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Synthesis of Highly Functionalized Bis(4*H*-chromene) and 4*H*-Benzo[*g*]chromene Derivatives via an Isocyanide-Based Pseudo-Five-Component Reaction

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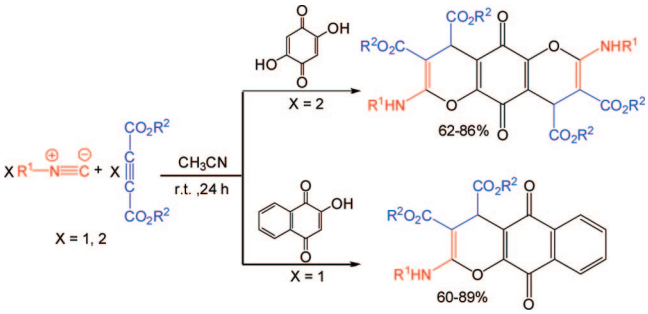

The reactive intermediates generated by the addition of alkyl, aryl, and alicyclic isocyanides to dialkyl acetylenedicarboxylates were trapped by 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione or 2-hydroxynaphthalene-1,4-dione to produce highly functionalized bis(4*H*-chromene)- and 4*H*-benzo[*g*]chromene-3,4-dicarboxylate derivatives in fairly good yields in CH_3CN at room temperature. These compounds are closely related to the ring systems pentalongin, dehydroherbarin, 1,3-disubstituted-3,4-dehydropyranonaphthoquinones, and 3-arylpyranonaphthoquinones, which have a broad spectrum of biological activity.

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[1−4]

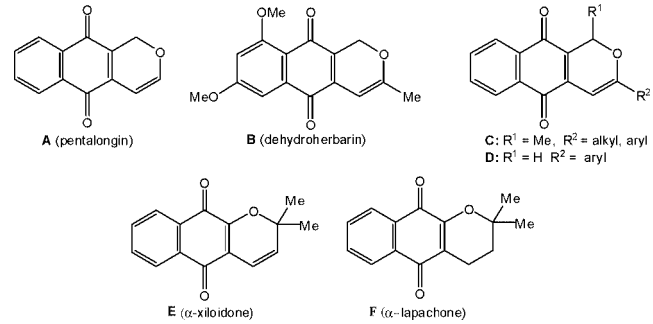

FIGURE 1. Some biologically active chromenes and isochromenes.

Recently, the synthesis of particular groups of naturally occurring pyranonaphthoquinones, such as pentalongin **A**,[5−7] dehydroherbarin **B**,[8] several 1,3-disubstituted-3,4-dehydropyranonaphthoquinones **C**,[9] and 3-arylpyranonaphthoquinones **D**[10,11] have been reported. The biological activities of these compounds were investigated too.[12] For example, pentalongin **A** is a natural product, which is reported in Rwanda and Kenya for the treatment of malaria and skin diseases (Figure 1). These compounds have been synthesized via multistep approach in the presence of transition metal catalysts under sensitive conditions.[8,9] Compounds **E** and **F** were used as antimultiresistant hospital bacteria, too. These compounds were semisynthetically obtained from lapachol.[13]

Multicomponent reactions (MCRs), due to their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry. Therefore, the design of novel MCRs, especially isocyanide-based multicomponent reactions (IMCRs), have attracted great attention from research groups working in areas such as drug discovery, organic synthesis, and materials science.[14−20]

It has been shown that alkyl or aryl isocyanide add to dialkyl acetylenedicarboxylate to generate zwitterionic species, which serve as intermediates in many different reactions. Recently, these highly reactive zwitterionic intermediates have been

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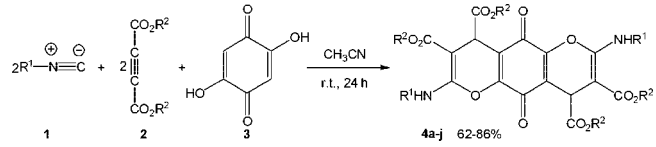
SCHEME 1. Synthesis of Bis(4*H*-chromene)-3,4-dicarboxylate Derivatives 4a−j



captured by suitable CH acids,[21−24] NH acid-like amides,[25] and OH acids like carboxylic acids[26,27] and oxime[28] substrates.

As part of our continuing interest in the development of new synthetic methods in heterocyclic compounds and isocyanide-based multicomponent reactions,[29−35] in the present work we wish to report the reaction of alkyl, aryl, and alicyclic isocyanides with dialkyl acetylenedicarboxylates in the presence of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione in CH_3CN at room temperature (Scheme 1).

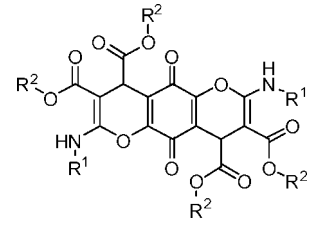
In a pilot experiment, 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione, dimethyl acetylenedicarboxylate, and cyclohexyl isocyanide in CH_3CN were stirred at room temperature. After completion of the reaction (after 24 h), the precipitated product was separated from the reaction mixture by filtration and was washed with *n*-hexane to afford product **4a** in 86% yield.

To explore the scope and limitations of this reaction, we extended the procedure to various alkyl, aryl, and alicyclic isocyanides and various dialkyl acetylenedicarboxylates with 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione.

As indicated in Table 1, the reactions proceed very efficiently and led to the formation of the corresponding highly functionalized bis(4*H*-chromene)-3,4-dicarboxylate derivatives **4a−j** in excellent yields at room temperature, without any undesirable byproducts.

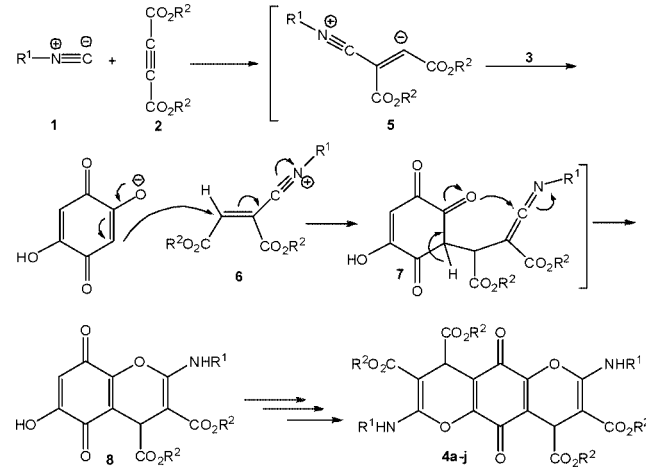
The structure of compounds **4a−j** was deduced from their IR, mass, ^{1}H NMR, ^{13}C NMR, and HMQC for **4a** and **10i** spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited a multiplet for the cyclohexyl ring δ 1.35−1.96 (20H, m, $10CH_2$ of 2cyclohexyls), two singlets identified as two methoxy groups (12H, $4OCH_3$, δ 3.66 and 3.71), a broad singlet at δ 3.79 (2H, br s, 2C*H*−NH of 2cyclohexyls), a singlet at δ 4.64 (2H, s, 2C*H*−CO_2Me), and a broad singlet at δ 8.57 for two NH groups (2H, br s, 2CH−N*H*). The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances in agreement with proposed structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

TABLE 1. Bis(4*H*-chromene)-3,4-dicarboxylate Derivatives 4a−j



entry	product	R^1	R^2	yield (%)
1	**4a**	cyclohexyl	Me	86
2	**4b**	*tert*-butyl	Me	70
3	**4c**	1,1,3,3-tetramethylbutyl	Me	73
4	**4d**	ethoxycarbonylmethyl	Me	62
5	**4e**	benzyl	Me	83
6	**4f**	2,6-dimethylphenyl	Me	70
7	**4g**	cyclohexyl	Et	82
8	**4h**	benzyl	Et	75
9	**4i**	2,6-dimethylphenyl	Et	65
10	**4j**	2,6-dimethylphenyl	^{t}*B*u	70

SCHEME 2. Proposed Pathway



Although the mechanism of this reaction has not been established experimentally, the formation of these heterocycles can be rationalized by initial Michael-type vinylisonitrilium cation **5**.[23,36−38] Then, the positively charged ion might be attacked by the anion of the 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione, which leads to the keteneimine **7**. Such an addition product may isomerize under the reaction conditions employed to produce the fused heterocyclic systems **4a−j** (Scheme 2).

The versatility of this multicomponent reaction with respect to the CH acid component was also studied (Scheme 3). As indicated in Scheme 3 and Table 2, 2-hydroxynaphthalene-1,4-dione **9** and dialkyl acetylenedicarboxylates **2** with various isocyanides **1** in CH_3CN led to the formation of 4*H*-benzo[*g*]chromene-3,4-dicarboxylate derivatives **10a−i** in good yields at ambient temperature.

The reaction proceeded under mild conditions and was compatible with a wide range of functional groups. Two

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SCHEME 3. Synthesis of 4*H*-Benzo[*g*]chromene-3,4-dicarboxylate Derivatives 10a−i

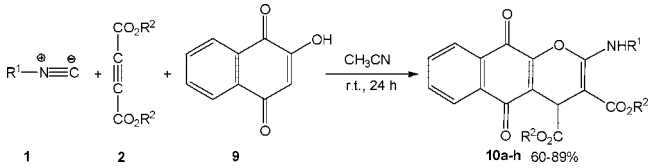
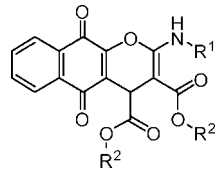


TABLE 2. 4*H*-Benzo[*g*]chromene-3,4-dicarboxylate Derivatives 10a−i



entry	product	R^1	R^2	yield (%)
1	**10a**	cyclohexyl	Me	89
2	**10b**	1,1,3,3-tetramethylbutyl	Me	75
3	**10c**	ethoxycarbonylmethyl	Me	60
4	**10d**	2,6-dimethylphenyl	Me	77
5	**10e**	cyclohexyl	Me	84
6	**10f**	1,1,3,3-tetramethylbutyl	Me	74
7	**10g**	ethoxycarbonylmethyl	Et	62
8	**10h**	2,6-dimethylphenyl	Et	74
9	**10i**	2,6-dimethylphenyl	^{t}Bu	64

substituents in the products can be varied independently of each other. Owing to the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries. Representative examples of this reaction are shown in Tables 1 and 2.

In conclusion, we have developed an efficient synthetic approach for the synthesis of the highly functionalized bis(4*H*-chromene)- and 4*H*-benzo[*g*]chromene-3,4-dicarboxylate derivatives from readily available substrates in fairly good yields. The advantages of the present procedure are the following: the reaction is performed by a simple mixing of the starting materials, neutral reaction conditions, easy workup procedure, and displaying good functional groups tolerance. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

Experimental Section

Typical Procedure for the Preparation of Product 4a. To a magnetically stirred solution of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (0.14 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.28 g, 2.0 mmol) in CH_3CN (5 mL) was added a solution of cyclohexyl isocyanide (0.22 g, 2.0 mmol) in CH_3CN (2 mL) at room temperature over 5 min. The mixture was then stirred for 24 h. After completion of the reaction, the precipitated product was separated from the reaction mixture by filtration and was washed with 5 mL of *n*-hexane. The desired product was obtained as a brownish red powder (0.55 g, yield 86%). Mp 257−258 °C; IR (KBr) (ν_{max}/cm^{-1}) 2933, 2859, 1751, 1673, 1602, 1446; MS, *m*/*z* (%) 456 (M^+ − 14, 5), 396 (50), 344 (30), 284 (100), 252 (40), 77 (35), 55 (65), 57 (70); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 1.35−1.96 (20H, m, 10CH_2 of 2cyclohexyl), 3.66 (6H, s, 2O−CH_3), 3.71 (6H, s, 2O−CH_3), 3.79 (2H, br s, C*H*−NH), 4.64 (2H, s, 2C*H*−CO_2Me), 8.57 (2H, br s, 2CH−N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 24.3, 25.4, 33.5, (C−cyclohexyl), 35.2 (*C*H−CO_2Me), 50.3 (CH−NH), 51.2, 52.8 (2O−CH_3), 70.7, 117.7, 147.8, 158.3 (C−alkene), 169.1, 172.2, 176.9 (3C═O). Anal. Calcd for $C_{32}H_{38}N_2O_{12}$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.76; H, 5.84; N, 4.28.

Typical Procedure for the Preparation of Product 10a. To a magnetically stirred solution of 2-hydroxynaphthalene-1,4-dione (0.17 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_3CN (5 mL) was added a solution of cyclohexyl isocyanide (0.11 g, 1.0 mmol) in CH_3CN (2 mL) at room temperature over 5 min. The mixture was then stirred for 24 h. After completion of the reaction, the precipitated product was separated from the reaction mixture by filtration and was washed with 5 mL of *n*-hexane. The desired product was obtained as a brownish red powder (0.38 g, yield 89%). Mp 177−178 °C; IR (KBr) (ν_{max}/cm^{-1}) 2936, 2859, 1732, 1680, 1637, 1598; MS, *m*/*z* (%) 456 (M^+ − 14, 5), 396 (50), 344 (30), 284 (100), 252 (40), 77 (35), 55 (65), 57 (70); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 1.42−2.08 (10H, m, 5CH_2 of cyclohexyl), 3.67 (3H, s, O−CH_3), 3.74 (3H, s, O−CH_3), 3.86 (1H, br s, C*H*−NH), 4.74 (1H, s, C*H*−CO_2Me), 7.27−8.15 (4H, m, arom), 8.64 (1H, br s, CH−N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 24.4, 24.4, 25.4, 33.4, 33.7, (C−cyclohexyl), 35.0 (*C*H−CO_2Me), 50.7 (CH−NH), 51.3, 52.7 (2O−CH_3), 72.3, 114.2, 123.8, 129.8, 130.0, 131.8, 135.1, 135.4, 156.9, 158.2 (C−alkene, C−arom), 169.3, 172.9, 177.7, 177.9 (4C═O). Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.88; H, 5.49; N, 3.32.

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Supporting Information Available: Experimental procedures and characterization data of products, IR, mass, ^{1}H, and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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