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ORIGINAL ARTICLE

One pot four component sequential synthesis of hexahydroquinoline derivatives in aqueous media via enaminone intermediates: A green protocol

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Abstract A convenient green chemistry method through one pot four component tandem synthesis of hexahydroquinoline via enaminone intermediate using dimedone, ammonium acetate, aryl aldehydes and malononitrile has been described in aqueous media without the use of any external catalyst. The excess of ammonium acetate used acts as a reagent as well as catalyst. The incorporation of water as solvent along with eradication of external catalyst renders the protocol to comply with the green chemistry aspects. Shorter reaction time, high atom economy, easy work up and purification of products by non-chromatographic method are the crucial features of this methodology. The crystal structure of hexahydroquinoline basically shaped by chromatographic free selective reaction was determined by single crystal X-ray diffraction analysis.

1. Introduction

MCRs with their requisition of substantially simpler method and operations as compared to the conventional multistep methods of heterocycle synthesis have gained enormous interest in diversity oriented synthesis in organic, medicinal and combinatorial chemistry [3,32]. Furthermore, the MCR tactics are determined to be economical owing to their reduction in steps thereby saving synthetic time, efforts and sustained expensive purification process besides the protection and deprotections [6,30]. Recently, MCRs have become an governing tool for atom efficient and waste free synthesis of complex building blocks of 'drug-like' motifs [13,14]. MCRs are tandem reactions which offer an influential approach for molecular complexity from simple preliminary materials. These reactions prevent the fall of overall steps by avoiding isolations of extremely reactive intermediates [4,10].

In recent days, aqueous mediated reactions have captured a considerable attention in organic synthesis as a result of both economic and environmental safety reasons. The consistent persuasion water as solvent for organic reaction arises due to

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its abundance, economical nature, high polarity, high reactivity, typical selectivity and existence of strong hydrogen bonding also supplemented by convenient work up and purification carried out by simple filtration or extraction [13,14,28]. In addition to this large surface tension, high specific heat capacity and the high cohesive energy, salting in or salting out effect, variation of pH and chemo enzymatic strategies are some of the unique properties of water that can significantly impact the conversions performed in this media. In particular, reactions with negative activation volume are reported to occur faster in water than in organic solvents [7,24].

Breslow, in 1980 rediscovered the use of water as solvent in organic reaction which proved that hydrophobic effects might strongly increase the rate of organic reaction [1]. Consequently the use of water as an environmentally benign solvent for chemical transformation has developed into the demand of the present day researchers.

Quinoline and their derivatives performing as a core unit in several natural products and drugs attributing to their diverse applications in the pharmaceutical industries uphold a remarkable place among the heterocyclic compounds [12]. Quinolines having 1,4-DHP nucleus have been reported as significant compounds due to their therapeutic and pharmacological properties such as vasodilator, antitumor, bronchodilator, geroprotective, antimalarial, anti-inflammatory, antiasthematic, and antibacterial activities [17,29].

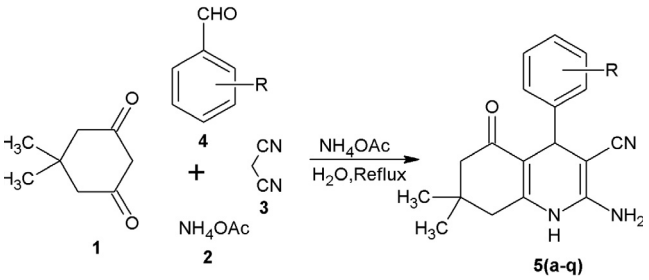
In particular, now days 1, 4-DHP nucleus containing drugs nimodipine, lacidipine posses improved calcium channel antagonist activity [18,21] (Fig. 1) and the cardiovascular agents such as nifedipine, nicardipine, and amlodipine are effective against treatment of hypertension [16].

Hantzsch and Liebigs reported the synthesis of 1,4-dihyropyridine by traditional method which involved cyclocondensation of aldehyde with ethyl acetoacetate and ammonia reflux in alcohol or in acetic acid for a prolonged time [8].

A brief review on the literature reveals that the synthesis of quinoline derivatives can be achieved by using organocatalysts [15], CAN [25], ionic liquids [11], $Sc(OTf)_3$ [5], iodotrimethylsilane (ITMS) [26], microwave irradiation [19,28,31], $Yb(OTf)_3$ [33], L-proline [9], $Bi(NO_3)_3{\cdot}5H_2O$ [20] etc.

Nevertheless, most of the reported methods still suffer from several drawbacks, such as the long reaction time, unsatisfactory yields, drastic reaction condition, use of organic solvents as well as expensive catalysts and tedious work up procedures. Hence there emerges a through need to develop an ecological and efficient methodology for the synthesis of hexahydroquinoline derivatives.

In prolongation of our efforts for the development of synthetic methodologies for the synthesis of heterocyclic compounds [23], we report herein an eco-friendly, expedient, atom economic and highly efficient protocol for the tandem synthesis of hexahydroquinoline derivatives via four component condensation of dimedone, aryl aldehydes, malononitrile and excess of ammonium acetate as a reagent and neutral catalyst in aqueous media (Scheme 1).



Scheme 1 Synthesis of hexahydroquinoline derivatives from tandem reaction.

2. Experimental

2.1. General

All reagents were purchased from Thomas Baker and S.D. fine chemicals. Melting points were measured by a Labstar melting apparatus and were uncorrected. Monitoring the progress of all reactions was carried out by the thin layer chromatography (TLC). Infrared spectra were recorded on a Perkin-Elmer, FTIR-1600 spectrophotometer in KBr with absorption in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were determined on a Bruker Avance (300 and 75 MHz) spectrometer as DMSO-d_6 solutions, using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are expressed in ppm and Coupling constants J are given in Hz. Mass spectra were recorded on a Performa spectrometer.

2.2. X-ray structure analysis

X-ray diffraction data of compound **5m** was collected at $T = 298$ K on a Bruker APEXII CCD diffractometer with graphite monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. Table 4 shows the unit cell parameters and other crystallographic details. The determination of cell refinement and data reduction were performed with program SAINT [2]. The structure was solved using direct methods of program SHELXS97 and refined anisotropically by full-matrix least-square on F^2 carried out with the program SHELXL97 [27].

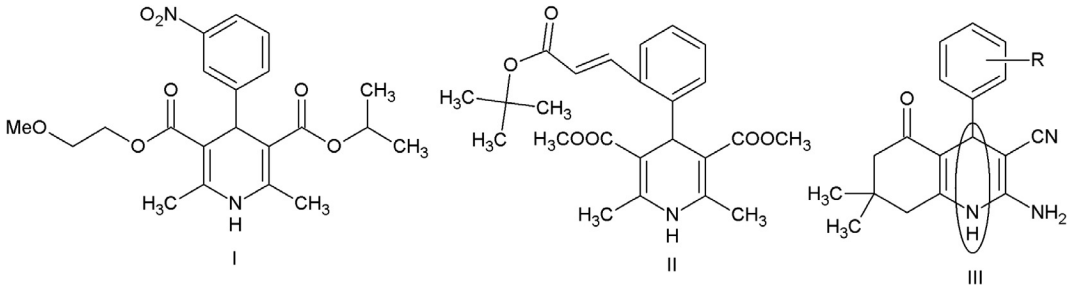


Figure 1 Nimodipine (I), Lucidipine (II) and Hexahydroquinoline (III) containing 1, 4-DHP Nucleus.