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ORIGINAL ARTICLE

Efficient one-pot synthesis of polyhydroquinoline derivatives using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as a heterogeneous and reusable catalyst in molten salt media

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KEYWORDS

Hantzsch;
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Multi-component;
Molten salt

Abstract Polyhydroquinoline derivatives have been prepared efficiently in a one-pot synthesis via Hantzsch condensation using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as a heterogeneous and reusable catalyst. The present method uses molten salt media instead of hazardous organic solvents. The present methodology offers several advantages such as simple procedure, excellent yields, and a short reaction time.

1. Introduction

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction. Clearly, for multi-step synthetic procedures, the number of reactions and purification steps is among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Therefore, in the last decade, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products (Devi and Bhuyan, 2004).

1,4-Dihydropyridyl compounds are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases. Cardiovascular agents such as nifedipine, nicardipine, amlodipine, and other related derivatives are dihydropyridyl compounds, effective in the treatment of hypertension (Nakayama and Kasoaka, 1996). 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic activities (Mannhold et al., 1992). Extensive studies have revealed that these compounds

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Table 1 One-pot synthesis of polyhydroquinolines in molten salt media using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

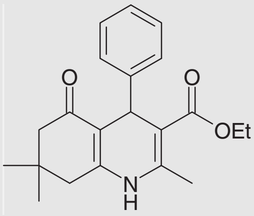
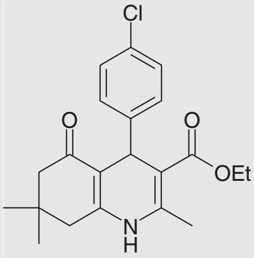
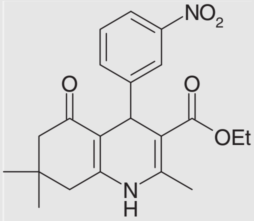
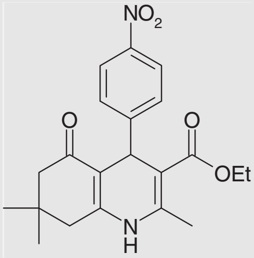
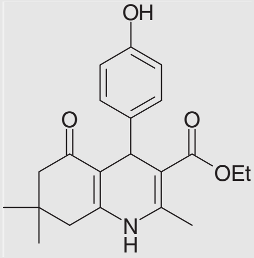
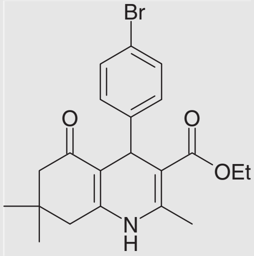
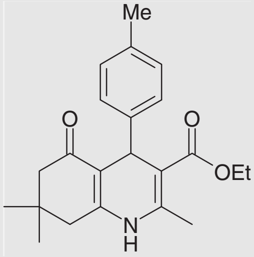
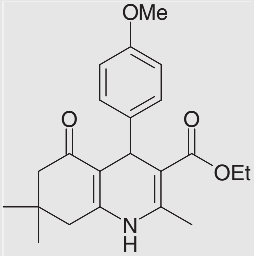
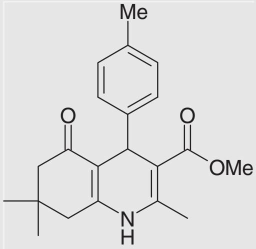
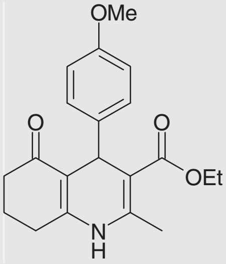
Entry	Product	Time (min)	Yield (%)
4a		6	92
4b		2	96
4c		4	96
4d		4	91
4e		4	85

Table 1 (*continued*)

Entry	Product	Time (min)	Yield (%)
4f		6	91
4g		4	74
4h		4	97
4i		4	74
4j		4	74

(*continued on next page*)

Table 1 (*continued*)

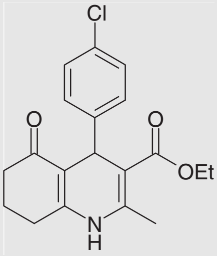
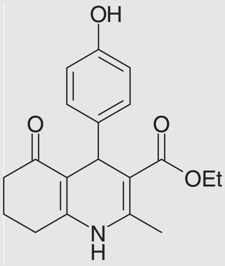
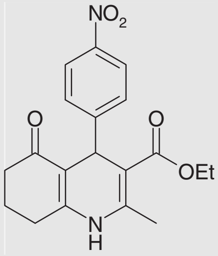
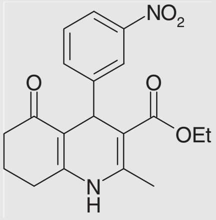
Entry	Product	Time (min)	Yield (%)
4k		6	98
4l		6	68
4m		4	79
4n		4	96

exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory activity, cerebral antischemic activity in the treatment of Alzheimer's disease, and chemosensitizer in tumor therapy (Boer and Gekeler, 1995).

Numerous methods have been reported for the synthesis of structurally related compounds polyhydroquinoline derivatives because of the biological importance associated with these compounds. The classical method involves three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or by refluxing in alcohol (Love and Snader, 1965). However, these methods suffer from several drawbacks such as long reaction times, use of large quantities of volatile organic solvents, low yields, and harsh reaction conditions. Recently several methods have been reported for the synthesis of these heterocycles (Maheswara et al., 2006; Kumar and Maurya, 2007). However, the search for a better catalyst for the synthesis of polyhydroquinoline derivatives using less hazardous solvents or solvent-free conditions is of prime importance.

Catalysis based on heteropoly acids (HPAs) and related compounds especially those comprising the strongest Keggin-type HPAs is an important field in which new and promising developments are being carried out both at research and technological levels (Rafiee et al., 2009). Their highly acidic nature is very interesting in industrial reactions. Salts of heteropoly acids have been studied in different organic transformations under heterogeneous conditions (Imada et al., 1994; Reddy et al., 2006).

Ionic liquids have been used as effective solvents for clean chemical reactions, namely as replacement for volatile organic and dipolar aprotic solvents. They may provide a medium for clean reactions with minimal waste and product extraction. It has been found that catalytic activity and product selectivity are accelerated when they are used. However the high cost of most conventional room temperature ionic liquids has led us to explore the use of more benign salts in the molten states as practical alternatives. Previously, molten tetraalkyl ammonium halides were used as cost-effective ionic liquids in a number of useful synthetic transformations (Lapidus et al., 2006; Khodaei et al., 2004).

2. Materials and methods

2.1. General

All compounds are known and were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^1H NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using $CDCl_3$ as a solvent. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. All chemicals were purchased from Merck chemical company and used without further purification. $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ was prepared from aqueous solutions of $H_3PW_{12}O_{40}$ and Cs_2CO_3 according to the literature (Zieba et al., 2009).

2.2. General procedure for preparation of polyhydroquinolines

A mixture of aldehyde **1** (1 mmol), cyclic diketone **2** (1 mmol), β-ketoester **3** (1 mmol), ammonium acetate (2 mmol) and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (0.01 mmol) in tetrabutylammonium bromide (2 mmol) was stirred at 110 °C for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured into water. The resulting precipitate was filtered and was purified by recrystallization from ethanol to afford the desired compound in pure form.

2.2.1. Compound *4a*

IR (KBr): 3287, 3078, 2963, 1697, 1611 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.85 (s, 1H, CH_3), 1.00 (s, 1H, CH_3), 1.12 (t, $^3J_{H\text{–}H}$ = 7.0 Hz, 3H, CH_3), 1.97 (d, $^2J_{H\text{–}H}$ = 16.1 Hz, 1H), 2.15 (d, $^2J_{H\text{–}H}$ = 16.1 Hz, 1H), 2.28 (s, 3H, CH_3), 2.29 (d, $^2J_{H\text{–}H}$ = 17.0 Hz, 1H), 2.41 (d, $^2J_{H\text{–}H}$ = 17.0 Hz, 1H), 3.97 (q, $^3J_{H\text{–}H}$ = 7.0 Hz, 2H, CH_2), 4.85 (s, 1H), 7.06–7.18 (m, 5H, arom), 9.04 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 15.0, 19.1, 27.3, 29.9, 33.0, 36.7, 40.3, 51.1, 59.9, 104.5, 110.8, 126.5, 128.3, 128.6, 145.8, 148.5, 150.4, 167.7, 195.1.

2.2.2. Compound *4n*

IR (KBr): 3506, 3285, 3193, 2447, 1912, 1678, 1518, 1484, 1306, 1284, 1166 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.09 (t, $^3J_{H\text{–}H}$ = 6.6 Hz, 3H, CH_3), 1.75 (m, 1H), 1.89 (m, 1H), 2.18–2.22 (m, 4H), 2.31 (s, 3H, CH_3), 3.96 (t, $^2J_{H\text{–}H}$ = 6.0 Hz, 2H, CH_2), 5.00 (s, 1H), 7.51 (t, $^3J_{H\text{–}H}$ = 7.3 Hz, 1H, arom), 7.60 (d, $^3J_{H\text{–}H}$ = 7.0 Hz, 1H, arom), 7.95-7.97 (m 2H, arom), 9.29 (s, 1H, NH). ^{13}CNMR ($CDCl_3$, 125 MHz): δ (ppm) 14.9, 19.2, 21.6, 26.9, 37.1, 37.4, 60.1, 103, 111.2, 121.7, 122.8, 130.4, 135.2, 146.9, 148.3, 150.7, 152.9, 167.3, 195.6.

3. Results and discussion

Herein, we would like to report the studies of a facile unsymmetric Hantzsch condensation in the presence of the heterogeneous catalyst $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ using substituted aldehyde (**1**), dimedone (**2**), acetoacetate ester (**3**), and ammonium acetate in molten tetra n-butylammonium bromide (TBAB) to produce polyhydroquinoline derivatives (**5**) in high yields (Scheme 1).

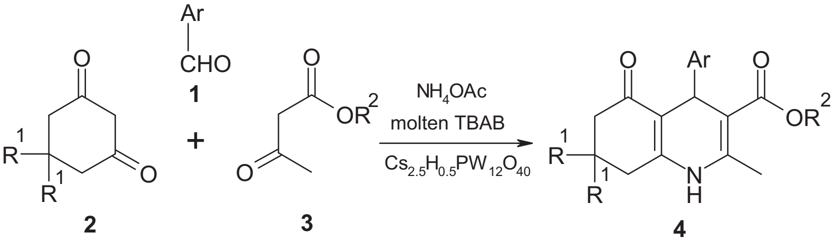
We optimized the conditions by examining the reaction involving *p*-chlorobenzaldehyde (1 mmol), ethylacetoacetate (1 mmol), dimedone (1 mmol), and ammonium acetate (2 mmol) to afford the appropriate polyhydroquinoline (**4b**). Best results were obtained in the presence of 1 mol% of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ and 2 mmol of Et_4NBr at 110 °C.

To generalize this methodology, we subjected a series of other aldehydes having electron-donating as well as electron-withdrawing substituents to obtain the corresponding polyhydroquinoline derivatives under the optimized reaction conditions (Table 1). As Table 1 shows yields are good to excellent in most cases.

The reusability of the catalysts is an important benefit and makes them useful for commercial applications. Thus, the recovery and reusability of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ were investigated. The recyclability of the catalyst in the reaction of *m*-nitro benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), cyclohexanedione (1 mmol) and ammonium acetate (2 mmol) in the presence of TBAB (2 mmol) was checked. The separated catalyst was reused after washing with ethanol and drying at 120 °C. The catalyst was recovered in excellent yields and catalyst was used in the mentioned reaction for three times, it showed the

Table 2 Recovery of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

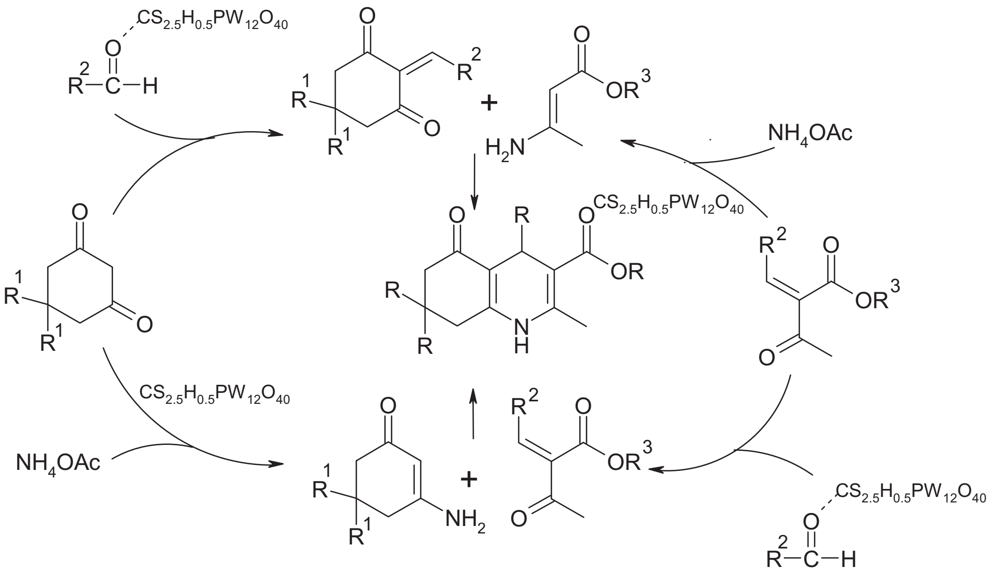
Number of recycles	Time (min)	Yield (%)
Fresh	4	96
1	4	92
2	4	92
3	4	90



Scheme 1 $Cs_{2.5}H_{0.5}PW_{12}O_{40}$-catalysed unsymmetric Hantzsch reaction.

Table 3 Comparison of the results of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as a catalyst in Hanzcsh reaction with the literature.

Entry	Catalyst (mol%)	Temperature (°C)	Time	Yield (%)	Reference
1	ZnO (10)	80	60 min	92	Matloubi Moghaddam et al. (2009)
2	MCM-14 (1)	90	15 min	89	Nagarapu et al. (2007)
3	Silica Sulfuric (20)	60	30 min	94	Mobinikhaledi et al. (2009)
4	$Yb(OTF)_3$ (5)	25	5 h	90	Donelson et al. (2006)
5	$Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (1)	110	6 min	92	–



Scheme 2 Proposed mechanism of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$-catalyzed synthesis of polyhydroquinolines.

same activity such as fresh catalyst without any considerable loss of its activity (Table 2).

The superiority of the present protocol over reported methods can be seen by comparing our results with those of some recently reported procedures, as shown in Table 3. The synthesis of compound 4a was used as a model reaction and the comparison is in terms of mol% of the catalysts, temperature, reaction time and percentage yields.

A reasonable pathway for the formation of polyhydroquinolines in the presence of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ is presented by Scheme 2.

4. Conclusion

In Conclusion, we have reported an efficient procedure for the synthesis of polyhydroquinoline derivatives using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as a reusable, non-toxic, non-corrosive and heterogeneous catalyst in molten salt media. The method offers advantages such as clean reaction, low loading of catalyst, high yields of products, short reaction times and use of various substrates, which makes it a useful and attractive strategy for the synthesis of polyhydroquinoline derivatives.

Acknowledgment

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