Novel One-Pot Three- and Pseudo-Five-Component Reactions: Synthesis of Functionalized Benzo[*g*]- and Dihydropyrano[2,3-*g*]chromene Derivatives

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A novel and efficient method has been developed for the synthesis of highly functionalized benzo[*g*]- and dihydropyrano[2,3-*g*]chromene derivatives via addition and subsequently cyclization of 2-hydroxynaphthalene-1,4-dione or 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione to the condensation product of an aldehyde with malononitrile in the presence of a catalytic amount of Et_3N in CH_3CN at ambient temperature. The procedures are very facile. The products can be obtained with simple filtration in high yields, and no more purification is needed. These compounds are closely related to ring systems such as β-lapachone, α-xiloidone, lambertellin, pyranokunthone B, and WS-5995A, which have a broad spectrum of biological activities.

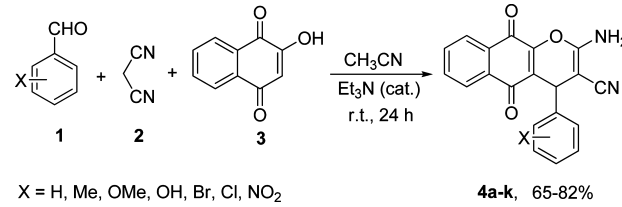
Benzo[*g*]chromenes show a variety of biological activities, including anticancer,[1,2] anti-inflammatory,[3] antimalarial,[4,5] and pesticides activities.[6] This moiety occurs in different natural products, including β-lapachone **A**, α-xiloidone **B**, lambertellin **C**, WS-5995A **D**, and pyranokunthone B **E**.[7−12] Compounds **F** and **G** were extracted from marine actinomycete strain CNQ-525 bacteria; these bacteria were isolated from ocean sediments which were collected at a depth of 152 m near La Jolla, California (Figure 1). Compounds **F** and **G** possess significant antibiotic properties and cancer cell cytotoxicities activities.[13] Because of importance of benzo[*g*]chromene derivatives, different synthetic methods have been developed for the synthesis of this group of compounds. Synthesis of α-lapachone **A** and α-xiloidone **B** have been reported via a semisynthetic approach.[14] Usually, benzo[*g*]chromenes have been synthesized via multistep approach in the presence of expensive catalysts under sensitive conditions.[15−17] For example, an eight-step procedure for the synthesis of chromenes has been reported by De Kimpe and et al.[17] Therefore, development of synthetic methods that could be used to prepare a variety of these templates remains an important task.

Multicomponent reactions (MCRs), because of their productivity, simple procedures, convergence, and facile execution, are one of the best tools in synthesis of organic compounds. Therefore, the design of novel MCRs for the synthesis of different groups of compounds, especially those compounds which are biologically active, have attracted great attention. Different research groups which are working in area such as drug discovery, materials science, natural products, and organic synthesis have attracted to use this synthetic method.[18−24]

Recently, our research group reported the synthesis of benzo[*g*]chromenes and *bis*-chromenes via an isocyanide-based multicomponet reaction.[25] In continuing of our interests in announcing new multicomponent reactions for the synthesis of heterocyclic compounds including 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamides, 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamides, fully substituted 3,4-dihydrocoumarins, highly substituted quinolizines, 4*H*-furo[3,4-*b*]pyrans, pyrano[2,3-*c*]pyrazoles, amides, fully substituted imino and spiroiminocyclopentenes, and 2,5-dihydro-2-methylfuran-3,4-dicarboxylates;[26−32] herein, we wish to report a new method for the synthesis of chromenes from reaction between an aldehyde, malononitrile, and 2-hydroxynaphthalene-1,4-dione in CH_3CN in the presence of a catalytic amount of triethylamine at room temperature (Scheme 1).

In a pilot experiment, a mixture of benzaldehyde and malononitrile in CH_3CN was stirred at room temperature for 30 min in the presence of a catalytic amount of triethylamine; then, 2-hydroxynaphthalene-1,4-dione was added to the reaction mixture. After completion of the reaction (after 24 h, monitored by TLC), the precipitated product was separated from the reaction mixture by filtration and washed with *n*-hexane (5 mL) to afford product **4a** in 82% yield.

Scheme 1. Synthesis of Products **4a**−**k**



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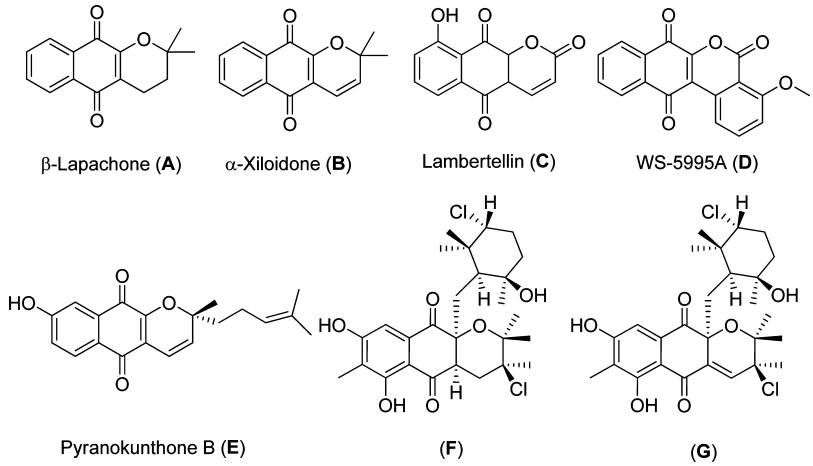
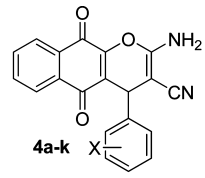


Figure 1. Examples of biologically active benzo[*g*]chromene derivatives.



Entry	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k
X	H	*p*-Me	*p*-Cl	*m*-OMe	*p*-Br	*m*-Br	*o*-Cl	*p*-OH	*m*-NO_2	*p*-NO_2	*p*-OMe
Yield (%)	82	76	80	75	68	70	73	65	80	75	70

Figure 2. Products **4a**−**k**.

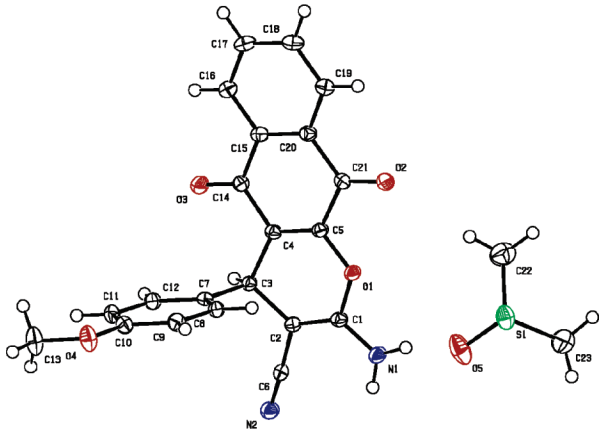
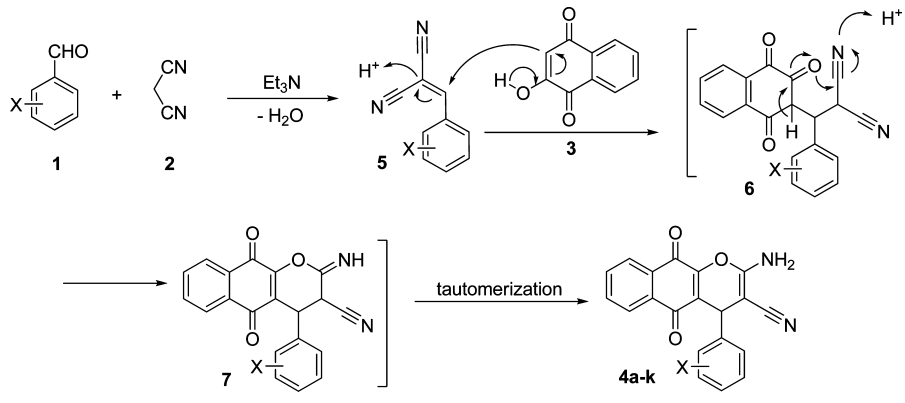


Figure 3. ORTEP diagram for **4k**. Note: A molecule of DMSO as a crystallizing solvent was trapped in crystal structure.

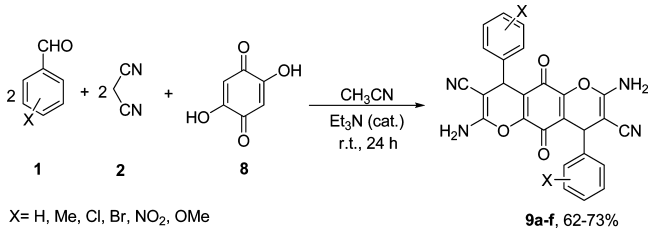
To explore the scope and limitations of this reaction, the procedure was extended to various aldehydes with electron withdrawing and electron donating groups. As indicated in Figure 2, the reactions proceeded very efficiently, and they led to the formation of the corresponding highly functionalized benzo[*g*]chromene derivatives **4a**−**k** in good yields at room temperature, without any undesirable byproduct. Because of the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries.

The structure of products **4a**−**k** was deduced from their IR, mass,^{1}H NMR, ^{13}C NMR, HMQC, and HH COSY spectra data for **4h**. As an example, the ^{1}H NMR spectrum of **4h** exhibited a singlet for the methine proton at $\delta = 4.49$ ppm, a multiplet at $\delta = 6.66-8.05$ ppm for aromatic and NH_2 protons, and a singlet at $\delta = 9.34$ ppm for OH proton. The ^{1}H-decoupled ^{13}C NMR spectrum of **4h** showed 18 distinct resonances in agreement with proposed structure. Investigation of correlations in HMQC and HH COSY

Scheme 2. Proposed Pathway for the Formation of Products **4a**−**k**



Scheme 3. Synthesis of Dihydropyrano[2,3-*g*]chromene Derivatives **9a**−**f**



spectra approved proposed structure. The mass spectra of products displayed molecular ion peaks at the appropriate *m*/*z* values.

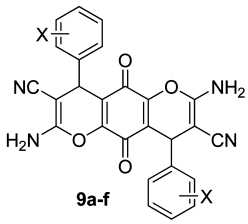
Finally, the structure of the product **4k** was confirmed unambiguously by single-crystal X-ray analysis (Figure 3).

Although the mechanism of this reaction has not been studied experimentally, the formation of product can be rationalized by initial Knoevenagel condensation reaction between an aldehyde **1** and malononitrile **2**; then, the obtained intermediate **5** has been attacked by the 2-hydroxynaphthalene-1,4-dione **3**, which leads to the intermediate **6**. Such an addition intermediate may contribute in a cyclization reaction to generate **7**; which may isomerize under the reaction conditions to produce the fused heterocyclic systems **4a**−**k** (Scheme 2).

The versatility of this multicomponent reaction with respect to the 2-hydroxynaphthalene-1,4-dione **3** was also studied (Scheme 3). As indicated in Scheme 3, product of condensation reaction between an aldehyde **1** and malononitrile **2** could be attacked by the 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione **8** to produce appropriate symmetric products **9a**−**f**. Representative examples of this reaction have been shown in Figure 4. Products **9a**−**f** have been characterized by their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra data.

To broaden the library of products and diversity of reaction, we decided to extend this reaction to use of salicylaldehyde and its derivatives (Scheme 4). As can be seen from Scheme 4, the reaction of salicylaldehyde **10** and malononitrile **2** with 2-hydroxynaphthalene-1,4-dione **3** and or 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione **8** in CH_3CN led to the formation of products **11a**−**c** and **12a**−**c** in good yields at ambient temperature, respectively. These products (**11a**−**c** and **12a**−**c**) were identified by their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra data.

In conclusion, we have developed an efficient synthetic approach for the synthesis of the highly functionalized 4*H*-benzo[*g*]chromene and dihydropyrano[2,3-*g*]chromenes 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, 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.



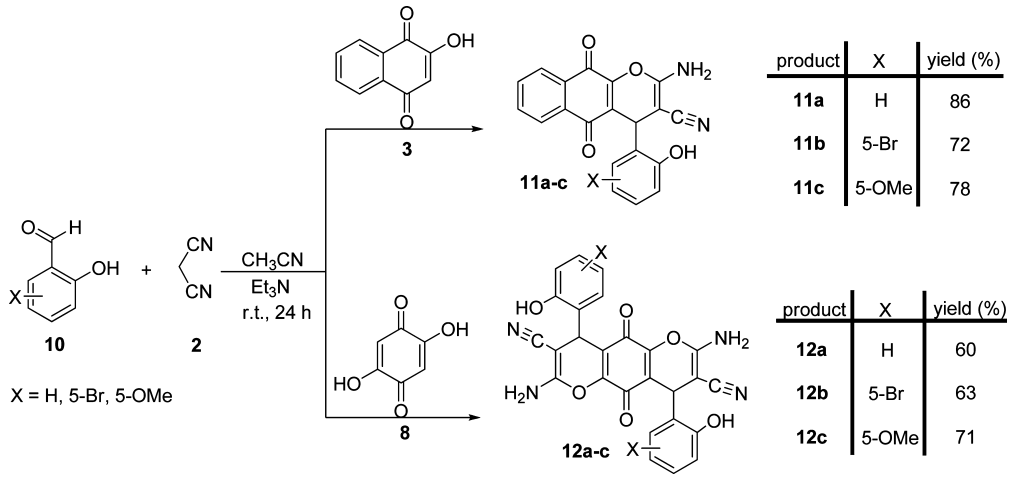
Entry	9a	9b	9c	9d	9e	9f
X	H	*o*-Me	*p*-Br	*p*-NO_2	*p*-Cl	*o*-OMe
Yield (%)	72	64	62	73	68	64

Figure 4. Products **9a**−**f**.

Experimental Section

Typical Procedure for the Preparation of Product 4h. To a magnetically stirred solution of *p*-hydroxybenzaldehyde (0.12 g, 1.0 mmol) and malononitrile (0.07 g, 1.0 mmol) in a screw capped vial, which contained CH_3CN (5 mL), a catalytic amount of Et_3N (0.01 g, 0.10 mmol) was added, and it was stirred for 30 min; then, 2-hydroxynaphthalene-1,4-dione (0.17 g, 1.0 mmol) was added to the reaction mixture at room temperature. The reaction mixture was stirred for 24 h. After completion of the reaction (monitored by TLC method), the precipitated product was separated from reaction mixture by filtration and was washed with 5 mL of *n*-hexane. The desired product was obtained as an orange powder (0.23 g, yield 65%). mp 257−258 °C. IR (KBr) (ν_{max}/cm^{-1}): 3399, 3327, 3188, 2202, 1668, 1596, 1509. MS, *m*/*z* (%): 344 (M^+, 25), 280 (20), 279 (20), 249 (25), 174 (50), 105 (100), 76 (60), 39 (60). ^{1}H NMR (300 MHz, DMSO-

Scheme 4. Synthesis of Products **11a**−**c** and **12a**−**c**



product	X	yield (%)
11a	H	86
11b	5-Br	72
11c	5-OMe	78

product	X	yield (%)
12a	H	60
12b	5-Br	63
12c	5-OMe	71

d$_6$): δ_H (ppm) 4.49 (1H, s, CH), 6.66−8.05 (10H, m, aroma and NH_2), 9.34 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ_C (ppm) 36.0 (CH), 58.3, 115.7, 119.9, 122.9, 126.2, 126.5, 128.9, 129.4, 130.9, 131.5, 134.5, 135.0, 148.9, 156.9, 158.7(C-alkene and arom), 177.4, 183.1 (2C═O).

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Supporting Information Available. Experimental procedures, characterization data, and spectra of products, IR, mass, ^{1}H, and ^{13}C NMR spectra of **4a**−**j**, **9a**−**f**, **11a**−**c**, **12a**−**c**, HMQC and HH COSY for **4h**, and crystallographic data for **4k** (CIF). This information is available free of charge via the Internet at http://pubs.acs.org/.

References and Notes

(1) Li, C. J.; Li, Y. L.; U.S. Patent Appl. Publ. US 2005222246 A1 20051006, 2005.
(2) Ough, M.; Lewis, A.; Bey, E. A.; Gao, J.; Ritchie, J. M.; Bornmann, W.; Boothman, D. A.; Oberley, L. W.; Cullen, J. J. *Canc. Biol. Ther.* **2005**, *4*, 95–102.
(3) Moon, D. O.; Choi, Y. H.; Kim, N. D.; Park, Y. M.; Kim, G. Y. *Int. Immunopharmacol.* **2007**, *7*, 506–514.
(4) De Andrade-Neto, V. F.; Goulart, M. O. F.; Da Silva Filho, J. F.; Da Silva, M. J.; Pinto, M. D. C. F. R.; Pinto, A. V.; Zalis, M. G.; Carvalho, L. H.; Krettli, A. U. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145–1149.
(5) Elisa, P. S.; Ana, E. B.; Ravelo, A. G.; Yapu, D. J.; Turba, A. G. *Chem. Biodiversity* **2005**, *2*, 264–274.
(6) Shestopalov, A. M.; Emelianova, Y. M.; Nesterov, V. N. *Russ. Chem. Bull.* **2003**, *52*, 1164–1171.
(7) Da Silva, A. J. M.; Buarque, C. D.; Brito, F. V.; Aurelian, L.; Macedo, L. F.; Malkas, L. H.; Hickey, R. J.; Lopes, D. V. S.; Noël, F.; Murakami, Y. L. B.; Silva, N. M. V.; Melo, P. A.; Caruso, R. R. B.; Castro, N. G.; Costa, P. R. R. *Biorg. Med. Chem.* **2002**, *10*, 2731–2738.
(8) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187–7194.
(9) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046–3049.
(10) Brown, P. M.; Krishnamoorthy, V.; Mathieson, J. W.; Thomson, R. H. *J. Chem. Soc. C.* **1970**, *10*, 9–110.
(11) Armstrong, J. J.; Turner, W. B. *J. Chem. Soc.* **1965**, 5927–5930.
(12) Keniry, M. A.; Poulton, G. A. *Magn. Reson. Chem.* **1991**, *29*, 46–48.
(13) Soria-Mercado, I. E.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2005**, *68*, 904–910.
(14) Machado, T. B.; Pinto, A. V.; Pinto, M. C. F. R.; Leal, I. C. R.; Silva, M. G.; Amaral, A. C. F.; Kuster, R. M.; NettodosSantos, K. R. *Int. J. Antimicrob. Agents* **2003**, *21*, 279–284.
(15) Goujon, J. Y.; Zammattio, F.; Pagnoncelli, S.; Boursereau, Y.; Kirschleger, B. *Synlett* **2002**, 322–324.
(16) Kabalka, G. W.; Venkataiah, B.; Das, B. C. *Synlett* **2004**, 2194–2196.
(17) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem.* **1999**, *64*, 1173–1179.
(18) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471–1499.
(19) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
(20) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
(21) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.
(22) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085–2093.
(23) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329.
(24) Abboub, F.; Amari, M.; Kolli, B. *J. Soc. Alger. Chim.* **2001**, *11*, 223–230.
(25) Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372–4374.
(26) Shaabani, A.; Maleki, A.; Mofakham, H.; Moghimi-Rad, J. *J. Org. Chem.* **2008**, *73*, 3925–3927.
(27) Shaabani, A.; Rezayan, A. H.; Rahmati, A.; Sarvary, A. *Synlett* **2007**, 1458–1460.
(28) Shaabani, A.; Rezayan, A. H.; Sarvary, A.; Rahmati, A.; Khavasi, H. R. *Catal. Commun.* **2008**, *9*, 1082–1086.
(29) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137–6141.
(30) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett.* **2008**, *10*, 2581–2584.
(31) Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3968–3970.
(32) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342–3345.

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