



METAL FREE POLY (4-VINYLPYRIDINE)-SUPPORTED IONIC LIQUID AS A GREEN AND SUSTAINABLE CATALYST FOR SKILFUL SYNTHESIS OF CHROMENE DERIVATIVES

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ABSTRACT

We report a novel environmental-benign synthesis of promising bioactive chromene derivatives *via* one-pot three-component reaction of dimedone substituted aromatic aldehydes and malononitriles using ethanol as green solvent at room temperature (25-30°C). The other attractive green aspects of the methodology include column chromatography/recrystallization free product isolation, formation of water as green waste, high atom economy, less energy consumption.

Keywords: Bioactive, Chromene, Multicomponent reaction, polyfunctionalized heterocycles, Green solvent.

1. INTRODUCTION

Environmentally benign methods like high propensity, discrimination, high yield, and simple reaction procedures have become the most important targets to reach in the field of organic chemistry. To achieve these, Multicomponent reactions (MCRs) [1, 2] have recently emerged as the most powerful tools in the synthesis of organic compounds and chemotherapeutic drugs by forming carbon-carbon and carbon-heteroatom bonds using a one-pot procedure. In MCRs, a number of different starting materials (for example three or more components) are allowed to react to give a preferred product using one-pot synthesis. These reactions have prodigious influence in organic synthesis as they provide various advantages, such as less reaction time, simple separation steps, and cost effectiveness, which eventually provides better yield as compared with multistep synthesis. These reactions can avoid purification intermediates and allow savings of both solvents and reagents. Other inherent characteristics of MCRs include regio- and chemo-selectivity, atom and step economy, target molecular diversity, and operational simplicity [3-7].

On the other hand, diversity-oriented synthesis is an application that is extensively used in biological and medical research and has led to the rapid development of broadly used synthons [8]. For the purpose of continuing our venture and furthering our acquaintance of the manufacture of chromenes heterocycles, we set out to

develop a new synthetic protocol for competent synthesis of polycyclic chromenes using, eco-friendly Poly (4-vinylpyridine)-supported ionic liquid as an robust solid heterogeneous acid catalyst in aqueous ethanol (1:1) at ambient conditions. And hence, research on design and synthesis of series of poly-functionalized heterocycles is a stuff of potential interest. Herein, we now report the synthesis of poly (4-vinylpyridine-co-1-sulfonic acid butyl-4-vinylpyridinium) chloroaluminate ([P₄VPy-BuSO₃H]Cl-X (AlCl₃)) (Scheme 1) as a supported ionic liquid containing both Lewis and Brønsted acid sites, according to the procedure given in the literature [9]. [P₄VPy-BuSO₃H] Cl-X(AlCl₃) was used as a catalyst for the synthesis of polycyclic chromenes.

2. EXPERIMENTAL

2.1. General

All the reagents were purchased from Spectrochem and Merck and were used without further purification. The reactions were monitored by TLC using 0.2 mm Merck silica gel 60 F254 precoated plates, which were seen with UV light. Melting points were measured by open capillary method.

2.2. General procedure for the synthesis of catalyst [P₄VPy-BuSO₃H]Cl-X(AlCl₃)

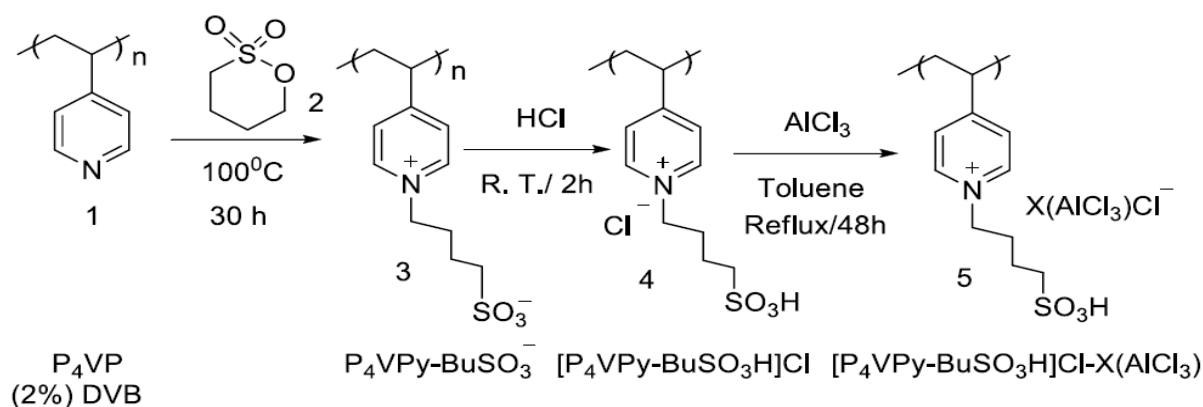
In a round bottomed flask (50 mL) equipped with a reflux condenser, 1 g of the P₄VPy was added to 1,4-

butane sultone (1.5 mL) and the mixture was stirred at 100°C for 30 h, filtered, washed with distilled water (20 mL), and dried at 80°C overnight to give $[P_4VP_y-BuSO_3]$. Then, HCl (3 M, 5 mL) was added to the obtained resin and the mixture was stirred at room temperature for 2 h, filtered, washed with distilled water (20 mL), and dried at 80°C overnight to give $[P_4VPy-BuSO_3H] Cl$. Afterwards, 1 g of the obtained resin was added to a solution of $AlCl_3$ (0.5 g) in toluene (10mL) and stirred under reflux condition for 24 h under N_2 atmosphere. Then, $AlCl_3$ (0.4 g) was added again and the mixture was stirred under reflux condition for 24 h and filtered and then the excess of $AlCl_3$ was removed by extraction with

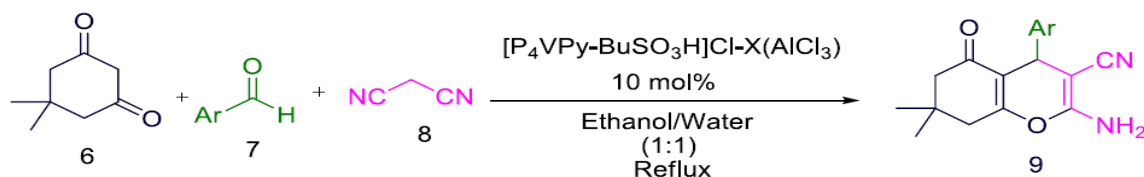
ethanol (95%) in an Soxhlet apparatus for 72 h.

3. RESULT AND DISCUSSION

In quest of a green methodology, we started our optimization study towards the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile derivatives (9), we selected the reaction of dimedone (6), substituted aromatic aldehydes (7) and malononitriles (8) using Poly(4-vinylpyridine)-supported ionic liquid with both Lewis and Brønsted acid sites as an eco-friendly solid acid heterogeneous catalyst in aqueous ethanol (1:1) at ambient conditions (30-35°C) (Scheme 2) as a model reaction.



Scheme 1: Synthesis of catalyst $[P_4VPy-BuSO_3H]Cl-X(AlCl_3)$



Scheme 2: Synthesis of 2-amino-7, 7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile derivatives

To optimize the reaction conditions. A full report on the effect of solvents, catalyst, reaction temperature, time, and catalyst loading on the synthesis of chromene derivative is provided in table 1. The best results were obtained in aqueous ethanol in the presence of 20% of urine carbon NPs at room temperature for stipulated time period (table 1).

To avoid various sorts of side reactions and simplify the whole process, the above reaction was initially conducted with Poly(4-vinylpyridine)-supported ionic liquid as catalyst in aqueous ethanol (1:1). At room temperature and in absence of catalyst there was no any

progress in the reaction (table 1 entry 1). When the reaction mixture was heated at 100°C there found only the traces of formation of product (table 1 entry 2), in the absence of either catalyst or solvent reaction did not proceed. When 5 mol% of catalyst was loaded under solvent free condition at 100°C, only 40 % of yield was obtained (table 1 entry 3). When methanol was employed at room temperature, the output of the catalysis gave a positive hint towards effectiveness of polar protic solvent (table 1 entry 4) giving 55% of yield. When reaction was checked in increased amount of catalyst (mol%) loading for the purpose of high yield,

there is increase in yield of product to 85 % (table 1 entry 5). Reaction was checked in acetonitrile at room temperature, only trace amount of product was formed (table 1 entry 6). When only water was employed as a reaction media, less amount of product was formed at room temperature, but when heated to reflux

temperature, moderate amount of yield was obtained (table 1 entry 7, 8). When IPA and dichloromethane was used, no satisfactory amount of yield was obtained (table 1 entry 9, 10, 11). When toluene and ethanol was used, satisfactory amount of yield was obtained (table 1 entry 12).

Table 1: Optimization of the reaction conditions for the synthesis of chromenederivatives^a

| Sr. no. | Catalyst (mol %) | Solvent | Temp (°C) | Time (h) | Yield (%) |
|---------|------------------|---------------------------------|-----------|----------|-----------|
| 1 | - | No solvent | rt | 5 | 0 |
| 2 | - | No solvent | 100 | 5 | trace |
| 3 | 5 | No solvent | 100 | 3 | 40 |
| 4 | 5 | CH ₃ OH | rt | 5 | 55 |
| 5 | 10 | CH ₃ OH | rt | 4 | 75 |
| 6 | 10 | CH ₃ CN | rt | 5 | trace |
| 7 | 10 | H ₂ O | rt | 6 | 30 |
| 8 | 10 | H ₂ O | Reflux | 1 | 65 |
| 9 | 10 | IPA | Reflux | 1 | trace |
| 10 | 10 | CH ₂ Cl ₂ | rt | 7 | trace |
| 11 | 10 | CH ₂ Cl ₂ | Reflux | 2 | 55 |
| 12 | 10 | Toluene | rt | 2.5 | 85 |
| 13 | 10 | EtOH | reflux | 1 | 90 |
| 14 | 10 | H ₂ O/ EtOH | reflux | 1 | 97 |

^aReaction conditions: Dimedone (100 mg), benzaldehyde (1 equivalent), malanonitrile (1 equivalent Poly(4-vinylpyridine)-supported ionic liquid (10 mol%), and solvent (2 ml) with continuous stirring at reflux temperature.

Table 2: Synthesis of chromenederivatives^a

| Entry | Aldehyde | Product | Time(min) | Yield ^b (%) | MP (obsd) (°C) | MP (literature) | |
|-------|---|---------|-----------|------------------------|----------------|-----------------|----------|
| | | | | | | (°C) | Ref. No. |
| 1 | C ₆ H ₅ - | 9a | 30 | 97 | 235-237 | 236-238 | [10] |
| 2 | 4-F-C ₆ H ₄ | 9b | 45 | 92 | 188-190 | 189-191 | [11] |
| 3 | 4-OH-C ₆ H ₄ | 9c | 25 | 95 | 202-203 | 204-205 | [12] |
| 4 | 4-NO ₂ -C ₆ H ₄ | 9d | 60 | 85 | 177-178 | 178-180 | [13] |
| 5 | 3-NO ₂ -C ₆ H ₄ | 9e | 30 | 95 | 209-210 | 210-211 | [13] |
| 6 | 2-Cl-C ₆ H ₄ | 9f | 60 | 90 | 212-213 | 212-214 | [14] |
| 7 | 4-Cl-C ₆ H ₄ | 9g | 90 | 92 | 213-214 | 212-214 | [14] |
| 8 | 4-me-C ₆ H ₄ | 9h | 120 | 85 | 207-208 | 208-210 | [15] |
| 9 | 3-Br-C ₆ H ₄ | 9i | 30 | 90 | 230-232 | 229-231 | [16] |
| 10 | 4-OMe-C ₆ H ₄ | 9j | 90 | 80 | 202-203 | 203-205 | [16] |
| 11 | 3,4-Di-OMe-C ₆ H ₃ | 9f | 60 | 90 | 228-230 | 229-231 | [17] |
| 12 | 3-OMe-C ₆ H ₄ | 9g | 90 | 92 | 196-198 | 195-197 | [17] |
| 13 | 4-OMe-C ₆ H ₄ | 9h | 95 | 93 | 204-205 | 203-205 | [16] |
| 14 | 4-Br-C ₆ H ₄ | 9i | 90 | 95 | 206-208 | 208-211 | [16] |
| 15 | 3-Me-C ₆ H ₄ | 9j | 90 | 93 | 222-223 | 224-225 | [18] |
| 16 | 3-OH-C ₆ H ₄ | 9k | 100 | 90 | 225-226 | 226-228 | [19] |
| 17 | 3,4-di-OH-C ₆ H ₃ | 9l | 120 | 90 | 241-242 | 241-243 | [19] |
| 18 | 4-Me ₂ N-C ₆ H ₄ | 9m | 70 | 93 | 214-215 | 213-215 | [20] |
| 19 | 2-Furyl | 9n | 75 | 95 | 227-228 | 226-228 | [20] |
| 20 | 2-Thienyl | 9o | 65 | 94 | 216-217 | 216-218 | [21] |

^aReaction conditions: Dimedone (100 mg), benzaldehyde (1 equivalent), malanonitrile (1 equivalent Poly(4-vinylpyridine)-supported ionic liquid (10 mol%), and solvent (2 ml) with continuous stirring at reflux temperature.

When aqueous ethanol (1:1) was employed, highest amount of yield was obtained, which indicates the necessity of aqueous media for getting best results (table 1 entry 14). Though, an additional increment in the catalyst amount up to 20 mol% resulted in no change in conversion percentage. This may be because of the enervation of the catalytic site or attainment of the maximum conversion efficiency of the catalyst. With the optimized reaction conditions in hand (table 1 entry 14), we surveyed the scope of various aldehydes with a range of substituents on the aromatic ring of aldehyde (table 2). Introduction of electron donating (4-OMe) as well as electron withdrawing substituent's (4-F, 4-Cl, 4-Br, NO₂) at the different positions of aldehydes were well tolerated and products were isolated in 97 % was

achieved and their structures were confirmed by melting points.

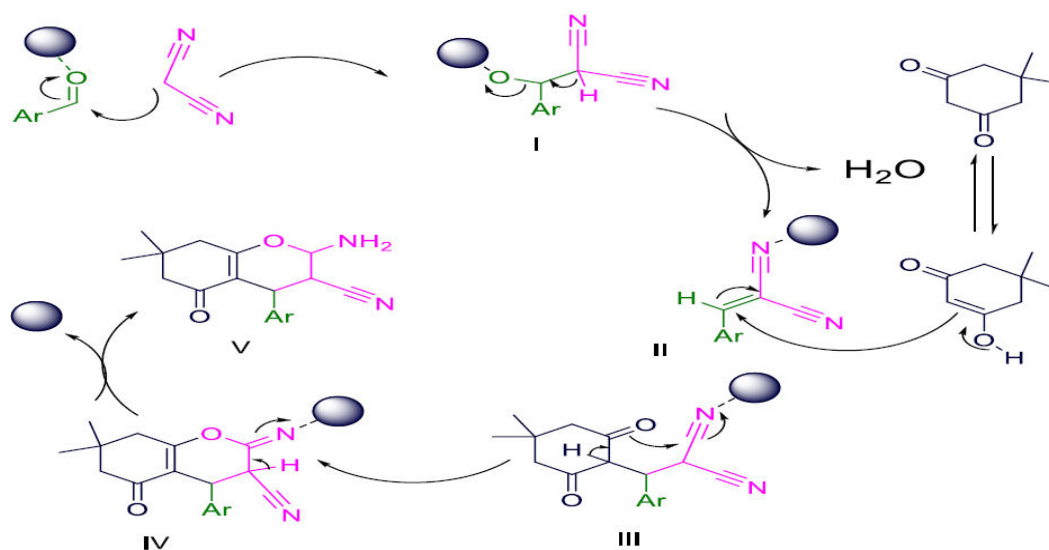
3.1. Mechanism of reaction for the synthesis of chromene derivative

The mechanism proposed for the synthesis of chromene in presence of Poly(4-vinylpyridine)-supported ionic liquid is shown in scheme 3. On the basis of this mechanism catalyst catalyzes the generation of olefin I that is readily prepared by the condensation reaction of aldehyde and malanonitrile to give the intermediate product II. Then the Michael addition of I with dimedone gives intermediate II. Finally the product V was obtained by intramolecular cyclization and tautomerization.

Table 3: Assessment of reported catalysts catalytic activity with WO₃ NRs for the synthesis of chromenes

| Entry | Catalyst | Catalyst loading | Solvent | Temp (°C) | Time (Min) | Yield (%) | ref |
|-------|---------------------------------|------------------|-----------------------|-----------|------------|-----------|-----------|
| 1 | No catalyst | - | EtOH:H ₂ O | Reflux | -- | -- | -- |
| 2 | ZnO NPs | 10 mol% | EtOH | Reflux | 20 | 83 | [22] |
| 3 | Urea | 10 mol% | EtOH:H ₂ O | Reflux | 480 | 85 | [23] |
| 4 | Na ₂ CO ₃ | 10 mol% | EtOH:H ₂ O | 120 | 100 | 95 | [24] |
| 5 | Aq PEG-400 | 1ml | EtOH:H ₂ O | Reflux | 180 | 85 | [25] |
| 6 | Cerium (III)chloride | 10 mol% | EtOH:H ₂ O | Reflux | 80 | 83 | [26] |
| 7 | Piperidine | | H ₂ O | Reflux | 380 | 75 | [27] |
| 8 | S-Proline | 10 mol% | EtOH:H ₂ O | Reflux | 180 | 80 | [28] |
| 9 | CuO NPs | 15 mol% | H ₂ O | 100 | 420 | 90 | [29] |
| 10 | DBSA | | H ₂ O | | 280 | 92 | [30] |
| 11 | TBAF | 10 mol% | H ₂ O | Reflux | 55 | 93 | [20] |
| 12 | I ₂ | 10 mol% | DMSO | 120 | 250 | 82 | [31] |
| 20 | This catalyst | 10 mol% | EtOH:H ₂ O | reflux | -- | 97 | This work |
| 21 | This catalyst | 10 mol% | Solvent free | 70 | -- | 97 | This work |

^aReaction conditions: Dimedone (100 mg), benzaldehyde (1 equivalent), malanonitrile, different catalysts with variable amounts, solvent (2 ml) with continuous stirring at reflux temperature.



Scheme 3: Plausible mechanism of reaction for chromene synthesis

4. CONCLUSION

To conclude, we report a novel environmental-benign synthesis of promising bioactive chromene derivatives via one-pot three-component reaction of dimedone (6), substituted aromatic aldehydes (7) and malon-onitriles (8) using ethanol as green solvent at room temperature (25-30°C). The other attractive green aspects of the methodology include column chromato-graphy/recrystallization free product isolation, formation of water as green waste, high atom economy, less energy consumption. Moreover, pro-duction of a class of biologically and pharmacologically important chromenes heterocycles immensely enhances the synthetic utility of the present method. Overall this new method meets all the urgent criteria set down by green chemistry principles and thereby opens new scopes for further development of sustainable multicomponent reactions.

5. REFERENCES

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