Ionic Liquid Catalyzed Convenient Synthesis of Imidazo[1,2-\textit{a}]quinoline under Sonic Condition

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Um protocolo eficiente para a síntese de derivados imidazol-[1,2-\textit{a}]-quinolina a partir de aldeídos, enaminonas ou malononitrila e utilizando como catalisador acetato de 1,8-diazabiciclo[5.4.0]-undec-7-en-8-ium ([DBU][Ac]) sob irradiação de ultrassom é descrito. Em comparação com outras metodologias, esta apresenta as vantagens de um tratamento reacional mais simples, condições reacionais mais suaves, rendimentos elevados e um procedimento ambientalmente aceitável.

An efficient protocol for the synthesis of imidazo[1,2-\textit{a}]quinoline from aldehydes, enaminones, and malononitrile using 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium ([DBU][Ac]) as a catalyst under ultrasound irradiation is described. Compared with other methods, this new method has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

Keywords: ionic liquid, imidazo[1,2-\textit{a}]quinoline, ([DBU][Ac]), green catalyst, multicomponent reaction, one pot synthesis

Introduction

The synthesis of organic compounds is one of the most important objectives in modern drug discovery. Organic reactions should be fast and the targeted products should be easily separated in high purity and yields. In this regard, there is much attention paid in the development of new processes and new synthetic approach. From this point of view, non-classical methods such as microwave-assisted synthesis, ultrasonic irradiation and supercritical fluids find relevance as attractive methods to achieve these goals.\(^1\)

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural products, many of which exhibit useful biological activity.\(^2,3\) The interest in bicyclic 5-6 systems with one ring junction and one extra nitrogen atom stems from imidazo[1,2-\textit{a}] quinoline ring systems found in many biologically active compounds. Imidazo[1,2-\textit{a}]quinoline is a synthetically designed scaffold with a broad range of biological activities. Some of its derivatives have pharmacological properties such as contraceptive,\(^4\) hypotensive,\(^5\) antiallergic and antiasthmatic agents.\(^6\) Several prospective nonsedative anxiolytic agents with the imidazoquinoline structure have been discovered.\(^7\)

In the last few years, the development of synthetic protocol employing ultrasound irradiation has led to an epoch-making change in organic reactions. Using ultrasound irradiation, a wide variety of heterocycles can be synthesized under milder conditions, within shorter reaction time and in higher yield.\(^8\) Recently, ionic liquids (ILs) have emerged as the potential for novel changes to synthetic routes and unit operations in research as well as in the chemical industry. Although the ionic liquid was initially introduced as an alternative green reaction medium, today it has marched far beyond showing its important role in controlling the reactions as catalyst.\(^9\) In recent times, basic ionic liquids have aroused unprecedented interest because they showed more advantages, such as catalytic efficiency and recyclability.

Literature survey revealed that there exist only two multicomponent reports by Tu \textit{et al.}\(^10\) and Ahmadi \textit{et al.}\(^11\) for the synthesis of imidazo[1,2-\textit{a}]quinoline under microwave irradiation and conventional heating, respectively. However, the generality of the existing reports is somewhat vitiated by the severe reaction conditions and the catalysts in the context of green synthesis. Thus, the development of an efficient and green approach for the preparation of heterocycles containing bridgehead nitrogen sought highly desirable. Prompted by these facts and as a part of our ongoing programme on
One-pot solvent-free rapid and green synthesis of 3,4-dihydropyrano[c]chromenes using grindstone chemistry

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Received 15 October 2012; accepted 22 December 2012

Abstract An easy solvent-free method is described for the synthesis of 3,4-dihydropyrano[c]chromenes by a one pot three component coupling reaction of aromatic aldehydes, malononitrile, and 4-hydroxycoumarin using basic ionic liquid as the catalyst by grindstone chemistry. The salient features of this one pot protocol are short reaction times, cleaner reaction profiles and simple workup.

1. Introduction

3,4-Dihydropyrano[c]chromene derivatives have recently attracted the attention of synthetic and medicinal chemists because of their wide range of biological and pharmaceutical activities such as diuretic, analgesic, myorelaxant (Bonsignore et al., 1993), anticoagulant (Cingolani et al., 1969), anticancer (Wu et al., 2003), anti-tumor (Baraldi et al., 1992; Perrella et al., 1994), and anti-HIV (Kashman et al., 1992; Patil et al., 1993). They are also used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer’s disease, amyotrophic lateral sclerosis, Parkinson’s disease, Huntington’s disease, AIDS associated dementia, Down’s syndrome and schizophrenia and myoclonus (Konkoy et al., 2000). These derivatives constitute numerous natural products like calanolides, calanone, calophyllolides etc. (Rueping et al., 2008).

They have been synthesized in the presence of a variety of catalysts such as DBU (Khurana et al., 2010), TBAB (Khurana and Kumar, 2009), diammonium hydrogen phosphate (Abdolmohammadi and Balalaei, 2007), heteropoly acids (Heravi et al., 2009), nano ZnO (Paul et al., 2011), KAI (SO3)2·12H2O (Karimi and Sedaghatpour, 2010), TMGT (Shaabani et al., 2005), MgO (Seifi and Sheibani, 2008), K2CO3 (Kidwai and Saxena, 2006), pyridine (Shaker, 1996), [bmim]OH (Gong et al., 2009), and Morpholine (Heravi et al., 2011). However, many of these methods are associated with several disadvantages such as long reaction time, drastic reaction conditions, difficult catalyst recovery, very expensive reagents, low yields and tedious workup. It was thought momentous to find a simple, inexpensive and reusable catalyst for the synthesis of 3,4-dihydropyrano[c]chromenes as our group is actively engaged in exploring the new facets of heterocyclic synthesis (Dadhania et al., 2011, 2012a,b; Patel et al., 2012; Avalani et al., 2012; Tarpada et al., 2012).

Solid-state syntheses have recently received much attention. These processes have many advantages such as high efficiency and selectivity, easy separation, purification and mild reaction conditions (Tanaka and Toda, 2000). They are not only envi-
Saccharomyces cerevisiae catalyzed one pot synthesis of isoindolo[2,1-a]quinazoline performed under ultrasonication

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**A R T I C L E   I N F O**

Article history:
Received 24 November 2012
Received in revised form 10 January 2013
Accepted 27 January 2013
Available online xxx

**K e y w o r d s:**
Baker's yeast
Ultrasound
Multicomponent synthesis
Biocatalysis
Enzymes

1. Introduction

Biocatalyzed reactions in organic media have become a popular approach with several reports appearing in the literature [1–4]. The use of aqueous media for such transformations is not desirable as most of the organic substrates are insoluble in water [5]. Biocatalysis in organic solvents have several advantages: high solubility of organic substrates to perform the reaction which is complicated in aqueous media, easy isolation of products and insolubility of enzymes in organic solvents which permits their easy recovery and reuse [6]. Baker's yeast is known to play vital role in functional group conversion and also been reported to catalyze organic transformations effectively such as reduction [7–9], hydrolysis [10], oxidation [11] and condensation [12]. Baker's yeast has been extensively used to carry out various organic reactions and can be used in the synthesis of various heterocyclic compounds such as polyhydroquinolines [13], 4H-pyrazines [5], isoaxolines [14] and 1,4-dihydropyridines [15]. Baker's yeast is also reported to show high activity and enantioselectivity in aqueous/organic biphasic systems [16–18]. Recently Silva et al. have reported asymmetric reduction of \((-\rightarrow)\)-carvone catalyzed by Baker's yeast in mono- and biphasic systems [19].

Isoindoles are ubiquitous structural motifs of the most common heterocyclic compounds found in both natural products and biologically active compounds. Due to the existence of an array of structurally diverse isoindoles, it is an important substructure of various biologically active natural products such as bhimamycin C and bhimamycin D which display bioactivities against human ovarian cancer cell lines and are also EP4 receptor agonists in the treatment of pain [20]. It exhibits variety of biological properties such as anti-neoplastic, antiviral [21], antimalarial [22], antitumor [23], and antimicrobial activities [24]. The unique scaffold and pharmacological properties associated with quinazoline nucleus attracted the attention of chemists toward the syntheses of various types of useful compounds in medicinal chemistry. It possesses wide variety of activities like antibacterials [25], antivirals [26,27], antitumours [28], and many other therapeutic activities [29]. Additionally fused indole derivatives such as indolocarbazoles [30,31], indolosiquinolines [32–34], indoloquinolines [35–38], and indoloquinoxalines [39–41] exhibit a number of remarkable pharmacological properties. Among them, isoindolo[2,1-a]quinazoline showed high cytotoxic activity against a wide range of human cancer cells and at the molecular level are inhibitors of tubulin polymerase and topoisomerase I. This confirms the prospects of using them as anticancer drugs [42,43] and TNF-\(\alpha\) inhibition against various inflammatory disorders [44]. Recently the syntheses of these derivatives are reported using camphor sulfonic acid; \(p\)-toluenesulfonic acid and Montmorillonite K10 as the heterogeneous catalyst by conventional method with longer reaction time [44].

Ultrasound irradiation is a powerful technique, which is being used frequently to accelerate organic transformations [45–48]. It is one of the most widely used laboratory methods for the disruption of cells of baker's yeast for the fast release of enzymes [49].

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1381-1177/5 – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molcatb.2013.01.024
1-Methylimidazolium trifluoroacetate [Hmim]Tfa: Mild and efficient Brønsted acidic ionic liquid for Hantzsch reaction under microwave irradiation

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MS received 25 February 2012; revised 17 April 2012; accepted 30 April 2012

Abstract. One pot synthesis of 1,4-dihydropyridine derivatives was achieved via condensation of various β-ketoesters with aromatic/aliphatic aldehydes and ammonium acetate. The reaction was catalysed by a stable and reusable Brønsted acidic ionic liquid (IL), 1-methyl-imidazolium trifluoroacetate ([Hmim]Tfa), under microwave (MW) irradiation. The synergistic combination of MW with IL can potentially go a long way to meet the increasing demand for chemical processes. This homogeneous catalytic procedure is simple and efficient. The catalyst can be reused at least four times with almost complete retention in its activity.

Keywords. 1,4-Dihydropyridine; Hantzsch synthesis; [Hmim]Tfa; homogeneous catalyst; microwave; multicomponent reaction.

1. Introduction

Current conventional methods of organic synthesis are orders of magnitude too slow to satisfy the ever-increasing demand for generation of organic compounds.1 The efficiency of microwave (MW) heating has resulted in remarkable reductions in reaction times (from days and hours to minutes and seconds). The time saved by using a MW heating approach is potentially important in traditional organic chemistry and assembly of heterocyclic systems.2 Not surprisingly, these features have also recently attracted interest of the drug discovery field and medicinal chemistry communities.3

In recent years, ionic liquids (ILs) have attracted immense interest and been successfully used in a variety of catalytic reactions as dual solvents–catalysts4 due to their relatively low viscosities, low vapour pressure, and high thermal and chemical stability.5 Brønsted acidic ionic liquids consist of desired characteristics of solid acids and mineral liquid acids and are designed to replace customary mineral acids like HCl, H2SO4 and HNO3.6

Heterocyclic rings containing nitrogen atoms are abundant in nature and of great importance to life because their structural subunit exists in many bioactive nuclei.7 1,4-DHPs represent an important class of biologically active molecules, several of which have found use in the treatment of cardiovascular disease.8,9 1,4-DHPs are analogues of NADH coenzymes10,11 and an important class of drugs which are potent blockers of calcium (Ca2+) currents.12 Hence, the development of new methods that lead to multisubstituted 1,4-DHPs via an efficient and convenient procedure are of great interest for pharmaceutical researchers.

More than a century ago, Hantzsch13 developed an efficient method for the synthesis of 1,4-DHPs. The classical method involves a one-pot condensation of an aldehyde with β-ketoesters and ammonia reflux in either in acetic acid or in alcohol for a longer time.14 Up till now, numerous literature exist describing various attempts to improve the Hantzsch reaction using alternative catalyst and greener methods.15–24 Almost all of the new methodologies of organic reactions have attempted to maximize reaction conversion and minimize reaction time. We have already demonstrated the efficient role of ionic liquids as dual solvent–catalysts in Biginelli reaction.25,26 In the present study, we report 1-methyl-imidazolium trifluoroacetate ([Hmim]Tfa) as an effective and reusable catalyst for Hantzsch pyridine synthesis (scheme 1).