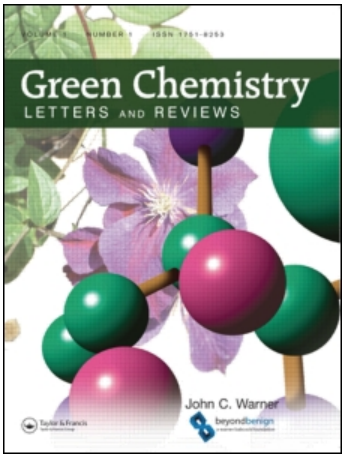

Green Chemistry Letters and Reviews

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

PEG-400 remarkably efficient and recyclable media for one-pot synthesis of various 2-amino-4*H*-chromenes

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Online publication date: 30 July 2010

To cite this Article Shitole, Nana V. , Shelke, Kiran F. , Sadaphal, Sandip A. , Shingate, Bapurao B. and Shingare, Murlidhar S.(2010) 'PEG-400 remarkably efficient and recyclable media for one-pot synthesis of various 2-amino-4*H*-chromenes', Green Chemistry Letters and Reviews, 3: 2, 83 — 87
To link to this Article: DOI: 10.1080/17518250903567246
URL: http://dx.doi.org/10.1080/17518250903567246

Green Chemistry Letters and Reviews
Vol. 3, No. 2, June 2010, 83–87

Taylor & Francis
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RESEARCH LETTER

PEG-400 remarkably efficient and recyclable media for one-pot synthesis of various 2-amino-4*H*-chromenes

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(Received 6 June 2009; final version received 11 December 2009)

Polyethylene glycol-400 has been found to be a recyclable and rapid reaction medium for the synthesis of 2-amino-4*H*-chromenes by the condensation of aromatic aldehyde, malononitrile, and α-naphthol. This method gives remarkable advantages such as simple work up, high yields, and a greener method by avoiding toxic catalyst and hazardous solvents.

Keywords: polyethylene glycol; 2-amino-4*H*-chromenes; α-naphthol; one-pot synthesis; aldehyde

Introduction

In recent years, research has been moving toward the development of environmentally benign reactions. One of the tools used to combine economic aspects of new reactions with environmental aspects is the multicomponent reaction strategy. This process consists of two or more synthetic steps, which is carried out without isolation of any intermediate, thus reducing reaction time, energy, and raw material use (*1*).

2-Amino-4*H*-chromenes represent an important class of compounds being the chain components of many naturally occurring products, and have been of interest in recent years due to their useful biological properties (*2*) such as anticoagulant, anticancer, spasmolytic, and antianaphylaction activity (*3*).

2-Amino-4*H*-chromenes are generally prepared by refluxing malononitrile, aldehyde, and activated phenol in the presence of hazardous organic bases such as piperidine in organic solutions, such as ethanol and acetonitrile for several hours (*4*). A literature survey reveals that several methods were reported for the synthesis of 2-amino-4*H*-chromenes such as using cetyltrimethyl ammonium chloride (*5*), tetrabutylammonium bromide (*6*), cetyltrimethyl ammonium bromide under ultrasound (*7*), K_2CO_3 (*8*), nanosize MgO (*9*), γ-alumina (*10*), heteropolyacid (*11*), hexadecyltrimethylammonium bromide (*12*), triethylbenzylammonium chloride (*13*), $TiCl_4$ (*14*), methanesulfonic acid (*15*), *N,N*-dimethylaminoethyl-benzyldimethyl-ammonium chloride (*16*), Mg/Al hydrotalcite (*17*), and piperidine under microwave (*18*).

In recent years, many organic researchers have been focused on the development of green methods to synthesize various organic compounds through the use of alternative reaction media to replace volatile and often hazardous solvents commonly used in organic synthesis (i.e. toluene, methanol, *N,N*-dimethyl formamide, dimethyl sulphoxide, etc.). Liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, non-toxic, and protic solvents (*19*). This class of oligomers has been established as greener and cleaner host recyclable solvents (*20*) and also functions as safer phase transfer catalyst (*21,22*). Hence, many organic reactions have been carried out using polyethylene glycol (PEG) as the solvent or co-solvent, such as in the synthesis of 2,4,5-triaryl-1*H*-imidazoles and 1,2,4,5-tetraaryl-1*H*-imidazoles (*23*), Suzuki-Miyaura cross-coupling reaction (*24*), cycloaddition reactions with isoeugenol, and anethole (*25*) synthesis of β-Enamino ketones (*26*). The use of PEG as a recyclable solvent system for the metal mediated radical polymerization of methyl methacrylate and styrene has also been reported (*27*). In view of the emerging importance of PEG as a novel reaction media, we wish to report a mild and highly efficient method for the synthesis of 2-amino-4*H*-chromenes in polyethylene glycol-400 (PEG-400) without any catalyst.

Results and discussion

In concern with the use of green solvents in organic synthesis, we report herein the use of PEG-400 as a

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ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518250903567246
http://www.informaworld.com

greener solvent for the synthesis of 2-amino-4*H*-chromenes (Scheme 1). Initially, we studied the reaction of 2-amino-4*H*-chromenes using benzaldehyde (**1a**), malononitrile (**2**), and α-naphthol (**3**) at room temperature using PEG-400 as a solvent. We found that the reaction required more time (6 h) with minimum yield of product (40%). We then varied the reaction temperature from 40 to 120°C and found that at 100°C the reaction gives better results, requiring only 2 h and giving an excellent yield of 90%. The reaction conditions and the obtained results are summarized in Table 1.

At the optimized reaction conditions, 2-amino-4*H*-chromenes were created using various derivatives of the aryl aldehyde. The results were summarized in Table 2.

Obtained results show that various substituents gave good results. Both electron donating as well as electron withdrawing groups work cleanly and fastly. The actual role of PEG-400 in the synthesis is represented in Scheme 2. The following mechanism suggests that PEG-400 might be displaying catalytic behavior as a general base and may facilitate formation of 2-amino-4*H*-chromenes.

To check the reusability of the medium PEG-400, we performed the experiment using the same reactants, benzaldehyde, malononitrile, and α-naphthol and we found surprising results with this medium. After three successive runs, we found that there was significant decrease in the yield of products. The results of recyclability were summarized in Table 3.

All observed results show that PEG-400 as an excellent medium over traditionally reported solvents. Hence, PEG-400 is an efficient medium for the synthesis of 2-amino-4*H*-chromenes.

Experimental

All the melting points were recorded in open capillary tubes and are uncorrected. IR spectra were recorded on FT/IR 410 type (A) spectrophotometer in KBr.^{1}H-NMR spectra were recorded on a 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units Δ (ppm) relative to tetramethylsilane as an internal standard

Table 1. Optimization of benzaldehyde derivatives with various temperatures (**1a**).

Sr. no.	Temperature (°C)	Time (h)	Yield (%)
1	RT	6	45
2	40	5	50
3	60	5	55
4	80	4	65
5	100	2	90
6	120	2	88

General procedure for the synthesis of 2-amino-4H-chromenes 4(a–j)

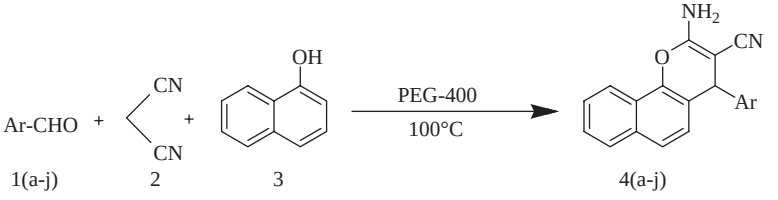
A mixture of α-naphthol (0.002 mol), malononitrile (0.002 mol), and aromatic aldehyde (0.002 mol) in PEG-400 (1 ml) was heated in an oil bath at 100°C for 2–3 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mass was cooled at room temperature and then poured over cold water. The obtained solid was filtered, washed with water, and crude solid was crystallized from ethanol. The purity of the product was checked by TLC. The aqueous filtrate was distilled at 100°C to remove water and thus the separated PEG-400 was reused. The PEG-400 was recovered and reused without loss of activity. Spectral data for selective compounds are listed.

2-Amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile (4a)

IR (KBr) (V_{max}, cm^{-1}): 3465, 3318, 3010, 2915, 2200, 1660, 1550, 1370, 1267, 1100, 1022, 811, 744; ^{1}H NMR Δ (ppm): 4.8 (s, 1H, CH), 7.0 (s, 2H, NH_2), 7.1–7.2 (m, 6H), 7.5–8.2 (m, 5H). GC/MS: 298 (M^+).

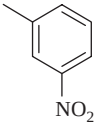
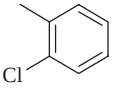
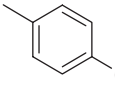
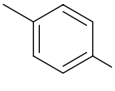
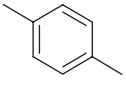
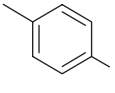
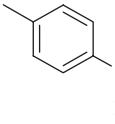
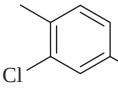
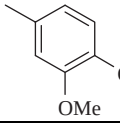
2-Amino-4-(4-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (4c)

IR (KBr) (V_{max}, cm^{-1}): 3476, 3320, 2200, 1664, 1550, 1360, 1275, 1040, 805, 750; ^{1}H NMR Δ (ppm): 5.1 (s,



Scheme 1. Three component synthesis of 2-amino-4*H*-chromenes using PEG-400.

Table 2. Synthesis of 2-amino-4*H*-chromenes using PEG-400.

Sr. no.	Ar-CHO	Product	Time (min)	Yield[a] (%)	Melting point (°C)	
					Found	Reported
1		**4a**	125	90	204–206	206–207 (*6*)
2		**4b**	150	85	211–213	214–216 (*6*)
3		**4c**	140	87	237–238	236–237 (*6*)
4		**4f**	150	93	231–232	231–232 (*16*)
5		**4e**	135	89	246–247	245 (*16*)
6		**4f**	155	87	204–205	205–206 (*16*)
7		**4g**	130	91	232–233	231–234 (*16*)
8		**4h**	135	86	200–201	203–205 (*16*)
9		**4i**	150	84	220–221	222–224 (*16*)
10		**4j**	170	81	136–137	137–139 (*16*)

[a]Yields were isolated.

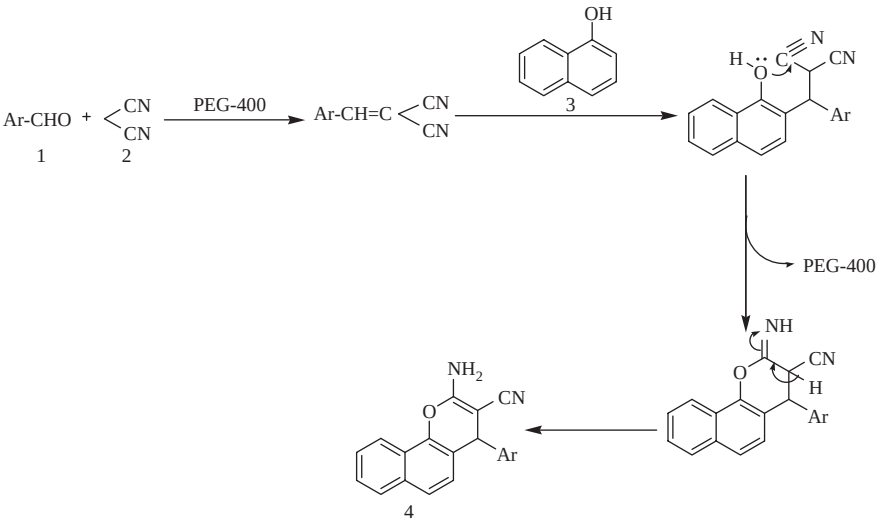
1H, CH), 7.0 (s, 2H, NH_2), 7.2–7.3 (m, 6H), 7.6–8.4 (m, 5H). GC/MS: 332.07 (M^+).

2-Amino-4-(4-nitrophenyl)-4H-benzo[h]chromene-3-carbonitrile (4g)

IR (KBr) (V_{max}, cm^{-1}): 3450, 3325, 2190, 1660, 1600, 1575, 1530, 1352, 1270, 1190, 1100, 800, 770; ^1H NMR Δ (ppm): 5.1 (s, 1H, CH), 7.1 (s, 2H, NH_2), 7.5–7.7 (m, 6H), 7.7–8.2 (d, 4H). GC/MS: 343 (M^+).

2-Amino-4-(4-(dimethylamino)phenyl)-4H-benzo[h]chromenecarbonitrile (4h)

IR (KBr) (V_{max}, cm^{-1}): 3465, 3340, 3090, 2955, 2863, 2806, 2195, 1662, 1570, 1400, 1380, 1262, 1190, 1100,



Scheme 2. Proposed mechanism for synthesis of 2-amino-4*H*-chromenes.

800, 750; ^{1}H NMR Δ (ppm): 2 (s, 6H·N$(CH_3)_2$), 4.(s,1H, CH), 7.03–7.1 (s, 2H, NH), 7.2–7.6 (m, 6H), 7.9–8.2 (d, 4H). GC/MS: 341 (M^+).

Conclusion

The use of PEG as a reaction medium offers a convenient, non-toxic, thermally stable, inexpensive, and recyclable reaction medium for synthesis of 2-amino-4*H*-chromenes. This procedure offers several advantageous including cleaner reactions, high yields of products as well as a simple experimental and work up procedure, which makes it a useful and attractive process for the synthesis of these compounds. The recyclability of the solvent makes for the development of a greener strategy and the reaction economically and potentially viable for commercial application.

Acknowledgements

We are grateful to the Head of the Department of Chemistry, Dr Babasaheb Ambedkar Marathwada University for providing the laboratory facility.

Table 3. The recycling of polyethylene glycol for benzaldehyde derivative.

Entry	Time (min)	Yield[a] (%)
0	125	90
1	130	90
2	130	87
3	130	89

[a]Yields were isolated.

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