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Five-component synthesis of dihydropyridines based on diketene

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ABSTRACT

A novel five-component strategy involving commercially available diketene, primary amines, malononitrile and various benzaldehydes for the synthesis of densely functionalized 1,4-dihydropyridines in good yields was achieved. The reaction pathway involves a sequential ring-opening of diketene/enamine formation/Knoevenagel-condensation/Michael addition and 6-*exo*-*tet* cyclization, resulting in multiple bond-formation events including two C–C and three C–N bonds ultimately leading to the formation of the respective 1,4-dihydropyridines.

1. Introduction

The 1,4-dihydropyridine (1,4-DHP) skeleton is one of the most versatile heterocyclic pharmacophores since it has been found as the central fragment in many clinical pharmaceuticals.[1] The most notable examples are the series of 1,4-DHP-based calcium channel blocker drugs such as nifedipine, felodipine, and nicardipine (Fig. 1), which are still widely prescribed for the treatment of hypertension and related cardiovascular diseases.[1,2] In addition, the results obtained from a study with 1,4-DHPs as an α_{1a}adrenoceptor-selective antagonist discloses their promising potential in treating benign prostatic hyperplasia.[3] Furthermore, in recent years, 1,4-DHPs were reported exhibiting miscellaneous new pharmacological functions. Radioprotection agents, cerebral anti-ischemic agents, platelet antiaggregatory agents, neuroprotective compounds, as well as HIV protease inhibitor have the dihydropyridine moiety in their complex structures.[4] Moreover, in terms of synthetic organic chemistry, their high reactivity has endowed the 1,4-DHPs with widespread applications in the synthesis of other useful chemicals.[5]

Multicomponent reactions (MCRs) represent one of the most powerful strategies in modern organic synthesis. Compared to the traditional multistep methods of heterocycle synthesis, MCRs require substantially simpler materials and operations, while providing significantly higher efficiency and molecular complexity. Most importantly, the large compound libraries available via MCRs perfectly cater to the requirement of high throughput screening in modern drug discovery.[6] The most classical synthesis of symmetrical 1,4-DHPs is the three-component condensation of aryl aldehydes, ammonia, or amines and 2 equiv of β-keto esters, which was reported in 1882 by Hantzsch.[7] Despite the long history, sustained interests in more advanced synthetic approaches to 1,4-DHPs has been triggered by the prolific pharmacological properties imbedded in 1,4-DHPs.[8,9]

The symmetrical DHP unit, although present in many commercial drugs, is not a requirement of receptors but the consequence of the Hantzsch synthetic methodology. Actually, unsymmetrical 1,4-DHPs also represent effective drug moieties (Felodipine, for example) or sometimes display even better pharmacological activities.[10] Therefore, the synthesis of unsymmetrical 1,4-DHPs justifies equal importance as for the symmetrical 1,4-DHPs in terms of drug discovery. However, the nature of the Hantzsch reaction employing two identical β-ketoesters predetermines the symmetrical structure of the products. The use of different β-ketoesters or analogues to prepare unsymmetrical 1,4-DHPs suffers from the intervention of side reactions due to homo-condensations.[11] To the best of our knowledge, few alternative strategies in unsymmetrical 1,4-DHP syntheses are currently available in the literature.[12] Thus, in terms of designing and screening new lead compounds, searching for new and facile MCRs

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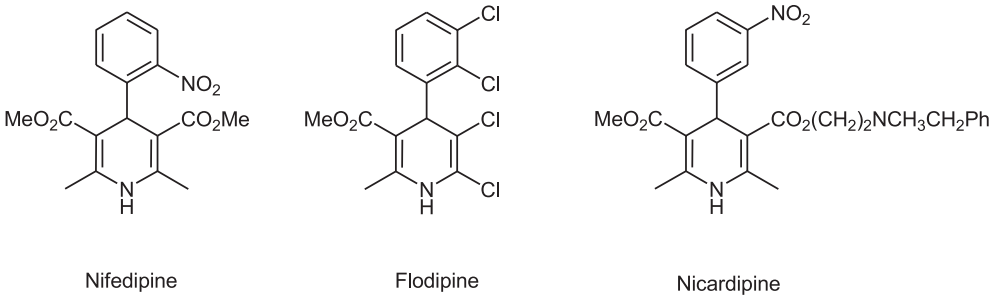


Fig. 1. Some biologically important 1,4-dihydropyridines.

to prepare 1,4-DHPs with new functional substituents is highly desirable work.

In general, despite extensive interest towards MCRs, there only a few reports concerning beyond four–component reactions, and in spite of intense interest towards the synthesis of 1,4-DHPs, a literature survey showed no reports concerning their synthesis via five-component reactions.[13]

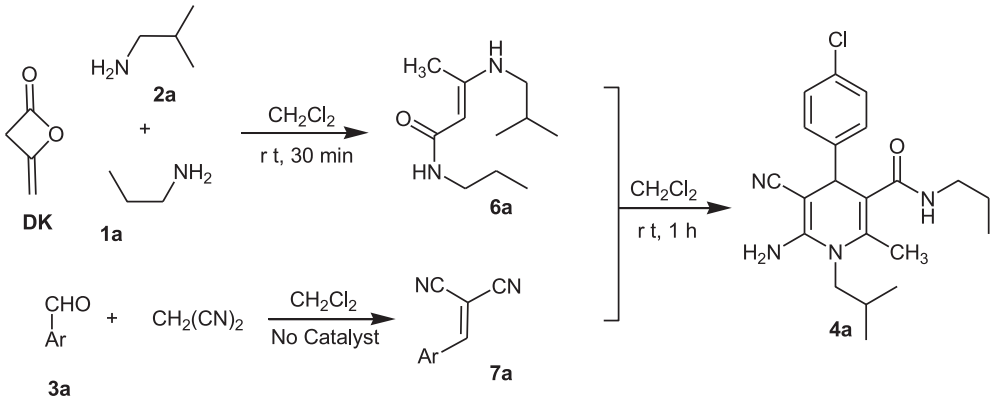
Our group has been engaged in recent years in developing new MCRs to synthesize novel functional heterocyclic compounds.[14,15] In this context, We have reported the synthesis of dihydropyridines,[16,15a] and aromatized them to the corresponding pyridines either chemically[17] or by electrochemical reactions.[18] We also revealed the utility of ketenes[19] and very recently we have disclosed the applications of diketene as a privileged synthon in the synthesis of heterocyclic compounds.[20] Armed with these experiences, the vast biological importance of 1,4-DHPs inspired us to design a practical and efficient multicomponent domino protocol for the preparation of novel multisubstituted unsymmetrical 1,4-DHPs, based on diketene, involving primary amines, malononitrile and benzaldehyde.

2. Results and discussion

Several years ago, we demonstrated that diketene (DK) is an emerging, reactive substrate by which a variety of important targets can be obtained under easier and more efficient methodologies.[21] Diketene has been found as a privileged synthon in the syntheses of several heterocyclic systems, owing to its high chemical activity towards nucleophiles.[22] DK is an important and common industrial intermediate and its derivatives have a wide variety of applications, including the manufacture of agrochemicals, dyes, pigments, pharmaceuticals (including vitamins), and stabilizers for PVC and polyester. Significantly, DK has both electrophilic (E) and nucleophilic (Nu) sites which undergo typical reactions with numerous substrates and to afford functionalized heterocycles.[23] Several heterocycles could be synthesized upon reaction of bifunctional nucleophiles with DK. Using DK as a starting material, five-, six- and seven-membered heterocycles may be synthesized efficiently *via* a variety of MCRs. DK has also been used in the total syntheses of natural products and multi-step syntheses of some complex molecules in a key step.[24,25] On the basis of these experiences, we decided to perform the reaction of a β-enamino ketone prepared from diketene and primary amines with the Knoevenagel adduct generated in situ from malononitrile and benzaldehyde, to evaluate the construction of useful 1,4-DHPs under mild reaction conditions.

Our study began with the simultaneous use of diketene, propylamine **1a** and isobutylamine **2a** in CH_2Cl_2 at room temperature (Scheme 1). Thus, in a pilot reaction, propylamine **1a** (1 mmol), and diketene (1 mmol) at room temperature were combined (for 15 min). Then 1 mmol of isobutylamine **2a** was added to it. After the formation of β-enamino ketone **6a**, malononitrile (1 mmol) and 4-chlorobenzaldehyde (1 mmol) were introduced and the reaction proceeds smoothly at room temperature until completion (monitored by TLC). After 1 h the reaction was completed (TLC) and the 1,4-DHP **4a** was isolated in 82% yield (entry 1, Table 1). To improve the yields, we examined this reaction using different solvents. However, the screened candidates did not display the expected improvements. EtOH, MeCN, or a mixture of EtOH-CH_2Cl_2 showed no superiority to CH_2Cl_2 (Table 1).

To validate the generality of this new synthetic protocol, a variety of benzaldehydes and aliphatic amines have been subjected to the reaction under the same conditions (Table 2), without using any catalyst, and the 1,4-DHPs **4** were obtained in excellent yields. A limitation of the reaction is that complex mixtures of products were observed when sterically hindered aliphatic amines (such as *t*-



Scheme 1. One-pot procedure for the synthesis of **4a**.