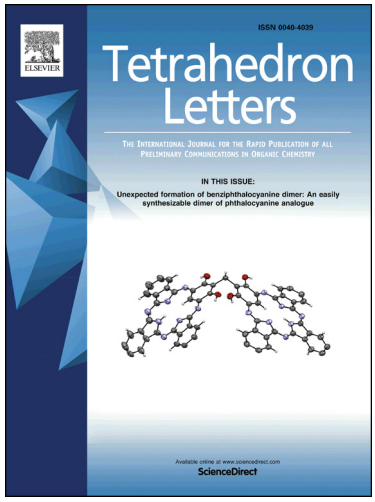

Electrocatalytic one pot synthesis of medicinally relevant 4H-benzo[g]chromene and pyrano[2,3-g]chromene scaffold via multicomponent-domino approach

Abhishek Upadhyay, Vinay K. Singh, Rahul Dubey, Narendra Kumar, L.K. Sharma, Rana Krishna Pal Singh

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Graphical Abstract

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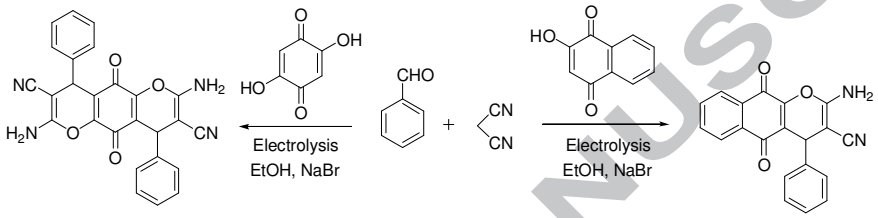

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Electrocatalytic one pot synthesis of medicinally relevant 4H-benzo[g]chromene and pyrano[2,3-g]chromene scaffold via multicomponent-domino approach

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ABSTRACT

A highly efficient one pot, multicomponent synthesis of 4H-benzo[g]chromene and pyrano[2,3-g]chromene derivatives are reported by electrochemically stimulated condensation of an aromatic aldehyde, malononitrile and some enolizable acidic compounds in ethanol at room temperature under constant current density. By utilizing common electrode materials and a simple constant current protocol, this method is a new alternative to conventional methods.

Electrochemical reaction is one of the most dynamic fields in organic synthesis and achieved considerable attention in recent years.[1] In the same way, multicomponent reactions are also attractive and greener synthetic tool to access diverse molecular scaffolds.[2] By merging both concepts, electrocatalyzed multicomponent reactions (EMCRs) has appeared as a very useful approach in organic synthesis. Multicomponent reactions allowing access to compounds with structural complexity and diversity in a single operation, with improved atom economy, synthetic efficiency and a minimum number of reactions and purification steps.[3] While in an electrochemical reaction, electric current serves as an economical and potentially renewable reagent that avoids the need of harmful and expensive reagent. It minimizes the waste produced in the reaction, reduced the energy requirements and reaction times, in addition electrochemical method can be considered as inherently safe. These features make electrocatalyzed multicomponent reactions (EMCRs) well suited for the construction of heterocyclic compound from readily available starting materials.

Chromenes has received overwhelming attention in the pharmaceutical industry as well as in the diversified field of organic synthesis due to their potential biological activities [4]. This moiety occurs in different natural products, including β-lapachone , WS-5995A , pyranokunthone B and pyranokunthone A (Fig. 1).[5] The literature reveals that benzochromenes are significant pharmacophores related with a wide range of pharmacological activities, such as anticancer,[6] antimalarial,[7] anti-inflammatory[8] and pesticides activities.[9] In addition chromene moieties are used as fluorescence markers [10] as well as laser dyes[11] in pharmacy and biology.

Due to the aforementioned properties and wide spectrum of applications, synthesis of benzo[g]chromene derivatives has been a domain of intense interest and the development of novel strategies to access the 2-amino-4H-benzo[g] chromene scaffold is a demanding task for organic chemists. Various methodologies for the synthesis of 2-amino-4H-benzo[g]chromene scafold has been reported such as by using different catalysts including NEt_3,[12] DBU,[13] potassium phthalimide-Noxyl,[14] Fe_3O_4 nanoparticles under ultrasonic irradiations,[15] [bmim]OH ionic liquid,[16] Zn(*L*-proline)$_2$,[17] lipase,[18] urea,[19] and microwave irradiation.[20] However, some of these methods suffer from certain restrictions and disadvantage such as multistep synthesis, use of toxic organic solvents, tedious work-up procedure, high catalyst loading, low yields, poor availability of the catalysts, incompatibility with the environment and long reaction time. Owing to the importance of 2-amino-4H-benzo[g]chromene nucleus from a pharmaceutical and biological point of view, there is still the need to develop efficient, mild and environmentally benign procedure for the synthesis of 2-amino-4H-benzo[g]chromene derivatives.

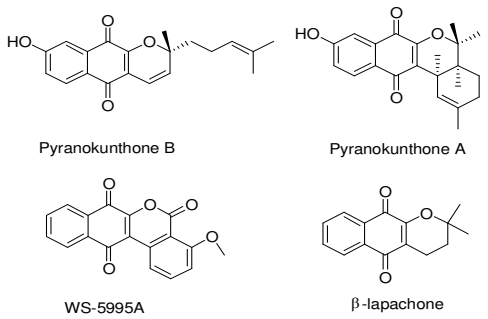
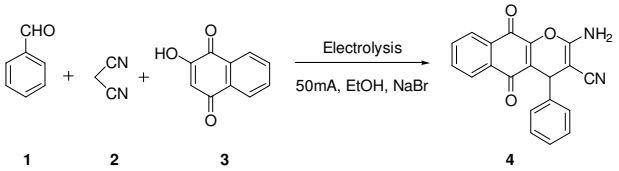
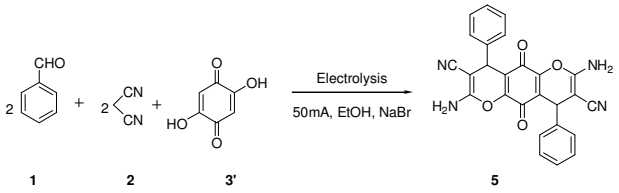


Figure 1. Some examples of biologically significant compounds having chromene core.

Recently, we have reported the synthesis of a series of heterocycles using MCRs or domino reactions catalyzed by electricity.[21] In the current paper, we report a an efficient domino protocol for the synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives **4** and 2,7-diamino-5,10-dioxo-4,9-diphenyl-4,9-dihydropyrano[2,3-g]chromene -3,8-dicarbonitrile derivative **5** from one-pot, three-component domino reactions of aromatic aldehyde, malononitrile and 2-hydroxynaphthalene-1,4-dione or 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione in an undivided cell at room temperature under a constant current density and catalyst-free conditions (Scheme 1).



Scheme 1. Synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile.



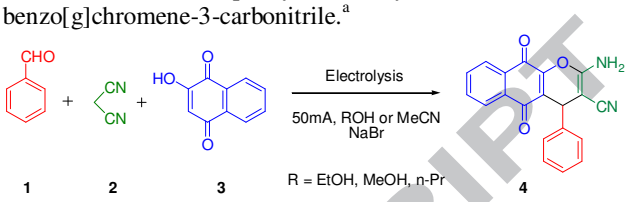
Scheme 2. Synthesis of 2,7-diamino-5,10-dioxo-4,9-diphenyl-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile.

At present time, organic reactions in green solvents such as water, ethanol and their mixtures in the presence of green catalyst have attracted much attention, because these solvents are safe, economical, and environmentally benign. For this reason, we concentrated our study to developing green novel synthetic methods for the preparation of benzo[g]chromene-3-carbonitrile derivatives. This is a one-pot electrocatalytic reaction which is not only operationally simple, efficient, safe and clean but also continually furnishes the corresponding products in good to excellent yields. Thus, to find the suitable reaction media, the reaction was carried out in various solvents (Table 1) under constant current at room temperature and found that ethanol was best solvent in term of yield and desired product.

Next to evaluate the synthetic potential of the proposed method and to optimize the electrolysis conditions for the synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile **4** from aromatic aldehyde, malononitrile and 2-hydroxynaphthalene-1,4-dione, we carried out the reaction at different amount of current in ethanol solvent in the presence of sodium bromide as an electrolyte. Excellent conversions of the starting materials were obtained under 10 mA/cm^2 current densities after 0.62 F/mol of electricity had been passed. The current density 10 mA/cm^2 (I = 50 mA, electrodes surface 5 cm^2) was found to be optimal for the electrochemical reaction and allowed for the highest yield of **4** (Table 1). The yield of reaction was reduced on further increase of the current density from 10 mA/cm^2 (I = 50 mA) which may be due to acceleration of undesired direct electrochemical processes.

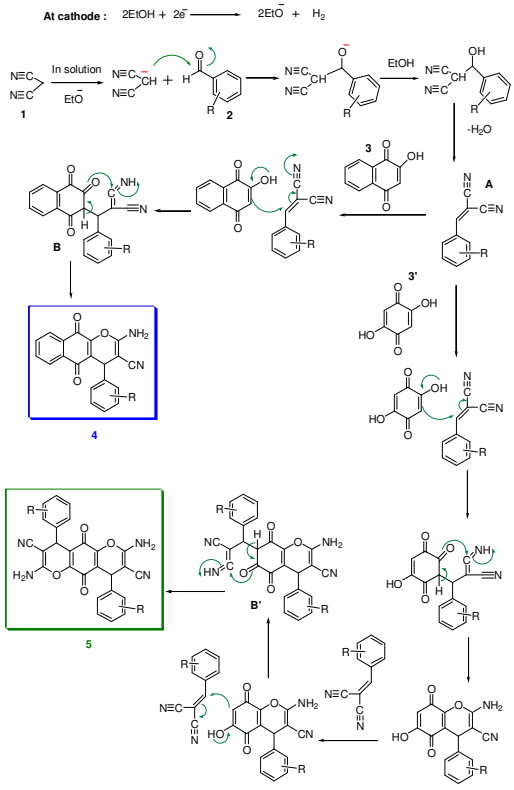
To evaluate the scope and limitations of this electrocatalytic protocol, we investigated a range of aromatic aldehydes (Table 2 and Table 3). As shown in Table 2, the aromatic aldehydes having different electron-withdrawing and electron-donating substituents efficiently reacted to afford the corresponding products in excellent yields, demonstrating that there was no considerable effect of substituent on yields of reaction. Further we carried out the same reaction with non-aromatic aldehyde but unfortunately reaction is not working under similar condition.

Table 1[a] Optimization of reaction conditions for synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H benzo[g]chromene-3-carbonitrile.[a]



Entry	Solvent	I (mA)	Current density (mA/cm^2)	Time (min)	Electricity Passed (F / mol)	Yield[b] (%)
1	EtOH	5	1	180	0.56	58
2	EtOH	10	3	120	0.74	70
3	EtOH	20	4	60	0.74	80
4	EtOH	50	10	20	0.62	90
5	EtOH	75	15	15	0.70	78
6	MeOH	50	10	20	0.62	76
7	n-PrOH	50	10	20	0.62	80
8	MeCN	50	10	20	0.62	78

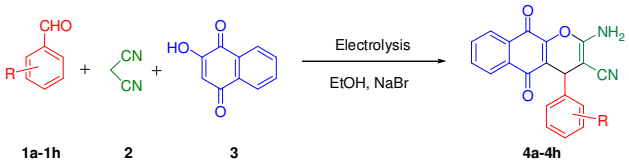
[a]General procedure: aromatic aldehydes (1 mmol), malononitrile (1 mmol), and 2-hydroxynaphthalene-1,4-dione (1 mmol) electrolyte(0.5 mmol), EtOH (25 mL), iron cathode (5 cm^2), graphite anode (5 cm^2).
[b]Yield of isolated product.



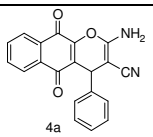
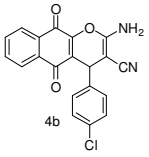
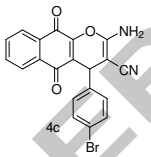
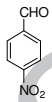
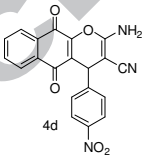
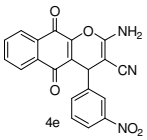
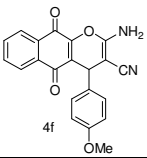
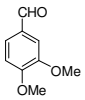
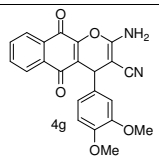
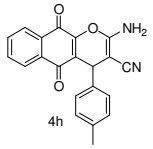
Scheme 3. A plausible mechanism for the formation of **4a-4h** and **5a-5d** compounds.

A possible mechanism for the formation of products **4** and **5** is shown in Scheme 3. The reaction initiates with the formation of alkoxide anion from alcohol at cathode, which abstract hydrogen from malanonitrile and form malononitrile anion. Then Knoevenagel condensation of malononitrile anion and Aromatic aldehyde takes place in the solution with the elimination of hydroxide anion and formation of corresponding benzylidenemalononitrile **A**. Subsequently the enolizable compound **3** and **3'** condensed with the Knoevenagel adduct **A** via 1,4-addition to give intermediate **B** and **B'**. Intermediate **B** and **B'** by intramolecular cyclization transformed into final product **4** and **5**.

Table 2 Electrochemical synthesis of 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives [a b]

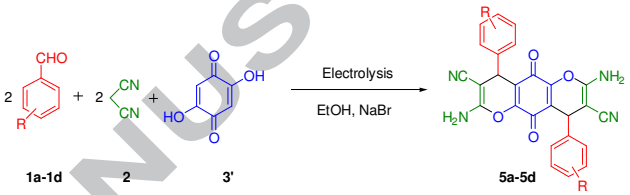


1a-1h **2** **3** **4a-4h**

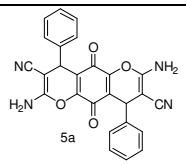
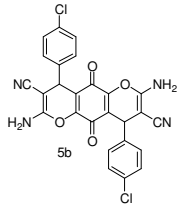
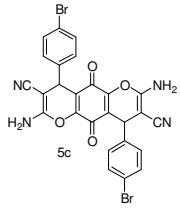
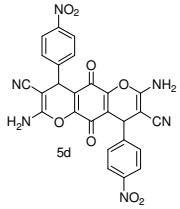
Entry	Aryl	Product	Time (min.)	Yield[c] (%)	Mp (^{0}C)
1	 1a	 4a	20	90	262-264
2	 1b	 4b	20	92	250-252
3	 1c	 4c	20	92	254-255
4	 1d	 4d	18	96	240-242
5	 1e	 4e	18	94	248-250
6	 1f	 4f	25	90	244-246
7	 1g	 4g	28	88	265-267
8	 1h	 4h	25	90	241-243

[a] For the experimental procedure, see supporting information.
[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[11, 14, 17]
[c] Yields of isolated pure compounds 4a – 4h.

Table 3 Electrochemical synthesis of 2,7-diamino-5,10-dioxo-4,9-diphenyl-4,9-dihydropyrano[2,3-g]chromene-3,8-derivatives [a b]



1a-1d **2** **3'** **5a-5d**

Entry	Aryl	Product	Time (min.)	Yield[c] (%)	Mp (^{0}C)
1	 1a	 5a	25	90	288-290
2	 1b	 5b	25	90	272-274
3	 1c	 5c	25	90	262-264
4	 1d	 5d	20	90	293-295

[a] For the experimental procedure, see supporting information.
[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[11]
[c] Yields of isolated pure compounds 5a – 5d.

In conclusion, we have developed a facile and efficient electrocatalytic procedure for the synthesis 2-amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile derivatives and 2,7-diamino-5,10-dioxo-4,9-diphenyl-4,9-dihydropyrano[2,3-g]chromene-3,8-derivatives with excellent yields by applying inexpensive and readily available electrode materials such as Iron and graphite. This method is appropriate for a wide range of substrates under constant current and ambient conditions. In addition, this electrocatalytic protocol represents a novel synthetic concept for multicomponent reactions, and allows for the combination of the synthetic qualities of conventional MCR with ecological benefits and convenience of simple electrocatalytic method.

Acknowledgments

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References

1. (a) Horn EJ, Rosen BR, Chen Y, Tang J, Chen K. Eastgate M D, Baran PS. Nature. **2016**;533:77; (b) Hartmer MF, Waldvogel SR. Chem. Commun. **2015**;51:16346.
2. (a) Sunderhaus JD, Martin SF, Chem. Eur. J. **2009**;15:1300; (b) Graaff CD, Ruijter E, Orru RVA. Chem. Soc. Rev. **2012**; 41:3969.
3. (a) Cioc RC, Ruijter E, Orru RVA. Green Chem. **2014**;16: 2958; (a) Sunderhaus JD, Dockendorff C, Martin SF. Org. Lett. **2007**;9:4223; (c) Dömling A, Wang W, Wang K. Chem. Rev. **2012**;112:3083; (d) Alvim HGO, Da Silva Júnior EN, Neto BAD. RSC Adv. **2014**;4:54282; (e) Dömling A. Chem. Rev. **2006**;106:17.
4. (a) Qiang DZ, Shi JB, Song BA, Liu XH. RSC Adv. **2014**;4: 5607; (b) De Andrade-Neto VF, Goulart MOF, Da Silva Filho JF, Da Silva MJ, Pinto MDCFR, Pinto AV, Zalis MG, Carvalho LH, Krettli AU. Bioorganic & Medicinal Chemistry Letters. **2004**;14:1145; (c) Sashidhara KV, Rosaiah JN, Bhatia G, Saxena JK. Eur. J. Med. Chem. **2008**;43:2592.
5. (a) Ríos-Luci C, Bonifazi EL, León LG, Montero JC, Burton G, Pandiella A, Misico RI, Padrón JM. European Journal of Medicinal Chemistry **2012**;53:264; (b) Magedov IV, Kireev AS, Jenkins AR, Evdokimov NM., Lima DT, Tongwa P., Altig J, Steelant WFA, slambrouck SV, Antipin MY, Kornienko A. Bioorganic & Medicinal Chemistry Lett. **2012**;22:5195; (c) Onegia B, Kraft C, Kohler I, Freund M, Jenett-Siems K, Siems K, Beyer G, Melzig MF, Bienzle U., Eich E. Phytochemistry **2002**;60:39; (d) Qabaja G, Perchellet EM , Perchellet J, Jones GB. Tetrahedron Lett. **2000**;41:3007.
6. Ough M, Lewis A, Bey EA, Gao J, Ritchie JM, Bornmann W, Boothman DA, Oberley LW, Cullen JJ. Cancer Biol. Ther. **2005**;4:95.
7. De Andrade-Neto VF, Goulart MOF, Da Silva Filho JF, Da Silva MJ, Pinto MDCFR, Pinto AV, Zalis MG, Carvalho LH, Krettli AU. Bioorg. Med. Chem. Lett. **2004**;14:1145.
8. Moon DO, Choi YH, Kim ND, Park YM, Kim GY. Int. Immunopharmacol. **2007**;7:506.
9. Shestopalov AM, Emelianova YM, Nesterov VN. Russ. Chem. Bull. **2003**;52:1164.
10. Bissell ER, Mitchell AR, Smith REJ. Org. Chem. **1980**;45: 2283.
11. Reynolds GA, Drexhage KH. Opt. Commun. **1975**;13:222.
12. Shaabani A, Ghadari R, Ghasemi S, Pedarpour M, Rezayan A H, Sarvary A, Ng SW. J. Comb. Chem. **2009**;11:956.
13. Khurana JM, Nand B, Saluja P. Tetrahedron. **2010**;66:5637.
14. Dekamin MG, Eslami M, Maleki A. Tetrahedron. **2013**;69: 1074.
15. Safaei-Ghomi J, Eshteghal F, Shahbazi-Alavi H. Ultrasonics Sonochem. **2016**;33:99.
16. Yu Y, Gu H, Li X. J. Heterocycl. Chem. **2011**;48:1264.
17. Maleki B, Babaee S, Tayebee R. Appl. Organomet. Chem. **2015**;29:408.
18. Yang F, Wang H, Jiang L, Yue H, Zhang H, Wang Z, Wang L. RSC Adv. **2015**;5,5213.
19. Brahmachari G, Banerjee B. ACS Sustainable Chem. Eng. **2014**;2:411.
20. Wang XH, Zhang XH, Tu SJ, Shi F, Zou X, Yan S, Han ZG, Hao WJ, Cao XD, Wu SS. J Heterocycl Chem. **2009**;46:832.
21. (a) Singh S, Sharma LK, Saraswat A, Siddiqui IR, Kehri HK, Singh RKP. RSC Adv. **2013**;3:4237; (b) Upadhyay A, Sharma LK, Singh VK, Singh RKP. Tetrahedron Lett. **2016**;57:5599; (c) Upadhyay A, Sharma LK, Singh VK, Dubey R, Kumar N, Singh RKP. Tetrahedron Lett. **2017**;58:1245. (d) Dubey R, Singh VK., Sharma LK, Upadhyay A, Kumar N, Singh RKP. New J. Chem. **2017**;4:7836.

Highlights

- One pot four-component electro-synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile derivatives
- Electro-induced condensation of ethyl acetoacetate, hydrazine hydrate, malononitrile and aromatic aldehydes.
- EGB promotes reaction in presence of NaBr as supporting electrolyte and ethanol as solvent.
- Small amount of current was used as energy source in the place of conventional heating.