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Rapid One-Pot DMAP-Promoted Synthesis of Biologically Important 3-Amino-1*H*-benzo[*f*]chromene-2-carbonitriles

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Abstract

An efficient environmentally friendly procedure for the synthesis of biologically important 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles through the one-pot, three-component reaction of *β*-naphthol, aromatic aldehydes, and malononitrile using *p*-dimethylaminopyridine (DMAP) as an effective and novel heterogeneous catalyst under thermal solvent-free conditions is described. The catalyst is inexpensive and readily available and can be recovered conveniently and reused efficiently such that a considerable catalytic activity still could be achieved after the third run. Other advantages of this procedure are high yields, relatively short reaction times, easy work-up, and absence of any volatile and hazardous organic solvents.

Keywords: 3-Amino-1*H*-benzo[*f*]chromene-2-carbonitriles, DMAP, Heterogeneous catalysis, Solvent-free

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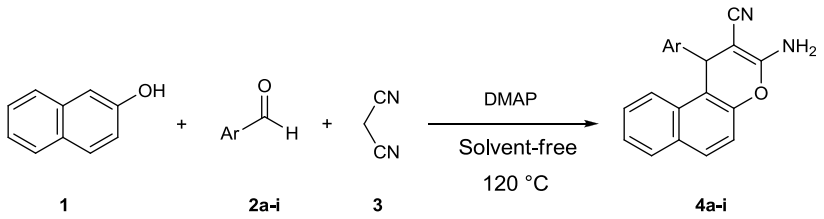
Introduction

Chromenes and fused chromenes are important oxygenated heterocyclic compounds with diverse and interesting biological activities. These compounds are reported to possess significant anticoagulant, diuretic, antivascular, antifungal, anticonvulsant, antiviral, antioxidative, antibacterial, and anticancer activities (Bonsignore *et al*., 1993; Thareja *et al*., 2010; O'Kennedy *et al*., 1997; Behrami 2014; Mohr *et al*., 1975). A number of these compounds are employed as cosmetics and pigments (Ellis, 1997), and potential biodegradable agrochemicals (Hafez *et al*., 1987). Also, several chromenes have been proven to be efficient DNA polymerase *β* inhibitors (Cain, 1960), apoptosis inducers (Skommer *et al*., 2006; Gao *et al*., 2010), and antitrypanosomal agents (Limsuwan *et al*., 2009). Due to these important properties of chromene derivatives, considerable attention has been focused on the development of environmentally friendly methodologies to synthesize chromene scaffold specially benzo[*f*]chromene derivatives. These compounds are generally synthesized *via* a one-pot three-component cyclocondensation of *β*-naphthol, aromatic aldehydes, and malononitrile in the presence of several catalysts such as *p*-toluenesulfonic acid (*p*-TSA) (Baghernejad *et al*., 2009), hexadecyltrimethylammonium bromide (HTMAB) (Jin *et al*., 2006), diazabicyclo[2.2.2]octane (DABCO) (Balalaie *et al*., 2008), cetyltrimethylammonium chloride (CTACl) (Ballini *et al*., 2001), 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) (Gong *et al*., 2008), Preyssler heteropolyacid (Heravi *et al*., 2007), thiourea dioxide (Verma and Jain, 2012), tetrabutylammonium bromide (TBABr) (Jin *et al*., 2003), and silica tungstic acid (STA) (Farahi *et al*., 2014). Methods utilizing microwave irradiation in the presence of K_2CO_3 (Kidwai *et al*., 2005) or ultrasonic irradiation using cetyltrimethylammonium bromide (CTABr) (Jin *et al*., 2004) as catalyst, have also been reported. Although some of these methods have convenient protocols with good to high yields, the majority suffer from at least one disadvantage such as unsatisfactory yields, toxic organic solvents, long reaction times, and the use of relatively expensive catalysts. These findings prompted us to perform investigations to find a new catalyst that will enable the synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles using simple experimental set-ups and eco-friendly conditions.

As a result of our interest in the synthesis of heterocyclic compounds (Davoodnia *et al*., 2007a; Davoodnia *et al*., 2007b; Khashi *et al*., 2014), and as part of our research on the development of environmentally friendly methods for synthesis of organic compounds using reusable catalysts (Davoodnia *et al*., 2010; Davoodnia *et al*., 2012; Nakhaei *et al*., 2015), we report here our results from efficient solvent-free synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles **4a-i** by one-pot, three-component reaction of *β*-naphthol **1**, aromatic aldehydes **2a-i**, and malononitrile **3**, using *p*-dimethylaminopyridine (DMAP) as a novel heterogeneous catalyst (Scheme 1).



Scheme 1. DMAP catalyzed synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles

Materials and Methods

All chemicals were available commercially and used without additional purification. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR (250 and 300 MHz) spectra were recorded using Bruker 250 and 300 spectrometers.

General Procedure for the Synthesis of 3-Amino-1H-benzo[f]chromene-2-carbonitriles 4a-i Catalyzed by DMAP

A mixture of *β*-naphthol (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol) and DMAP (0.1 mmol, 10 mol%) was heated on the oil bath at 120 °C for the indicated time. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and cold EtOH/H_2O (5 mL/5 mL) was added. This resulted in the precipitation of the product, which was collected by filtration and then recrystallized from ethanol (96%) to give compounds **4a-i** in high yields.

Selected spectral data

3-Amino-1-(4-bromophenyl)-1H-benzo[f]chromene-2-carbonitrile ***4b*** ^{1}H NMR (300 MHz, d_6-DMSO): δ (ppm) 5.37 (s, 1H, CH), 7.05 (s, 2H, NH_2), 7.18-7.50 (m, 7H, arom-H), 7.78-7.99 (m, 3H, arom-H); IR (KBr disc): *υ* (cm^{-1}) 3433 and 3340 (NH_2), 2183 (CN).

3-Amino-1-(4-chlorophenyl)-1H-benzo[f]chromene-2-carbonitrile ***4d*** ^{1}H NMR (300 MHz, d_6-DMSO): δ (ppm) 5.37 (s, 1H, CH), 7.07 (s, 2H, NH_2), 7.19-7.49 (m, 7H, arom-H), 7.79-7.98 (m, 3H, arom-H); IR (KBr disc): *υ* (cm^{-1}) 3445 and 3302 (NH_2), 2205 (CN).

3-Amino-1-(4-nitrophenyl)-1H-benzo[f]chromene-2-carbonitrile ***4i*** ^{1}H NMR (250 MHz, d_6-DMSO): δ (ppm) 5.32 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.10-7.50 (m, 7H, arom-H), 7.75-7.95 (m, 3H, arom-H); IR (KBr disc): *υ* (cm^{-1}) 3473 and 3329 (NH_2), 2194 (CN).

Results & discussion

At the outset, we examined the reaction by using *β*-naphthol **1** (1 mmol), 4-chlorobenzaldehyde **2d** (1 mmol), and malononitrile **3** (1 mmol) as model subs-

trates for the synthesis of compound **4d**. No product was obtained in the absence of the catalyst at 120 °C under solvent-free conditions even after 180 min. Pleasingly, we discovered that the reaction was efficiently catalyzed by DMAP under solvent-free conditions at an elevated temperature, providing a high yield of product **4d**. The reaction conditions were then optimized by conducting the reaction at different temperatures and employing different loadings of the catalyst. The results are summarized in Table 1. The efficiency of the reaction is mainly affected by the amount of the catalyst. When the amount of the catalyst was increased, a ramp in the yield of the product **4d** was observed. The optimal amount of the catalyst was 10 mol% (entry 9); increasing the amount of the catalyst beyond this value did not increase the yield of the product. The effect of temperature was investigated by carrying out the same model reaction at different temperatures under solvent-free conditions. The yield increased as the reaction temperature was raised and at 120 °C the product was obtained in high yield. Higher temperature did not increase the yield of the product. Also, the reaction was carried out in various solvents. As shown, in comparison with conventional methods the yields of the reaction under solvent-free conditions are higher and the reaction time is shorter. Therefore, our optimized conditions are 10 mol% of DMAP at 120 °C under solvent-free conditions. All subsequent reactions were carried out using these conditions.

Table 1: Optimization of reaction conditions for the synthesis of compound 4d catalyzed by DMAP

Entry	Catalyst (mol%)	Solvent	T (°C)	Time (min)	Isolated yield (%)
1	-----	-----	120	180	-----
2	5	-----	100	120	40
3	5	-----	120	90	61
4	5	-----	140	90	60
5	7	-----	100	90	52
6	7	-----	120	70	76
7	7	-----	140	75	76
8	10	-----	100	80	71
9	10	-----	120	30	90
10	10	-----	140	35	89
11	15	-----	120	45	88
12	10	H_2O	Reflux	120	45
13	10	MeOH	Reflux	75	70
14	10	EtOH	Reflux	60	79
15	10	$MeCO_2Et$	Reflux	100	62
16	10	CH_2Cl_2	Reflux	120	51

Reaction conditions: β-naphthol (1 mmol), 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol).

To evaluate the scope of this catalytic transformation, the optimized reaction conditions were subsequently applied to the reaction of β-naphthol and malononitrile with a variety of different aromatic aldehydes under the optimized reaction conditions. In all cases the expected products were obtained in high yields in relatively short reaction times. The results are summarized in Table 2. As

shown, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the corresponding 3-amino-1*H*-benzo[*f*]chromene-2-carbonitrile products in high yields.

Table 2: Synthesis of the 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles 4a-i using the DMAP catalyst under the optimized conditions

Entry	Ar	Product	Time (min)	Isolated yield (%)	Melting point (ºC)	
					Found	Reported [Lit.]
1	C_6H_5	**4a**	45	85	287-289	287-288 (Gong *et al*., 2008)
2	4-BrC_6H_4	**4b**	35	90	216-218	220-221 (Farahi *et al*., 2014)
3	2-ClC_6H_4	**4c**	60	85	259-261	265-267 (Jin *et al*., 2006)
4	4-ClC_6H_4	**4d**	30	90	208-209	206-208 (Jin *et al*., 2003)
5	4-FC_6H_4	**4e**	30	95	230-232	231-232 (Gong *et al*., 2008)
6	4-MeC_6H_4	**4f**	70	82	266-268	270-271 (Gong *et al*., 2008)
7	4-$MeOC_6H_4$	**4g**	75	80	216-218	194-196 (Jin *et al*., 2006)
8	3-$O_2NC_6H_4$	**4h**	45	88	231-234	232-235 (Farahi *et al*., 2014)
9	4-$O_2NC_6H_4$	**4i**	30	92	190-192	187-188 (Gong *et al*., 2008)

Reaction conditions: *β*-naphthol (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), DMAP (0.1 mmol, 10 mol%), 120 ºC, solvent-free.

The results obtained in the current study using the DMAP catalyst were compared with those previously reported for the synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitrile using a variety of different catalysts. As shown in Table 3, it is clear that the DMAP catalyst gave shorter reaction time than all of the other conditions (except for the reactions catalyzed by K_2CO_3 or CTABr under microwave and ultrasonic irradiation, respectively).

Table 3: Comparison of the efficiencies of various catalysts for the one-pot, three-component synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T/ºC	Other			
p-TSA	CH_3CN	reflux	-----	180-240	89-91	(Baghernejad *et al*., 2009)
HTMAB	H_2O	reflux	-----	360	81-85	(Jin *et al*., 2006)
DABCO	EtOH	r.t.	-----	120-240	47-91	(Balalaie *et al*., 2008)
CTACl	H_2O	reflux	-----	360	74-75	(Ballini *et al*., 2001)
[bmim]OH	H_2O	reflux	-----	4-100	80-97	(Gong *et al*., 2008)
Preyssler heteropolyacid	H_2O	reflux	-----	165-255	91-93	(Heravi *et al*., 2007)
Thiourea dioxide	H_2O	50	-----	480	80-89	(Verma and Jain, 2012)
TBABr	H_2O	reflux	-----	360	74-82	(Jin *et al*., 2003)
STA	-----	120	-----	90-300	65-95	(Farahi *et al*., 2014)
K_2CO_3	-----	105	MW	2-3	87-93	(Kidwai *et al*., 2005)
CTABr	H_2O	r.t.	Ultrasonic	150	72-83	(Jin *et al*., 2004)
DMAP	-----	120	-----	30-75	80-95	this work

The reusability of the catalyst was also investigated. After completion of the reaction, the reaction mixture was cooled to room temperature, and cold ethanol/water was added. The precipitated product was collected by filtration, and washed repeatedly with cold ethanol/water. The combined filtrate was evaporated to dryness under reduced pressure. The solid catalyst was collected, dried at 70 ºC

under vacuum for 1 h, and reused for the same experiment. We found that the catalyst could be used at least three times with only a slight reduction in activity (90% for 1st use; 89% for 2nd use; 87% for 3rd use).

Conclusion

In conclusion, we have reported a new catalytic method for the synthesis of 3-amino-1*H*-benzo[*f*]chromene-2-carbonitriles from the one-pot reaction of *β*-naphthol, aromatic aldehydes, and malononitrile in the presence of DMAP as an efficient heterogeneous catalyst. This method provided the desired products in high yields over relatively short reaction times, following a facile work-up process. Furthermore, the catalyst could be readily recycled, and reused at least three times without any discernible reduction in its catalytic activity. No hazardous organic solvent were used, resulting in eco-friendly process.

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References

[1] B. Baghernejad, M.M. Heravi, H.A. Oskooie, A novel and efficient catalyst to one-pot synthesis of 2-amino-4H-chromenes by *p*-toluenesulfonic acid, *Journal of the Korean Chemical Society*, **53** (2009), 631-634. http://dx.doi.org/10.5012/jkcs.2009.53.6.631

[2] S. Balalaie, S. Ramezanpour, M. Bararjanian, J.H. Gross, DABCO-catalyzed efficient synthesis of naphthopyran derivatives via one-pot three-component condensation reaction at room temperature, *Synthetic Communications*, **38** (2008), 1078-1089. http://dx.doi.org/10.1080/00397910701862865

[3] R. Ballini, G. Bosica, M.L. Conforti, R. Maggi, A. Mazzacanni, P. Righi, G. Sartori, Three-component process for the synthesis of 2-amino-2-chromenes in aqueous media, *Tetrahedron*, **57** (2001), 1395-1398. http://dx.doi.org/10.1016/S0040-4020(00)01121-2

[4] A. Behrami, Antibacterial activity of coumarine derivatives synthesized from 4-Chloro-chromen-2-one. The comparison with standard drug, *Oriental Journal of Chemistry*, **30** (2014), 1747-1752. http://dx.doi.org/10.13005/ojc/300433

[5] L. Bonsignore, G. Loy, D. Secci, A. Calignano, Synthesis and pharmacological activity of 2-oxo-(2*H*) 1-benzopyran-3-carboxamide derivatives, *European Journal of Medicinal Chemistry*, **28** (1993), 517-520. http://dx.doi.org/10.1016/0223-5234(93)90020-F

[6] J. Cain, Mircœstrol: An œstrogen from the plant Pueraria Mirifica, *Nature (London),* **188** (1960), 774-777. http://dx.doi.org/10.1038/188774a0

[7] A. Davoodnia, M. Bakavoli, M. Bashash, M. Roshani, R. Zhiani, Synthesis of new 5-aryl pyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,3,4]tetrazolo[1,5-*c*]pyrimidine derivatives, *Turkish Journal of Chemistry*, **31** (2007), 599-603.

[8] A. Davoodnia, M. Bakavoli, R. Moloudi, M. Khashi, N. Tavakoli-Hoseini, 7-Deazapurines: Synthesis of new pyrrolo[2,3-d]pyrimidin-4-ones catalyzed by a Brønsted-acidic ionic liquid as a green and reusable catalyst, *Chinese Chemical Letters*, **21** (2010), 1-4. http://dx.doi.org/10.1016/j.cclet.2009.09.002

[9] A. Davoodnia, M. Bakavoli, N. Pooryaghoobi, M. Roshani, A convenient approach to the synthesis of new substituted isoxazolo[5,4-d] pyrimidin-4(5h)-ones, *Heterocyclic Communications*, **13** (2007), 323-325. http://dx.doi.org/10.1515/hc.2007.13.5.323

[10] A. Davoodnia, A. Zare-Bidaki, H. Behmadi, A rapid and green method for solvent-free synthesis of 1,8-dioxodecahydroacridines using tetrabutylammonium hexatungstate as a reusable heterogeneous catalyst, *Chinese Journal of Catalysis*, **33** (2012), 1797-1801. http://dx.doi.org/10.1016/S1872-2067(11)60449-X

[11] G.P. Ellis, In: A. Weissberger, E.C. Taylor (eds), *Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones*, chap. XI, Alkylchromones, Wiley, New York, 1977, 581-631. http://dx.doi.org/10.1002/9780470187012.ch11

[12] M. Farahi, B. Karami, S. Alipour, L. Taghavi Moghadam, Silica tungstic acid as an efficient and reusable catalyst for the one-pot synthesis of 2-amino-*4H*-chromene derivatives, *Acta Chimica Slovenica,* **61** (2014), 94-99.

[13] M. Gao, K.D. Miller, G.D. Hutchins, Q.H. Zheng, Synthesis of carbon-11-labeled 4-aryl-4H-chromens as new PET agents for imaging of apoptosis in cancer, *Applied Radiation and Isotopes*, **68** (2010), 110-116. http://dx.doi.org/10.1016/j.apradiso.2009.09.067

[14] K. Gong, H. L. Wang, D. Fang, Z. L. Liu, Basic ionic liquid as catalyst for the rapid and green synthesis of substituted 2-amino-2-chromenes in aqueous media, *Catalysis Communications*, **9** (2008), 650-653. http://dx.doi.org/10.1016/j.catcom.2007.07.010

[15] E.A.A. Hafez, M.H. Elnagdi, A.G.A. Elagemey, F.M.A.A. El-Taweel, Nitriles in heterocyclic synthesis: Novel synthesis of benzo[c]coumarin and of

benzo[c]pyrano[3,2-c]quinoline derivatives, *Heterocycles*, **26** (1987), 903-907. http://dx.doi.org/10.3987/r-1987-04-0903

[16] M.M. Heravi, K. Bakhtiari, V. Zadsirjan, F.F. Bamoharram, O.M. Heravi, Aqua mediated synthesis of substituted 2-amino-4H-chromenes catalyzed by green and reusable Preyssler heteropolyacid, *Bioorganic & Medicinal Chemistry Letters*, **17** (2007), 4262-4265. http://dx.doi.org/10.1016/j.bmcl.2007.05.023

[17] T.S. Jin, J.C. Xiao, S.J. Wang, T.S. Li, Ultrasound-assisted synthesis of 2-amino-2-chromenes with cetyltrimethylammonium bromide in aqueous media, *Ultrasonics Sonochemistry*, **11** (2004), 393-397. http://dx.doi.org/10.1016/j.ultsonch.2003.10.002

[18] T.S. Jin, J.C. Xiao, S.J. Wang, T.S. Li, X.R. Song, An efficient and convenient approach to the synthesis of benzopyrans by a three-component coupling of one-pot reaction, *Synlett*, **13** (2003), 2001-2004. http://dx.doi.org/10.1055/s-2003-42030

[19] T.S. Jin, J.S. Zhang, L.B. Liu, A.Q. Wang, T.S. Li, Clean, One-pot synthesis of naphthopyran derivatives in aqueous media, *Synthetic Communications*, **36** (2006), 2009-2015. http://dx.doi.org/10.1080/00397910600632096

[20] M. Khashi, A. Davoodnia J. Chamani, DMAP-catalyzed synthesis of novel pyrrolo[2,3-d]pyrimidine derivatives Bearing an aromatic sulfonamide moiety, *Phosphorus, Sulfur, and Silicon and the Related Elements*, **189** (2014), 839-848. http://dx.doi.org/10.1080/10426507.2013.858253

[21] M. Kidwai, S. Saxena, M.K. Rahman Khan, S.S. Thukral, Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents, *Bioorganic & Medicinal Chemistry Letters*, **15** (2005), 4295-4298. http://dx.doi.org/10.1016/j.bmcl.2005.06.041

[22] S. Limsuwan, E.N. Trip, T.R.M.H. Kouwen, S. Piersma, A. Hiranrat, W. Mahabusarakam, S.P. Voravuthikkunchai, J. Maarten von Dijl, O. Kayser, Rhodomyrtone: A new candidate as natural antibacterial drug from Rhodomyrtus tomentosa, *Phytomedicine*, **16** (2009), 645-651. http://dx.doi.org/10.1016/j.phymed.2009.01.010

[23] S.J. Mohr, M.A. Chirigos, F.S. Fuhrman, J.W. Pryor, Pyran copolymer as an effective adjuvant to chemotherapy against a murine leukemia and solid tumor, *Cancer Research*, **35** (1975), 3750-3754. PubMed ID: 1192431

[24] A. Nakhaei, A. Davoodnia, A. Morsali, Extraordinary catalytic activity of a Keplerate-type giant nanoporous isopolyoxomolybdate in the synthesis of 1,8-

dioxo-octahydroxanthenes and 1,8-dioxodecahydroacridines, *Research on Chemical Intermediates*, **41** (2015), 7815-7826. http://dx.doi.org/10.1007/s11164-014-1861-9

[25] P. O'Kennedy, R.D. Thornes, *In Coumarins: Biology, Applications and Mode of Action*, John Wiley and Sons, Chichester, 1997.

[26] J. Skommer, D. Wlodkowic, M. Mattö, M. Eray, J. Pelkonen, HA14-1, a small molecule Bcl-2 antagonist, induces apoptosis and modulates action of selected anticancer drugs in follicular lymphoma B cells, *Leukemia Research*, **30** (2006), 322-331. http://dx.doi.org/10.1016/j.leukres.2005.08.022

[27] S. Thareja, A. Verma, A. Kalra, S. Gosain, P.V. Rewatkar, G.R. Kokil, Novel chromeneimidazole derivatives as antifungal compounds: Synthesis and in vitro evaluation, *Acta Poloniae Pharmaceutica-Drug Research*, **67** (2010) 423-427. PubMed ID: 20635539

[28] S. Verma, S. L. Jain, Thiourea dioxide catalyzed multi-component coupling reaction for the one step synthesis of naphthopyran derivatives, *Tetrahedron Letters*, **53** (2012), 6055-6058. http://dx.doi.org/10.1016/j.tetlet.2012.08.118

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