Journal of Saudi Chemical Society (2016) xxx, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Microwave assisted highly efficient one-pot multi-component synthesis of novel 2-(tetrasubstituted-1H-pyrrol-3-yl)-4H-chroman-4-ones catalyzed by heterogeneous reusable silica gel supported polyphosphoric acid (PPA/SiO_2)

Sumit Kumar *, **Nishant Verma**, **Naseem Ahmed** *

Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee 247 667, Uttarakhand, India

Received 13 October 2015; revised 3 January 2016; accepted 20 January 2016

KEYWORDS

Multicomponent reaction;
Green catalysis;
PPA–SiO_2;
Heterogeneous catalyst;
Pyrrole

Abstract A solvent-free, eco-friendly and facile approach for the synthesis of highly functionalized tetrasubstituted pyrroles has been reported through one-pot four-component reaction of aldehyde, amine, nitroalkane and 1,3-diketone using silica gel supported polyphosphoric acid (PPA–SiO_2) under microwave condition. The reaction occured through the *in situ* formation of *β*-keto enamine and nitrostyrene analog following Michael addition and finally intramolecular annulation affording the products in good yields. The key features of the present method include clean reaction, mild conditions, low catalyst loading, straightforward, high to excellent yields, short reaction time, avoiding use of harmful metal catalyst and organic solvent, environmentally friendly compared to the existing methods, recovery and reusability of catalyst and easy workup procedure.

1. Introduction

In the last few decades, tremendous attempts have been dedicated to prepare small heterocyclic compounds owing to their high level of structural diversity and broad therapeutic efficacy. Pyrrole is considered as 'privileged scaffolds' and each substitution in the pyrrole nucleus provides the compounds with extensive pharmacological properties [1]. Pyrrole represents one of the most important heterocyclic compound, which is frequently found as a structural fragment in several natural products [2a] and pharmaceuticals [2b] and widely used as versatile building units in synthetic organic transformation

* Corresponding authors. Tel./fax: +91 1332 285745.
E-mail addresses: sumitdcy@iitr.ac.in (S. Kumar), nasemfcy@iitr.ac.in (N. Ahmed).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.01.005

[2c]. The pyrrole core moiety is important in many biological compounds such as atorvastatin [2d], sunitinib [2e], ketorolac [2f], tolmetin [2f], enzyme catalase, vitamin B12, pigments like heme, chlorophyll, bilirubin and melanin [2g–j] (Fig. 1). Apart from this, tetrasubstituted pyrroles are of great importance because of having pharmacological properties like antiviral [3a], antibacterial [3b], antifungal [3c], antioxidant [3d], and anticancerous [3e] and they also inhibit the cytokine-mediated diseases [3f].

Therefore, new research avenues are concerned on the development of facile and efficient protocols for the preparation of highly functionalized pyrroles. Consequently, for the preparation of structurally diverse pyrroles, a huge number of synthetic methodologies have been developed [4]. The synthesis of pyrrole nucleus is normally achieved by applying Hantzsch [5] or Knorr [6] or Paal Knorr reaction [7]. Although these methods are very helpful for the synthesis of pyrroles, they have serious drawbacks such as unsatisfactory yields, multistep synthetic operations, accessibility of starting materials, regiospecificity, functional group compatibility and drastic reaction conditions. Recently, tetra-substituted pyrroles were reported using multicomponent reaction catalyzed by $FeCl_3$ [4a], $NiCl_2{\cdot}6H_2O$ [3f], graphite [8], PS-PTSA [9], Pd catalyzed Suzuki coupling of β-keto enamine or esters and nitromethane [10] and reaction of enamino esters and nitroolefins [11]. However, most of these approaches have some limitations such as long reaction time, unsatisfactory yields, high temperature, costly catalysts, utilization of organic solvents and tedious work-up procedures. Consequently, the scope of efficient and facile synthetic method for the preparation of tetrasubstituted pyrroles is still an attractive aim for the chemists.

In recent years, microwave-assisted multicomponent reactions (MCRs) are of great importance in synthesis of pyrrole moiety, due to their simplicity, high selectivity, rapid construction of complex molecules without isolation of any intermediates, reduced reaction time, good yielding, environmentally benign, high variability, excellent atom-economy, less time consuming and easy work-up [12]. Moreover, the possibility of extending one-pot reactions into solid-phase syntheses promises various prospects for developing novel lead structures of pharmaceuticals. In this perspective, our attention was drawn for the preparation of pyrrole nucleus through one-pot four-component reaction using solid phase heterogeneous catalyst.

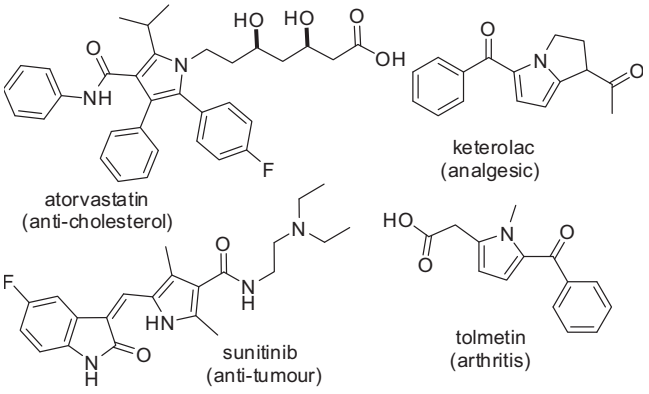

Figure 1 Some pharmaceutical products containing pyrrole moiety.

The heterogeneous catalysts have attracted a great attention in organic transformations because they have good thermal and mechanical stabilities, superior over homogeneous catalysts, easily recover from the reaction mixture by simple filteration, reuse several times, being more economical and environmentally viable [13]. In this context, silica supported polyphosphoric acid (PPA–SiO_2) is found as an efficient proton source in organic transformations. PPA–SiO_2 has been explored as a powerful catalyst for several organic transformations under mild conditions [14–16]. The unique feature of silica supported polyphosphoric acid over traditional protonic acids and Lewis acid catalysts is stability, cost effective, ease of handling and recycling and reusability.

In continuation of our interest to explore eco-friendly approach under solvent-free condition [17], herein, we wish to describe a simple and efficient microwave assisted approach, for the synthesis of 2-(tetrasubstituted-1H-pyrrol-3-yl)-4H-chroman-4-ones using PPA–SiO_2 as catalyst by employing one pot multicomponent condensation reaction of 4-oxo-4H-chromane-2-carbaldehyde, amines, 1,3-diketone and nitroalkanes at 90 °C as shown in Scheme 1.

2. Results and discussion

The approach offered two new each C—C bonds and C—N bonds through this one pot condensation reaction. The reaction involves *in situ* generation of β-keto enamine and nitrostyrene analog followed by Michael addition and thereafter intramolecular annulation. On the basis of this approach, the starting materials are easily available for the synthesis of 20-member combinatorial library of 2-(tetrasubstituted-1H-pyrrol-3-yl)-4H-chroman-4-one. The 4-oxo-4H-chromane-2-carbaldehyde (**1**) was synthesized by following the literature procedure [18].

Firstly, the reaction conditions were examined using four substrates such as 4-oxo-4H-chromane-2-carbaldehyde **1** (1 mmol), N,N-dimethylbenzene-1,4-diamine **2d** (1 mmol), acetylacetone **3b** (1 mmol) in nitromethane **4** (1 mL) by applying various catalysts as a model reaction (Table 1). The reaction parameters including the reaction solvents, heating conditions and reaction time were screened.

We scrutinized the reaction by applying various catalysts such as $FeCl_3$, $FeCl_3{\cdot}SiO_2$, $FeCl_3{\cdot}6H_2O$, PTSA, K-10, TiO_2–SiO_2, $InCl_3$, CF_3SO_3H, PS-PTSA, $NbCl_5$, and PPA–SiO_2 in similar reaction conditions. Catalysts such as CF_3SO_3H, $FeCl_3{\cdot}6H_2O$, PTSA, $FeCl_3$, $NbCl_5$, and $InCl_3$ resulted in a low to moderate yield of the product **5i** (Table 1, entries 1–6) However, among all catalysts screened, PPA–SiO_2 (10 mg) was found as the most effective catalyst for this coupling reaction. Owing to various advantages with heterogeneous acid catalyzed reactions, we performed the reaction with K-10, TiO_2–SiO_2, $FeCl_3{\cdot}SiO_2$ and PS-PTSA obtaining moderate to high yields of **5i** (Table 1, entries 7–10). Then we performed the reaction in the presence of PPA–SiO_2 and it dramatically accelerated the reaction affording the product **5i** in an impressive yield (Table 1, entry 11).

The catalyst loading of PPA–SiO_2 was also studied for maximum efficiency and it was found that 10 mg of PPA–SiO_2 was enough to get optimum product yield in a neat condition (Table 1, entries 11–14). Any extra amount of the catalyst did not enhance the yields significantly (Table 1, entry

Please cite this article in press as: S. Kumar et al., Microwave assisted highly efficient one-pot multi-component synthesis of novel 2-(tetrasubstituted-1H-pyrrol-3-yl)-4H-chroman-4- ones catalyzed by heterogeneous reusable silica gel supported polyphosphoric acid (PPA/SiO_2), Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.01.005