

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

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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

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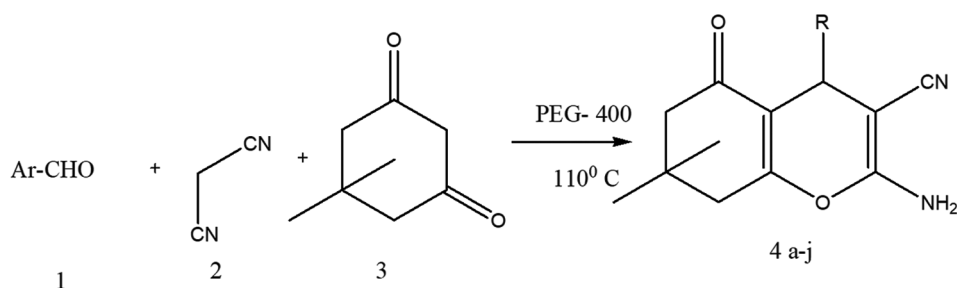
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Scheme 1: Reaction of Benzaldehyde(Substituted benzaldehyde) With Malononitrile & Dimedone

Spectral data of synthesized benzopyran

| Product | Spectral data |
|---------|---|
| 4a | 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-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-4H-chromene-3-carbonitrile (4b) Yield 92% of white solid; mp 205–206°C, ¹ H NMR: δ 9.26 (s, 1H), 6.92–6.94 (m, 4H), 6.67 (d, <i>J</i> = 8 Hz, 2H), 4.08 (s, 1H), 2.48 (s, 2H), 2.25 (d, <i>J</i> = 16 Hz, 1H), 2.08 (d, <i>J</i> = 16 Hz, 1H), 1.05 (s, 3H), 0.93 (s, 3H). |
| 4c | 2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-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-4H-chromene-3-carbonitrile (4d) Yield 89% of pale yellow solid; mp 213–214°C, ¹ H NMR: δ 8.07 (d, <i>J</i> = 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, <i>J</i> = 16 Hz, 1H), 2.14 (d, <i>J</i> = 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-4H-chromene-3-carbonitrile (4e) Yield 86% of gray white solid; mp 190–192°C, ¹ H NMR: δ 7.48–7.44 (m, 1H), 7.03 (s, 2H), 6.30 (m, 1H), 6.05 (d, <i>J</i> = 4 Hz, 1H), 4.34 (s, 1H), 2.44 (s, 2H), 2.33 (d, <i>J</i> = 16 Hz, 1H), 2.16 (d, <i>J</i> = 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-4H-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-4H-chromene-3-carbonitrile (4g) Yield 78% of gray white solid; mp 219–220°C, ¹ H NMR: δ 7.48–7.46 (m, 1H), 7.03 (s, 2H), 6.33 (m, 1H), 6.05 (d, <i>J</i> = 4 Hz, 1H), 4.34 (s, 1H), 2.46 (s, 2H), 2.33 (d, <i>J</i> = 16 Hz, 1H), 2.14 (d, <i>J</i> = 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-4H-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-4H-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-4H-chromene-3-carbonitrile (4j) Yield 84% of white solid; mp 219–220°C, ¹ H NMR: δ 7.08 (d, <i>J</i> = 8 Hz, 2H), 7.04 (d, <i>J</i> = 8 Hz, 2H), 6.96 (s, 2H), 4.14 (s, 1H), 2.53 (s, 2H), 2.25–2.26 (m, 4H), 2.07 (d, <i>J</i> = 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

Table 2: Synthesis of benzopyrans using PEG-400.

| Entry | Reactant | Product | Time | Yield | MP (°C) |
|-------|---|---------|------|-------|---------|
| 1 | C ₆ H ₅ -CHO | 4a | 7.5 | 90 | 228–229 |
| 2 | 4-OH-C ₆ H ₅ -CHO | 4b | 6 | 92 | 205–206 |
| 3 | 4-Cl-C ₆ H ₅ -CHO | 4c | 7 | 87 | 215–217 |
| 4 | 3-NO ₂ -C ₆ H ₅ -CHO | 4d | 6.5 | 89 | 213–214 |
| 5 | Thiophene-2-CHO | 4e | 7 | 86 | 190–192 |
| 6 | 4-OMe-C ₆ H ₅ -CHO | 4f | 7.5 | 90 | 194–195 |
| 7 | Furfural | 4g | 8 | 78 | 219–220 |
| 8 | 3-Cl-C ₆ H ₅ -CHO | 4h | 6.5 | 88 | 231–232 |
| 9 | 4-NO ₂ -C ₆ H ₅ -CHO | 4i | 6 | 86 | 180–182 |
| 10 | 4-Me-C ₆ H ₅ -CHO | 4j | 7.5 | 84 | 219–220 |

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.

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.

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