Tetrahedron Letters 52 (2011) 5327–5332

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst

Abu T. Khan *, Mohan Lal, Shahzad Ali, Md. Musawwer Khan

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India

ARTICLE INFO

Article history:
Received 20 June 2011
Revised 31 July 2011
Accepted 2 August 2011
Available online 11 August 2011

Keywords:
Multicomponent reactions
Pyran annulated heterocyclic derivatives
4-Hydroxy-coumarin
4-(Dimethylamino)pyridine (DMAP)

ABSTRACT

The one-pot three-component reaction for the synthesis of pyran annulated heterocycles is reported by condensing aromatic aldehydes, ethyl cyanoacetate, or malononitrile and C–H activated acidic compounds in the presence of catalytic amount of 4-(dimethylamino)pyridine (DMAP) in ethanol under reflux conditions. The significant features of the present protocol are simple, environmentally benign, high yields, non-aqueous work-up procedure, no chromatographic separation and recyclability of the catalyst.

Multicomponent reactions (MCRs) have gained considerable attention due to powerful bond forming efficiency in combinatorial and medicinal chemistry.[1] The nature of the catalyst and solvent[2,3a] also play a crucial role in the determination of the product and selectivity. Therefore, development of an inexpensive, mild, and reusable catalyst for MCRs remains of interest to the synthetic organic chemist. We have demonstrated effectiveness of various catalysts in organic synthesis using MCRs strategy.[3] We conceived that DMAP might be a better catalyst which can be explored further for multicomponent reactions for the synthesis of pyran annulated heterocycles. A few years ago, the importance and usefulness of 4-(dimethylamino)pyridine (DMAP) in organic synthesis has been reviewed as an efficient catalyst.[4]

Pyran annulated coumarins are widely distributed in nature[5a] and exhibit diverse physiological activities.[5b] Compounds having dihydropyran structural motif exhibit a wide range of biological activities, such as diuretic, analgesic, myorelaxant activity,[6] anticoagulant,[7] anticancer,[8] anti-tumoral,[9] and anti-HIV.[10] In addition, they are also useful for the treatment of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[11] Moreover, they are also used as cosmetics, pigments,[12] and useful as photoactive materials.[13] A considerable effort has been made for the synthesis of pyran annulated heterocyclic derivatives due to their wide applications. Recently, a few methods have been reported by employing three-component reaction using DBU,[14a] TBAB,[14b] diammonium hydrogen phosphate,[14c] heteropoly acids.[14d] Nevertheless, these protocols reported by others are quite useful, still there is further scope to develop a new methodology using a less expensive catalyst under mild reaction conditions and applicable to a wide range of substrates in great demand.

In this Letter, we report 4-(dimethylamino)pyridine (DMAP) catalyzed synthesis of pyran annulated heterocyles, which are obtained through one-pot three-component condensation reaction of aldehydes, ethyl cyanoacetate or malononitrile, and 4-hydroxycoumarin as well as condensation of aldehydes, malononitrile, and cyclic 1,3-diketones (Scheme 1).

For this study, a mixture of 4-chlorobenzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) in ethanol was treated with DMAP (0.1 mmol) at room temperature. After consumption of starting aldehyde as checked by TLC, 4-hydroxycoumarin was added to the reaction mixture and kept for stirring under reflux conditions. After the completion of the reaction monitored by TLC, the reaction mixture was brought to room temperature and the solid precipitate was filtered off. The desired product **4a** was obtained in 61% yield, which was characterized by ^{1}H NMR, ^{13}C NMR, and by elemental analysis.

The reaction was optimized using different catalysts for obtaining the best yield of **4a** are summarized in Table 1. It was noted that 20 mol % of the DMAP in ethanol provides the best result in terms of yield and time. Under solvent-free conditions, the product was obtained in a moderate yield (56%).

After the optimization of the reaction conditions, the reaction of benzaldehyde with ethyl cyanoacetate and 4-hydroxycoumarin was carried out under the same reaction conditions and it afforded the product **4b** in 76% yield. The reaction of various other aromatic aldehydes having substituents such as Me, NO_2, OH,

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2582349.
E-mail address: atk@iitg.ernet.in (A.T. Khan).

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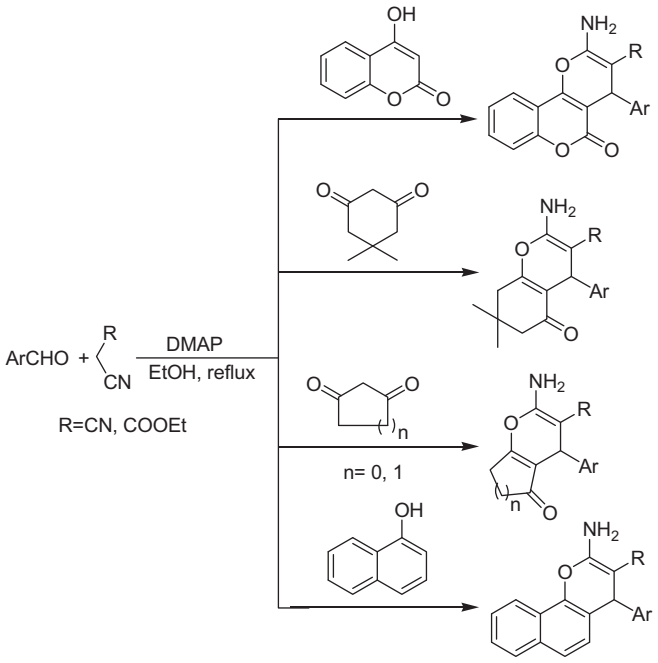
doi:10.1016/j.tetlet.2011.08.019



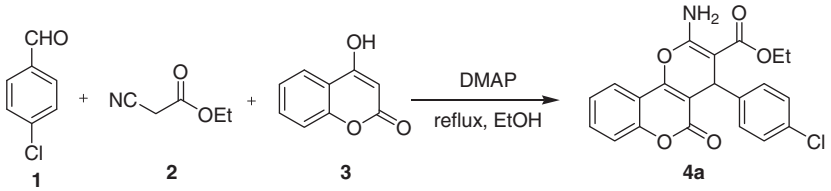
Scheme 1. Synthesis of pyran annulated heterocycles.

Cl, and Br were examined with ethyl cyanoacetate and 4-hydroxycoumarin using identical reaction conditions and resulted in products **4c–i** (Table 2, entries 3–9) in good yields. Similarly, the reaction of aromatic aldehydes with malononitrile and 4-hydroxycoumarin was also carried out using same mol % of DMAP under identical reaction conditions and the products **4j–k** were obtained in excellent yields.

The present protocol was extended using dimedone and the reaction of benzaldehyde, ethyl cyanoacetate, and dimedone was carried out under similar reaction conditions. The desired product **4l** was obtained in 94% yield. The reaction of other aromatic aldehydes substituted with Cl, Me, NO_2, and MeO was also performed with dimedone and ethyl cyanoacetate, the desired products **4m–p** were isolated in good yields (Table 3, entries 2–5). The reaction of 4-chloroaldehyde with malononitrile and dimedone was performed and the product **4q** was obtained in good yield.

The scope of presented protocol further investigated with other C–H activated acidic compounds such as 1,3-cyclopentadione and 1,3-cyclohexadione using 4-chlorobenzaldehyde and malononitrile under similar reaction condition and the results were summarized in Table 3 (entries 7–9). The reaction of 4-chloroaldehyde with malononitrile and α-naphthol was performed and the product **4u** was obtained in good yield. From the above observation, it is important to mention that the reaction was fast and also provided better yields using either aldehyde having electron withdrawing group viz. NO_2 or with malononitrile. All the products were charac-

Table 1
Optimization of reaction conditions



Entry	Catalyst	Solvent	Catalytic amount (mol %)	Time (h)	Yield[a] (%)
1	DMAP	Neat	20	3	56
2	Piperidine	EtOH	20	4	40
3	DMAP	EtOH	10	5	61
4	DMAP	EtOH	20	3	78
5	DMAP	EtOH	30	3	76
6	DMAP	MeOH	20	3	69
7	DMAP	Water	20	4	62

[a] Isolated yield.

Table 2
Synthesis of dihydropyrano[3,2-*c*]chromene derivatives using aromatic aldehydes, ethyl cyanoacetate or malononitrile, and 4-hydroxycoumarin catalyzed by DMAP[15]

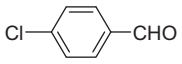
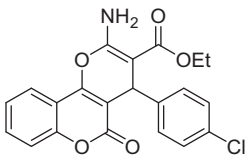
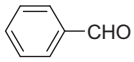
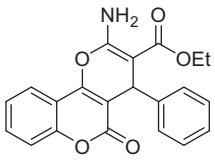
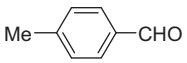
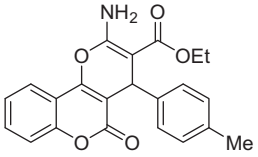
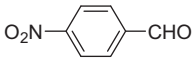
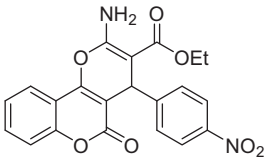
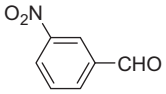
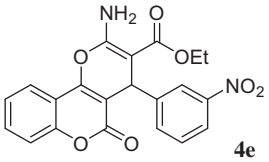
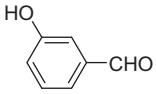
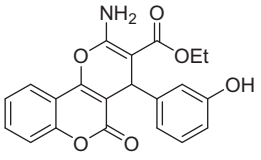
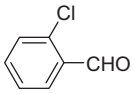
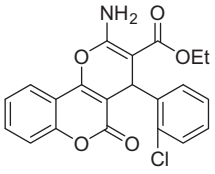
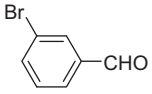
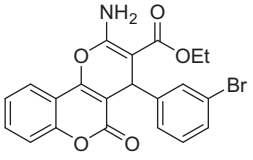
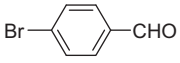
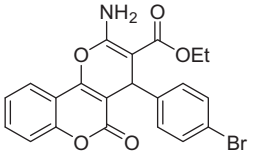
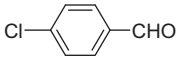
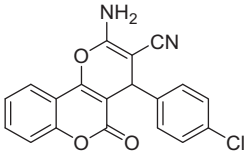
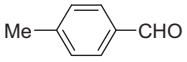
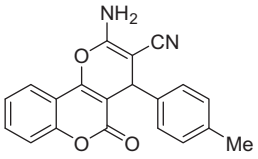
Entry	Aromatic aldehydes	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
					194–195 [192–194][14a]
1		**4a**	2.5	78	
					
2		**4b**	3.5	76	187–189

Table 2 (*continued*)

Entry	Aromatic aldehydes	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
3		 **4c**	4.0	76	114–117
4		 **4d**	1.5	82	241–244 [241–243][14a]
5		 **4e**	3.5	80	242–245 [247–250][14c]
6		 **4f**	3.0	67	208–210
7		 **4g**	5.0	64	209–212
8		 **4h**	4.5	81	196–198
9		 **4i**	4.0	80	142–144
10		 **4j**	[5]	94	264–266 [263–265][14d]
11		 **4k**	[10]	92	258–260 [253–255][14a]

[a] Isolated yield.

Table 3
Synthesis of chromene derivatives using diketones, ethyl cyanoacetate or malononitrile, and aromatic aldehydes catalyzed by DMAP[15]

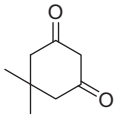
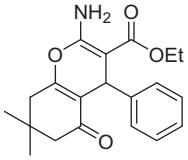
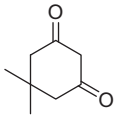
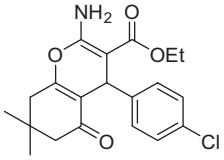
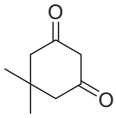
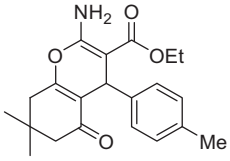
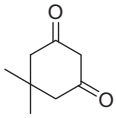
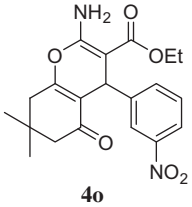
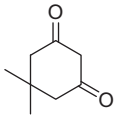
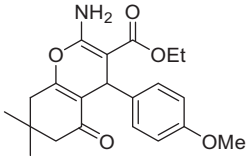
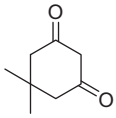
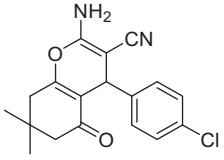
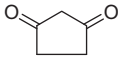
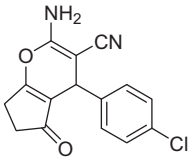
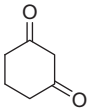
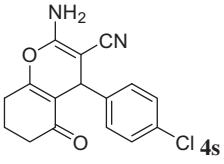
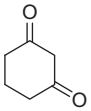
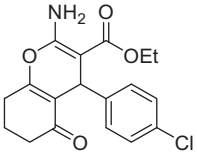
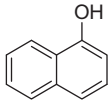
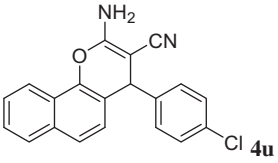
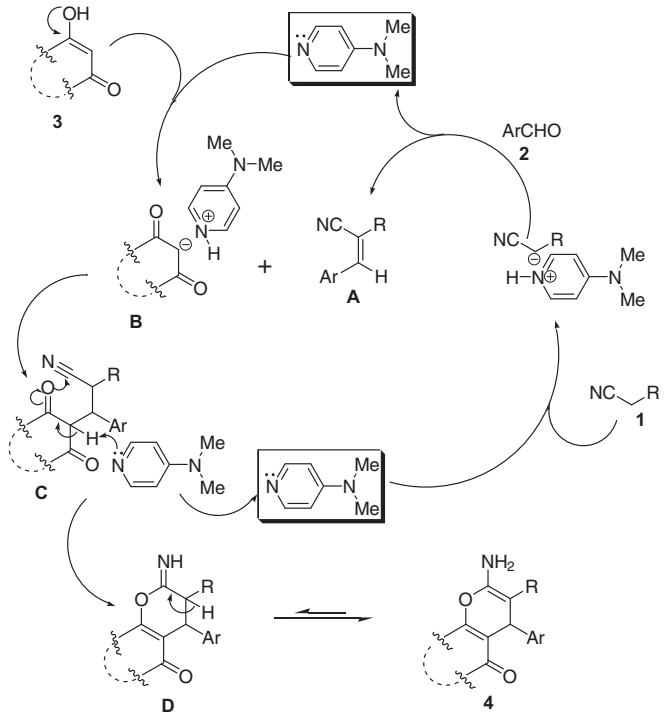
Entry	1,3-Diketones	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
1		 **4l**	3.5	94	144–146
2		 **4m**	5.0	92	139–142
3		 **4n**	4.5	91	151–152
4		 **4o**	1.5	91	154–156
5		 **4p**	3.5	91	131–134
6		 **4q**	[15]	94	213–215 [212–214][14e]
7		 **4r**	[10]	98	216–218
8		 **4s**	[10]	95	241–243
9		 **4t**	2.5	95	163–165

Table 3 (*continued*)

Entry	1,3-Diketones	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
10		 **4u**	[20]	92	244–243

[a] Isolated yields.



Scheme 2. Plausible mechanism for the formation of pyran annulated heterocyclic compounds.

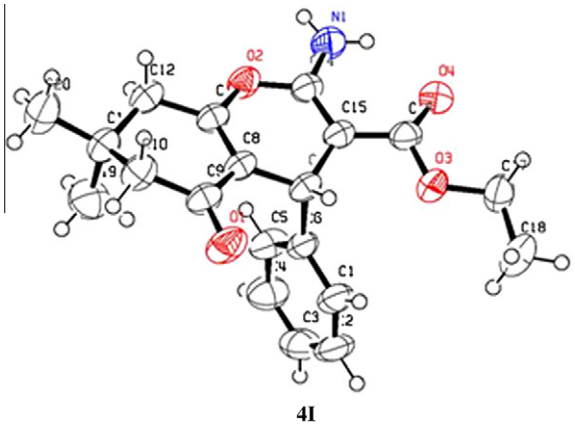


Figure 1. ORTEP diagram of **4l** (CCDC 828132).

terized by IR, ^{1}H NMR, and ^{13}C NMR spectra and by elemental analysis.

The formation of various pyran annulated heterocyclic compounds can be rationalized as follows. Initially, the Knovengel

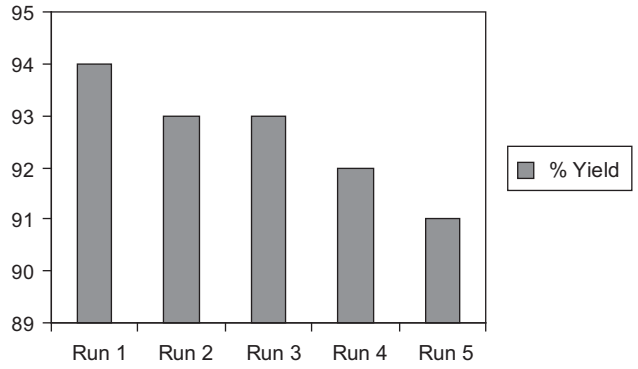


Figure 2. Reusability of the catalyst.

product **A** was formed by the reaction of aldehyde and alkyl nitrile in the presence of DMAP, which reacts with in situ generated carbanion from activated C–H acidic compounds to give intermediate **C**. The intermediate **C** was cyclized to **D** in the presence of DMAP. Finally, **D** tautomerized to give the desired product **4** as shown in Scheme 2.

Moreover, the structure of compound **4l** was further confirmed by X-ray crystallographic analysis (Fig. 1).[16]

Further the role of catalyst was ascertained by the reaction of **A**, which is obtained from the reaction of 4-chlorobenzaldehyde and malononitrile in the presence of DMAP, with 4-hydroxycoumarin in the presence of DMAP and without DMAP. The product **4j** was obtained with DMAP within 5 min in 94% yield, whereas the same reaction without catalyst gave only 63% yield after 1 h of stirring under reflux conditions.

The reusability test was performed as follows: A mixture of 4-chlorobenzaldehyde (2 mmol), malononitrile (2 mmol), 4-hydroxycoumarin, and DMAP (0.4 mmol) was stirred in ethanol (8 mL) under reflux condition. After completion of the reaction, the solid precipitate was filtered using a Buchner funnel. The precipitate was washed with ethanol (0.5 mL). The filtrate containing catalyst was reused for similar scale of reaction for the same substrates. The procedure was repeated five times which is depicted in Figure 2.

In summary, we have devised a simple and efficient protocol for the synthesis of pyran annulated heterocycles using DMAP as catalyst via one-pot three-component condensation reaction of an aldehyde, ethyl cyanoacetate or malononitrile, and either 4-hydroxycoumarin or 1,3-cyclic ketones or 2-naphthol in excellent yields. The advantages offered by this DMAP versus known catalysts are (i) inexpensive, (ii) reusable, and (iii) no need chromatographic separation. The significant features of this protocol are good yields and applicable to the broad range of substrates especially the less reactive alkyl nitrile such as ethyl cyanoacetate also provides the desired pyran annulated heterocycles, which are not much studied earlier.

Acknowledgments

M.L. is thankful to CSIR, New Delhi for his research fellowship. S.A. and M.M.K acknowledge UGC, New Delhi for their research fellowships. The authors are grateful to the Department of Science and Technology for providing single XRD facility under FIST program as well as to the Director, IIT Guwahati for providing general facility. We are also grateful to the referees for their valuable comments and constructive suggestions.

Supplementary data

Supplementary data (X-ray crystallographic data (CIF files) of **4a** and **4l** and spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.019.

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15. *General procedure for the synthesis of pyran annulated heterocyclic compounds*: Into a mixture of an aromatic aldehyde (1 mmol) and ethyl cyanoacetate or malononitrile (1 mmol) in 4 mL of ethanol was added the catalyst DMAP (0.025 g, 0.2 mmol) and kept for stirring at room temperature. The solid precipitate was formed immediately in case of malononitrile or it took 20–30 min. for ethyl cyanoacetate. Then C–H activated acidic compound (1 mmol) was added into the reaction mixture and it was kept for stirring under reflux conditions. After sometime, the reaction mixture was converted into clear solution. After the completion of the reaction, the solid precipitate came out under hot conditions at the stipulated time mentioned in the Table 2 and Table 3. The reaction mixture was brought to room temperature and the solid precipitate was filtered off to obtain the desired product. *Ethyl 2-amino-4-(3-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate* (***4l***): Yield 0.320 g, 94%. Solid, mp 144–146 °C. IR ν_{max} (KBr): 3403, 3290, 2956, 1667, 1614, 1524, 1371 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.10 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.19 (q, J = 16.4 Hz, 2H), 2.42 (s, 2H), 3.98-4.07 (m, 2H), 4.70 (s, 1H), 6.17 (brs, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 27.5, 29.2, 32.4, 33.9, 40.8, 50.9, 59.8, 80.9, 116.9, 126.2, 127.9, 128.4, 145.9, 158.5, 161.5, 169.3, 196.5 ; Anal. Calcd for $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10. Found C, 70.29; H, 6.71; N, 4.01.
16. Complete crystallographic data of **4l** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 828132, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).