, 127.7, 128.3, 128.6, 128.7 and 129.5 (10CH), 130.1, 132.9 and 135.5 (3C$_{ipso}$), 151.3, 154.1 and 155.2 (3C), 169.9 and 172.3 (O–C=C–O). IR (KBr, ν_{max}/cm^{-1}): 3320 (OH), 3135 (NH), 1611 (C=C). MS, *m*/*z* (%): 441 (M$^+$, 75), 365 (75), 105 (100), 77 (60), 57 (30). Found (%): C, 76.13; H, 6.18; N, 3.21. Calc. for $C_{28}H_{27}NO_4$ (441.5) (%): C, 76.17; H, 6.16; N, 3.17.

For **3d**: yellow powder, yield 0.41 g (85%), mp 188–190 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 2.35 (Me), 4.32 (dd, 1H, CH, $^3J_{HH}$ 5.1 Hz, $^2J_{HH}$ 15.2 Hz), 4.54 (dd, 1H, CH, $^3J_{HH}$ 5.1 Hz, $^2J_{HH}$ 15.2 Hz), 6.08 (br. t, 1H, NH), 6.48 and 6.80 (2s, 2H, 2CH), 6.95–7.78 (m, 16H, 3Ph and OH), 15.57 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) d: 18.2 (Me), 43.2 (CH_2), 95.1 (HO–*C*–Ph), 95.9 and 114.2 (2CH), 110.0 and 121.6 (2C), 125.5, 127.0, 127.3, 127.7, 127.8, 128.4, 128.6, 128.8, and 129.7 (15CH), 130.2, 132.9, 135.2, and 137.7 (4C$_{ipso}$), 151.5, 154.4 and 155.3 (3C), 170.2 and 172.4 (O–C=C–O). IR (KBr, ν_{max}/cm^{-1}): 3375 (OH), 3135 (NH), 1618 (C=C). MS, *m*/*z* (%): 475 (M$^+$, 40), 368 (50), 105 (100), 91 (55), 77 (60). Found (%): C, 78.28; H, 5.33; N, 3.90. Calc. for $C_{31}H_{25}NO_4$ (475.5) (%): C, 78.30; H, 5.30; N, 3.95.

For **3e**: yellow powder, yield 0.43 g (88%), mp 187–189 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.14 (CMe_3), 5.50 (br. s, 1H, NH), 7.00 (s, 1H, CH), 7.05 (t, 2H, CH$_{meta}$ of Ph, $^3J_{HH}$ 7.2 Hz, $^3J_{HH}$ 8.0 Hz), 7.13 (t, 1H, CH$_{para}$ of Ph, $^3J_{HH}$ 7.2 Hz), 7.32 (d, 2H, CH$_{ortho}$ of Ph, $^3J_{HH}$ 7.2 Hz), 7.33 (s, 1H, CH), 7.41 (t, 1H, CH$_{para}$ of Ph, $^3J_{HH}$ 7.4 Hz), 7.48 (t, 2H, CH$_{meta}$ of Ph, $^3J_{HH}$ 7.6 Hz), 7.90 (t, 2H, CH$_{ortho}$ of Ph, $^3J_{HH}$ 7.6 Hz), 9.75 (s, 1H, CHO), 11.17 (s, 1H, OH), 16.07 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.8 (C*Me*$_3$), 51.7 (*C*Me$_3$), 93.2 (HO–*C*–Ph), 99.4 (CH), 110.8, 118.4 and 123.3 (3C), 126.7 (CH), 125.9, 127.5, 127.9, 129.1, 129.4 and 129.5 (10CH), 129.4 and 135.5 (2C$_{ipso}$), 153.0, 159.0, 160.7 (3C), 170.9 and 171.8 (O–C=C–O), 195.8 (CHO). IR (KBr, ν_{max}/cm^{-1}): 3375 (OH), 3145 (NH), 1719 (C=O), 1645 (C=C). MS, *m*/*z* (%): 455 (M$^+$, 50), 382 (100), 356 (50), 105 (100), 77 (30), 57 (25). Found (%): C, 73.92; H, 5.44; N, 3.12. Calc. for $C_{28}H_{25}NO_5$ (455.5) (%): C, 73.83; H, 5.53; N, 3.07.

For **3f**: yellow powder, yield 0.48 g (98%), mp 234–236 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 4.30 (dd, 1H, CH, $^3J_{HH}$ 5.3 Hz, $^2J_{HH}$ 15.1 Hz), 4.51 (dd, 1H, CH, $^3J_{HH}$ 5.3 Hz, $^2J_{HH}$ 15.1 Hz), 5.94 (t, 1H, NH, $^3J_{HH}$ 5.3 Hz), 6.90 (d, 2H, CH$_{ortho}$ of Ph, $^3J_{HH}$ 7.1 Hz), 7.00 (s, 1H, CH), 7.04–7.87 (m, 13H, 3Ph), 7.37 (s, 1H, CH), 9.75 (s, 1H, CHO), 11.19 (s, 1H, OH), 15.77 (s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 43.2 (CH_2), 93.5 (HO–*C*–Ph), 98.2, 112.7 and 120.3 (3CH), 107.7, 110.1 and 123.1 (3C), 125.6, 127.0, 127.2, 127.5, 127.8, 128.5, 128.9, 129.7 and 130.2 (15CH), 135.2 and 137.5 (2C$_{ipso}$), 151.5, 154.9 and 155.0 (3C), 171.4 and 171.9 (O–C=C–O), 195.2 (CHO). IR (KBr, ν_{max}/cm^{-1}): 3365 (OH), 3135 (NH), 1710 (C=O), 1645 (C=C). MS, *m*/*z* (%): 489 (M$^+$, 30), 382 (40), 105 (100), 91 (50), 77 (60). Found (%): C, 76.13; H, 4.80; N, 2.83. Calc. for $C_{31}H_{23}NO_5$ (489.5) (%): C, 76.06; H, 4.74; N, 2.86.