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## ORIGINAL ARTICLE

# An efficient one-pot multi component synthesis of polyhydroquinoline derivatives through Hantzsch reaction catalysed by Gadolinium triflate

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## KEYWORDS

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1,4-Dihydropyridine;  
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**Abstract** Gadolinium(III) trifluoromethanesulfonate (Gadolinium triflate)  $Gd(OTf)_3$  catalysed efficient Hantzsch reaction via four-component coupling reactions of aldehydes, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), ethyl acetoacetate and ammonium acetate at ambient temperature was described as the preparation of polyhydroquinoline derivatives. The process presented here is operationally simple, environmentally benign and has excellent yield. Furthermore, the catalyst can be recovered conveniently and reused efficiently.

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## 1. Introduction

Multi component reactions (Domling and Ugi, 2000; Ugi, 2001, 2003; Zhu, 2003; Domling, 2006) allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity (Burke and Schreiber, 2004). They also have considerable advantages in terms of user and environmental friendliness because of the step reduction and atom economy associated to their use.

4-Substituted 1,4-dihydropyridines (DHPs) comprise a large family of medicinally important compounds. In recent

years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridine compounds owing to their significant biological activity (Di Stilo et al., 1998; Kawase et al., 2002; Suarez et al., 2003). In particular, dihydropyridine drugs such as nifedipine, nicardipine, amlodipine (Fig. 1) and others are effective cardiovascular agents for the treatment of hypertension (Buhler and Kiowski, 1987; Reid et al., 1985). 4-Aryl-1,4-dihydropyridines are analogues of NADH coenzymes, which have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and hepta-protective agents (Godfraid et al., 1986; Sausins and Duburs, 1988; Mager et al., 1992; Mannhold et al., 1992). Quinolines having 1,4-dihydropyridine nucleus are very important compounds because of their pharmacological properties. Members of this family are being used as antimalarial, anti-inflammatory, anti-asthmatic, antibacterial and tyrosine kinase inhibiting agents (Chen et al., 2001; Roma et al., 2000).

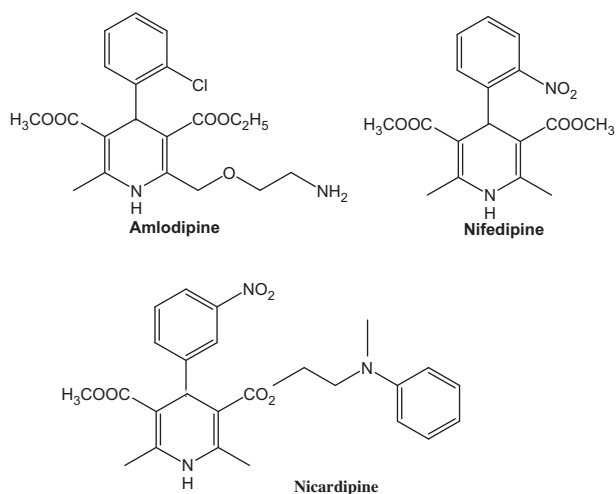
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**Figure 1** Dihydropyridine drugs.

Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives. The classical methods involve the three-component condensation of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol (Hantzsch and Liebig, 1882; Loev and Snader, 1965).

In recent years, several new efficient methods have been developed including the use of MCM-41 (Nagarapu et al., 2007), microwave (Tu et al., 2001), TMS iodide (Sabitha et al., 2003), ionic liquid (Ji et al., 2004), autoclave (Watanabe et al., 1983), fluoroboric acid (Chen et al., 2007),  $K_7[PW_{11}CoO_{40}]$  (Heravi et al., 2007), metal triflates (Wang et al., 2005; Donelson et al., 2006), molecular iodine (Ko et al., 2005), silica-supported acids (Maheswara et al., 2006; Gupta et al., 2007), ceric ammonium nitrate (Ko and Yao, 2006; Reddy and Raghu, 2008), PTSA-SDS (Kumar and Maurya, 2008), tris(pentafluorophenyl)borane (Chandrasekhar et al., 2008), boronic acids (Sridhar and Perumal, 2005; Debache et al., 2008), grinding (Kumar et al., 2008), organo-catalyst (Kumar and Maurya, 2007; Baghbanian et al., 2010) and Hafnium(IV)bis(perfluorooctanesulfonyl) imide complex (Hong et al., 2010). These methods, however, suffer from drawbacks such as unsatisfactory yields, acidic or basic catalysts, extended reaction times, elevated temperatures, tedious work-up, anhydrous organic solvents and the use of stoichiometric and/or relatively expensive reagents. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of 1,4-DHPs and polyhydroquinolines in terms of operational simplicity, reusability, economic viability, and greater selectivity.

Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are quite stable in water and reusable, as well as highly effective for the activation of nitrogen containing compounds. Therefore, lanthanide triflates are unique catalysts compared to conventional Lewis acids in several carbon-carbon bond forming reactions and have found a wide application in organic synthesis (Green and Wuts, 1999). In addition, these metal triflates can be used either in aqueous or in non-aqueous media and the reactions can be conveniently carried out under mild conditions and do not require anhydrous conditions or an inert atmosphere.

In 1994 Kobayashi and Hachiya (1994) used Gadolinium triflate as a water-tolerant Lewis acid in the aldol reactions of silyl enol ethers with aldehydes in aqueous media. Gadolinium triflate has been used extensively as Lewis acid catalyst in acetylation of alcohols and amines (Alleti et al., 2005), alkylation of pyrroles (Unaleroglu and Yazici, 2007), Michael additions (Alleti et al., 2008) and acetylation of alcohols and phenols (Yoon et al., 2008).

Gadolinium triflate has several advantages over other Lewis acids, it is stable in water and therefore does not decompose under aqueous work-up conditions, unlike other conventional Lewis acids. Thus, recyclization of the Gadolinium triflate is often possible and renders the procedure relatively environmentally acceptable by utilizing these properties; this catalyst has been successfully applied to several synthetic reactions. However, there is no report on the use of Gadolinium triflate for the synthesis of polyhydroquinoline derivatives.

In continuation of our interest towards the development of new routes to the synthesis of heterocyclic compounds, such as 3,4-dihydropyrimidin-2(1H)-ones/-thiones/imines (Mansoor et al., 2011),  $\beta$ -amino ketone compounds (Mansoor et al., 2012a), amidoalkyl naphthols (Mansoor et al., 2012b) and 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives (Mansoor et al., 2012c) by multi-component reactions, we turned our attention towards the one-pot synthesis of polyhydroquinoline derivatives through Hantzsch a four component coupling reaction of aldehyde, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of a reusable Gadolinium triflate catalyst at room temperature. In this paper, we wish to highlight our finding about the  $Gd(OTf)_3$  catalysed four-component Hantzsch reaction using ethanol as a solvent at ambient temperature.

## 2. Experimental

### 2.1. Methods and apparatus

All reactions were performed at room temperature. All chemicals were purchased from Aldrich Chemical Co. and solvents were used without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed by UV light. Melting points were determined with Shimadzu DS-50 thermal analyser.  $^1H$  NMR spectra were recorded at Bruker AM 300 (300 MHz) in  $CDCl_3$  using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a Saturn 2000GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyser flowchart.

### 2.2. General experimental procedure for the synthesis of polyhydroquinolines

Aldehyde (2 mmol), dimedone (2 mmol), ammonium acetate (2 mmol), ethyl acetoacetate (2 mmol) and  $Gd(OTf)_3$  (5 mol%) in ethanol (5 mL) were successively charged into a 50 mL round bottomed flask, equipped with a magnetic stirrer. Then the reaction mixture proceeded at room temperature for about 5–6 h and a solid product was gradually formed. After completion of reaction as indicated by thin

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