Indian Journal of Advances in Chemical Science

Article

Synthesis of Benzopyrans using Catalyst PEG-400 as an Efficient and Recyclable Reaction Media

Prashant G. Kumdale[1], Nana V. Shitole[2]*

[1]Department of Chemistry, Shivneri College, Latur, Maharashtra, India, [2]Department of Chemistry, Shri Shivaji College, Parbhani, Maharashtra, India

ABSTRACT

A mild and efficient method was developed for the synthesis of benzopyrans through the one-pot three-component condensation of aldehyde, malononitriles, and dimedone in the presence of polyethylene glycol-400 as an efficient and recyclable reaction medium. This process is characterized by mild reaction condition, easy workup, and environmental friendliness.

Key words: Aldehyde, Malononitrile, Dimedone, Polyethylene glycol-400, Benzopyran.

1. INTRODUCTION

Multicomponent reaction (MCR) is a highly efficient approach to access complex structures in simple synthetic manipulations from three or more reactants. High atom economies, excellent efficiencies, and process usability in the construction of heterocycles are advantages of MCR [1-3]. Tetrahydrobenzo [b] pyrans are an important class of heterocyclic compounds that form important core structures for new drugs with diverse biological activities [4,5]. In addition, substituted 4H-pyrans can be used as pigments, pesticides, and photoactive materials [6,7]. These compounds include tetramethylammonium hydroxide [8], RE (PFO) 3 [9], iodine [10], NaBr [11], Na2SeO4 [12], solid acids [13,14], ion-exchange resins [15], magnetic nano catalysts [16,17], 1,4-diazabicyclo [2.2.2] octane-based ionic liquids (ILs) [18], and metal complexes [19]. Many of the reported methods involve extended reaction times [10,12], use of volatile organic solvents [9,10,14,15], and use of microwave or ultrasonic irradiation [11,16]. It suffers from limitations such as poor recyclability [8,10-12]. Moreover, most of them are practical only with aromatic aldehydes [13,15-19], as reactions with aliphatic aldehydes give poor yields [9]. ILs as environmentally friendly reaction media or catalysts are gaining increasing attention due to their low vapor pressure, high thermal stability, high solubility, and easy recovery and reuse [20,21]. The concept of assisted ionic liquid catalysis (SILC) has been proposed, which combines the advantages of ILs and heterogeneous catalysis, offering high designability of catalytic sites, high "solubility," and easy handling, separation, and recycling [22]. Developing new synthetic methods to facilitate the production of desired molecules are an area of intense research. With this regard, efforts have been made constantly to introduce new methodologies which are efficient and more compatible with the environment. One of the most desirable approaches to address this challenge constitutes a search of surrogates for traditionally employed organic solvents which suffer from various health and environmental concerns [23,24]. From the view point of green chemistry, polyethylene glycol (PEG)-400 is found to be an interesting solvent system.

2. GENERAL EXPERIMENTAL PROCEDURE FOR SYNTHESIS OF BENZOPYRANS (4A-J)

A mixture of benzaldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) in PEG-400 (1 mL) was heated in an oil bath at 110°C for 6–8 h. The progress of the reaction was monitored by thin-layer chromatography. After the reaction was completed, the reaction mass was cooled to room temperature and then poured into cold water. The solid obtained was filtered, washed with water, and the crude solid was crystallized from ethanol to give the pure product without the need for further purification. The aqueous filtrate was distilled at 100°C to remove water, and the PEG-400 thus separated was reused. PEG-400 was recovered and reused without loss of activity.

3. RESULTS AND DISCUSSION

We would like to report a highly efficient method for the synthesis of benzopyrans using PEG-400 as a greener solvent. This protocol is a one-pot three-component coupling of benzaldehyde, malononitrile, and dimedone (Scheme 1).

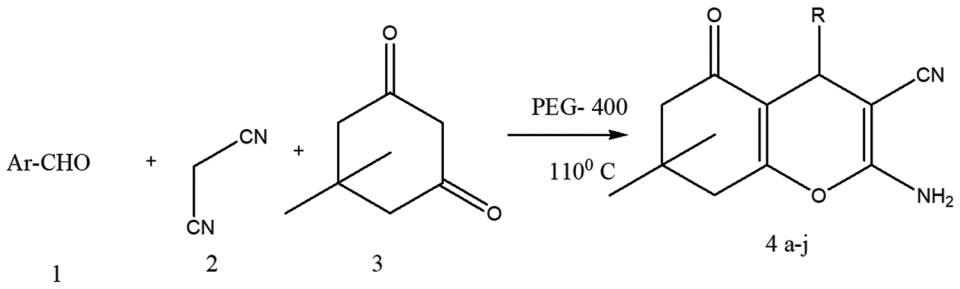
To evaluate the effect of temperature, the reaction of 4-hydroxybenzaldehyde, malononitrile, and dimedone in PEG-400 was considered as a standard model reaction to optimize the reaction conditions. During this investigation, efforts were mainly focused on different temperatures. The effect of temperature was also studied by performing a model reaction in PEG-400 at different temperature. As shown in Table 1 (entries 1-2), the reaction did proceed, but the yield obtained remained low even after a longer reaction time (26 h) when the reaction temperature was 60°C–70°C. However, at elevated temperature (60–140°C), the use of PEG-400 gave better results in terms of yield and reaction time.

Thus, the conditions of item 6, shown in Table 1, were the optimized reaction conditions. The results obtained show that with different

***Corresponding author:**
Nana V. Shitole
E-mail: pkpk7389@gmail.com

ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2023.1101010

Received: 04th December 2022;
Revised: 18th December 2022;
Accepted: 25th December 2022



Scheme 1: Reaction of Benzaldehyde(Substituted benzaldehyde) With Malononitrile & Dimedone

Spectral data of synthesized benzopyran	
Product	**Spectral data**
4a	2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4a) Yield 90% of white solid; mp 228–229°C.
4b	2-Amino-7,7-dimethyl-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4b) Yield 92% of white solid; mp 205–206°C, 1H NMR: δ 9.26 (s, 1H), 6.92–6.94 (m, 4H), 6.67 (d, *J =8* Hz, 2H), 4.08 (s, 1H), 2.48 (s, 2H), 2.25 (d, *J =16* Hz, 1 H), 2.08 (d, J =16Hz, 1H), 1.05 (s 3H), 0.93 (s 3 H).
4c	2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c) Yield 87% of white solid; mp 215–217°C.
4d	2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4d) Yield 89% of pale yellow solid; mp 213–214°C, 1H NMR: δ 8.07 (d, *J =8* Hz, 1H), 7.99 (s, 1H), 7.61–7.68 (m, 2H), 7.19 (s, 2H), 4.43 (s, 1H), 2.55 (s, 2H), 2.26 (d, *J =16* Hz, 1H), 2.14 (d, *J =16* Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H).
4e	2-Amino-4-(Thiophen-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e) Yield 86% of gray white solid; mp 190–192°C,1H NMR: δ 7.48–7.44 (m, 1H), 7.03 (s, 2H), 6.30 (m, 1H), 6.05 (d, *J =4* Hz, 1H), 4.34 (s, 1H), 2.44 (s, 2H), 2.33 (d, *J =16* Hz, 1H), 2.16 (d, *J =16* Hz, 1H), 1.06 (s, 3H), 0.97 (s, 3H)
4f	2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4f) Yield 90% of white solid; mp 194–195°C.
4g	2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g) Yield 78% of gray white solid; mp 219–220°C,1H NMR: δ 7.48–7.46 (m, 1H), 7.03 (s, 2H), 6.33 (m, 1H), 6.05 (d, *J =4* Hz, 1H), 4.34 (s, 1H), 2.46 (s, 2H), 2.33 (d, *J =16* Hz, 1H), 2.14 (d, *J =16* Hz, 1H), 1.06 (s, 3H), 0.97 (s, 3H)
4h	2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4h) Yield 88% of white solid; mp 231–232°C.
4i	2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4i) Yield 86% of pale-yellow solid; mp 180–182°C.
4j	2-Amino-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4j) Yield 84% of white solid; mp 219–220°C,1H NMR: δ 7.08 (d, *J =8* Hz, 2H),7.04 (d, J =8 Hz, 2H), 6.96 (s, 2 H), 4.14 (s, 1H), 2.53 (s, 2H), 2.25–2.26 (m, 4H), 2.07 (d, *J =8* Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H).

Table 1: Optimization of 4-hydroxy benzaldehyde derivatives with different temperatures.

Entry	Temperature	Reaction time (h)	Yield (%)
1	60	26	28
2	70	24	40
3	80	20	54
4	90	10	70
5	100	8	76
6	110	6	92
7	140	6	92

Reaction conditions: 1 (1 mmol), 2d (1 mmol), 3 (1 mmol), in PEG-400 at 110°C, Isolated yields

substituents, the reactions give better results, electron donating agents such as methyl, hydroxyl, methoxy, as well as electron withdrawing agents such as nitro and chloro groups, work cleanly and faster. Under the optimized reaction conditions, we performed all the derivatization of benzopyrans and the results are summarized in Table 2. In this procedure, PEG-400 not only acts as a phase transfer catalyst but also as a pure solvent by significantly enhancing the intramolecular cyclization.

Table 2: Synthesis of benzopyrans using PEG-400.

Entry	Reactant	Product	Time	Yield	MP (°C)
1	C_6H_5-CHO	4a	7.5	90	228–229
2	4-OH-C_6H_5-CHO	4b	6	92	205–206
3	4-Cl-C_6H_5-CHO	4c	7	87	215–217
4	3-NO_2-C_6H_5-CHO	4d	6.5	89	213–214
5	Thiophene-2-CHO	4e	7	86	190–192
6	4-OMe-C_6H_5-CHO	4f	7.5	90	194–195
7	Furfural	4g	8	78	219–220
8	3-Cl-C_6H_5-CHO	4h	6.5	88	231–232
9	4- NO_2-C_6H_5-CHO	4i	6	86	180–182
10	4-Me-C_6H_5-CHO	4j	7.5	84	219–220

To check the reusability of the medium (PEG-400), we performed an experiment using the same reactants, 4-hydroxybenzaldehyde, malononitrile, and dimedone in PEG-400 and found surprising results with this medium. After three consecutive runs, we found that there was no longer a significant decrease in product yield, and the recyclability results are summarized in Table 2, entry 1.

All observed results showed that PEG-400 is an excellent medium compared to all mentioned solvents. Therefore, PEG-400 is an effective medium for the synthesis of benzopyrans.

4. CONCLUSION

We have developed an alternative process using polyethylene glycol that provides a practical, non-toxic, thermostable, inexpensive, and recyclable reaction medium for the synthesis of benzopyrans. This method has several advantages, including cleaner reactions, higher product yields, and easier experimental and work-up procedures, making it a useful and attractive method for the synthesis of these compounds. The recyclability of solvents may make the development and reaction of environmentally friendly strategies economical and enable their commercial application.

5. REFERENCES

1. A. Dömling, W. Wang, K. Wang, (2012) Chemistry and biology of multi-component reaction, ***Chemical Reviews,*** **112:** 3083-3135.
2. R. C. Cioc, E. Ruijter, R. V. Orru, (2014) A Multicomponent reactions: Advanced tools for sustainable organic synthesis, ***Green Chemistry,*** **16:** 2958-2975.
3. L. Fan, C. C. Yao, M. Shu, (2016) Three-component synthesis of new *o*-hydroxyphenyl substituted pyrazolo [3,4-*b*] pyridines promoted by $FeCl_3$, ***Heterocyclic Communications,*** **22:** 63-67.
4. K. S. Pandit, P. V. Chavan, U. V. Desai, M. A. Kulkarni, P. P. Wadgaonkar, (2015) Tris-hydroxymethyl aminomethane (THAM): A novel organo catalyst for a environmentally benign synthesis of medicinally important tetrahydrobenzo [*b*] pyrans and pyran-annulated heterocycles, ***New Journal of Chemistry,*** **39:** 4452-4463.
5. G. Brahmachari, B. Banerjee, (2014) Facile and one-pot access to diverse and densely functionalized 2-amino-3-cyano-4H-pyrans and pyran-annulated heterocyclic scaffolds via an eco-friendly multi-component reaction at room temperature using urea as a novel organo-catalyst, ***ACS Sustainable Chemistry and Engineering,*** **2:** 411-422.
6. D. Armesto, W. M. Horspool, N. Martin, (1989) Synthesis of cyclotutenes by the novel photochemical ring contraction of 4-substituted 2-amino-3,5-dicyano-6-phenyl-4*H*-pyrans, ***The Journal of Organic Chemistry,*** **54:** 3069-3072.
7. H. R. Saadati-Moshtaghin, F. M. Zonoz, (2017) Preparation and characterization of magnetite-dihydrogen phosphate as a novel catalyst in the synthesis of tetrahydronbenzo [*b*] pyrans, ***Materials Chemistry and Physics,*** **199:** 159-165.
8. S. Balalaie, M. Sheikh-Ahmadi, M. Bararjanian, (2007)Tetra-methyl ammonium hydroxide: An efficient and versatile catalyst for the one-pot synthesis of tetrahydronbenzo [*b*] pyran derivatives in aqueous media, ***Catalysis Communications,*** **8:** 1724-1728.
9. L. M. Wang, J. H. Shao, H. Tian, Y. H. Wang, B. Liu, (2006) Rare earth perfluorooctanoate [$RE(PFO)_3$] catalyzed one-pot synthesis of benzopyrans derivatives, ***Journal of Fluorine Chemistry,*** **127:** 97-100.
10. R. S. Bhosale, C.V. Magar, K. S. Solanke, S. B. Mane, S. S. Choudhary, R. P. Pawar, (2007) Molecular iodine: An efficient catalyst for the synthesis of tetrahydrobenzo [*b*] pyrans, ***Synthetic Communications,*** **37:** 4353-4357.
11. I. Devi, P. J. Bhuyan, (2004) Sodium bromide catalyzed one-pot synthesis of tetrahydrobenzo [*b*] pyrans via a three-component cyclocondensation under microwave irradiation and solvent free conditions, ***Tetrahedron Letters,*** **45:** 8625-8627.
12. R. Hekmatshoar, S. Majedi, K. Bakhtiari, (2008) Sodium selenate catalyzed simple and efficient synthesis of tetrahydro benzo [*b*] pyran derivatives, ***Catalysis Communications,*** **9:** 307-310.
13. T. Shamsi, A. Amoozadeh, S. M. Sajjadi, E. Tabrizian, (2017) Novel type of SO_3H-functionalized nano-titanium dioxide as a highly efficient and recyclable heterogeneous nano catalyst for the synthesis of tetrahydrobenzo [*b*] pyrans, ***Applied Organometallic Chemistry,*** **31:** e3636.
14. M. Abdollahi-Alibeik, F. Nezampour, (2013) Synthesis of 4*H*-benzo [*b*] pyrans in the presence of sulfated MCM-41 nanoparticles as efficient and reusable solid acid catalyst, ***Reaction Kinetics, Mechanisms and Catalysis,*** **108:** 213-229.
15. M. Keshavarz, N. Iravani, M. H. A. Azqhandi, S. Nazari, (2016) Ion-pair immobilization of L-prolinate anion onto cationic polymer support and a study of its catalytic activity as an efficient heterogeneous catalyst for the synthesis of 2-amino-4*H*-chromene derivatives, ***Research on Chemical Intermediates,*** **42:** 4591-4604.
16. M. Esmaeilpour, J. Javidi, F. Dehghani, F. N. Dodeji, (2015) A green one-pot three-component synthesis of tetrahydrobenzo [*b*] pyran and 3,4-dihydropyrano [*c*] chromene derivatives using Fe3O4@SiO2-imid-PMA magnetic nanocatalyst under ultrasonic irradiation and reflux conditions, ***RSC Advances,*** **5:** 26625-26633.
17. F. Shahbazi, K. Amani, (2014) Synthesis, characterization and heterogeneous catalytic activity of diame-modified silica-coated magnetite polyoxometalate nanoparticles as a novel magnetically-recoverable nano catalyst, ***Catalysis Communications,*** **55:** 57-64.
18. F. Shirini, M. S. N. Langarudi, N. Daneshvar, (2017) Preparation of a new DABCO-based ionic liquid [H2-DABCO] [H2PO4]2 and its application in the synthesis of tetrahydrobenzo [*b*] pyran and pyrano [2,3-*d*] pyrimidinone derivatives, ***Journal of Molecular Liquids,*** **234:** 268-278.
19. J. Rakhtshah, S. Salehzadeh, (2017) Multi-wall carbon nanotube supported Co (II) Schiff base complex: An efficient and highly reusable catalyst for the synthesis of 1-amidoalkyl-2-naphthol and tetrahydrobenzo [*b*] pyran derivatives, ***Applied Organometallic Chemistry,*** **31:** e3560.
20. J. P. Hallett, T. Welton, (2011) Room-temperature ionic liquids: Solvents for synthesis and catalysis, ***Chemical Reviews,*** **111:** 3508-3576.
21. S. Mahato, S. Santra, R. Chatterjee, G. V. Zyryanov, A. Hajra, A. Majee, (2017) Bronsted acidic ionic liquid-catalyzed tandem reaction: An efficient approach towards regioselective synthesis of pyrano [3,2-*c*] coumarins under solvent-free conditions bearing lower E-factors, ***Green Chemistry,*** **19:** 3282-3295.
22. S. G. Zhang, J. H. Zhang, Y. Zhang, Y. Q. Deng, (2017) Nanoconfined ionic liquids, ***Chemical Reviews,*** **117:** 6755-6833.
23. C. K. Z. Andrade, L. M. Alves, (2005) Environmentally benign solvents in organic synthesis: Current topics, ***Current Organic Chemistry,*** **9:** 195.

24. (a) B. Das, M. Krishnaiah, P. Thirupathi, K. Laxminarayana, (2007) An Efficient and Convenient Protocol for the Synthesis of Novel 12-Aryl- or 12-Alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one Derivatives, ***Tetrahedron Letters,* 48:** 4263; (b) S. Chandrasekhar, N. R. Reddy, S. S. Sultana, C. Narsihmulu, K. V. Reddy, (2006) l-Proline catalysed asymmetric aldol reactions in PEG-400 as recyclable medium and transfer aldol reactions, ***Tetrahedron,* 62:** 338; (c) J. H. Li, X. C. Hu, Y. Liang, Y. X. Xie, (2006) PEG-400 promoted Pd (OAc)2/DABCO-catalyzed cross-coupling reactions in aqueous media, ***Tetrahedron,* 62:** 31; (d) X. C. Wang, Z. J. Quan, Z. Zhang, (2007) A Simple and Green Synthesis of Tetrahydrobenzo[α]-xanthen-11-one, ***Tetrahedron,* 63:** 8227.

***Bibliographical Sketch**

Associate Professor Dr.Nana V. Shitole
M.Sc, SET, NET(JRF), Ph.D
Department of Chemistry
Shri Shivaji College, Parbhani-431401 MS, India
Date of Joining :19 Sept 2005
Teaching Experience – 17 Years for UG & PG
Research Experience -11 Years
PG Teacher & Research Supervisor
Two Research student
Research Paper Published in Journal - 47
Book/Chapter Published -03.