



Synthesis of polysubstituted 1,4-dihydropyridines via three-component reaction



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ABSTRACT

An efficient one-pot synthesis of novel *N*-substituted 1,4-dihydropyridine derivatives via a three-component reaction of primary amines, dialkyl acetylenedicarboxylates, and methyl (arylmethylidene) pyruvates has been reported. The reaction is performed using ZnCl₂ (40 mol %) in dichloroethane in good to high yields through a domino Michael/cyclization sequence. Notably, the ready availability of the starting materials, high bond-forming efficiency, good to high yields and the high level of practicability of the reaction and work up make this approach an attractive complementary method for access to *N*-substituted 1,4-dihydropyridines.

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1. Introduction

The design and efficient synthesis of bioactive compounds is one of the main objectives of organic and medicinal chemistry. In recent years, multicomponent reactions have become important tools in the preparation of structurally diverse chemical libraries of drug-like polyfunctional compounds.¹ However, to ensure sufficient molecular diversity and complexity, there is a continuous need for novel reactions with high efficiency and selectivity.² Development of more efficient synthetic methods in order to assemble diverse molecules with minimal by-products, in a highly efficient and atom-economical manner attracted a great deal of attention from chemists around the world.² To this day 4-aryl-1,4-dihydropyridine-3,5-dicarboxylic esters of the nifedipine type (**1**) are one of the most widely used and studied medications among calcium-channel blockers.³ Furthermore, they are also used as cognition enhancers, neuro-protectants, and platelet antiaggregatory agents.⁴ Additionally a number of 1,4-DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure.⁵ For example, **2** is suitable in treatment of multidrug resistance,⁶ SNAP⁵⁰⁸⁹

3 could reduce hyperplasia,⁷ and DHPs **4**, and **5** have antimicrobial activity⁸ and antitubercular activity,⁹ respectively (Fig. 1).

It is shown that the existence of ester groups in the structure of DHP and their positions has an important role in its antihypertensive activity.^{3d–f} So far, many protocols for the synthesis of DHPs have been reported.¹⁰ As a part of our current studies on the development of new routes in heterocyclic synthesis via novel one-pot MCRs,¹¹ we report here for the first time a novel three-component reaction of methyl (arylmethylidene) pyruvates **6**, primary amines **7**, and dialkyl acetylenedicarboxylates **8** in the presence of zinc chloride (40 mol %) for the synthesis of polyfunctionalized 1,4-dihydropyridines (Scheme 1).

2. Results and discussion

Recently, we have focused our research and development efforts on the preparation of new compound libraries containing biologically active heterocyclic skeletons. In this way, methyl (arylmethylidene) pyruvates (**6**) have been used as suitable starting materials. They play an important role as an attractive starting material for the following reasons: (a) they have higher reactivities in comparison to usual β,γ -unsaturated α -ketones; (b) they contain active functional groups, which can be used for further synthesis; and (c) their preparation is easy, i.e., they can be synthesized

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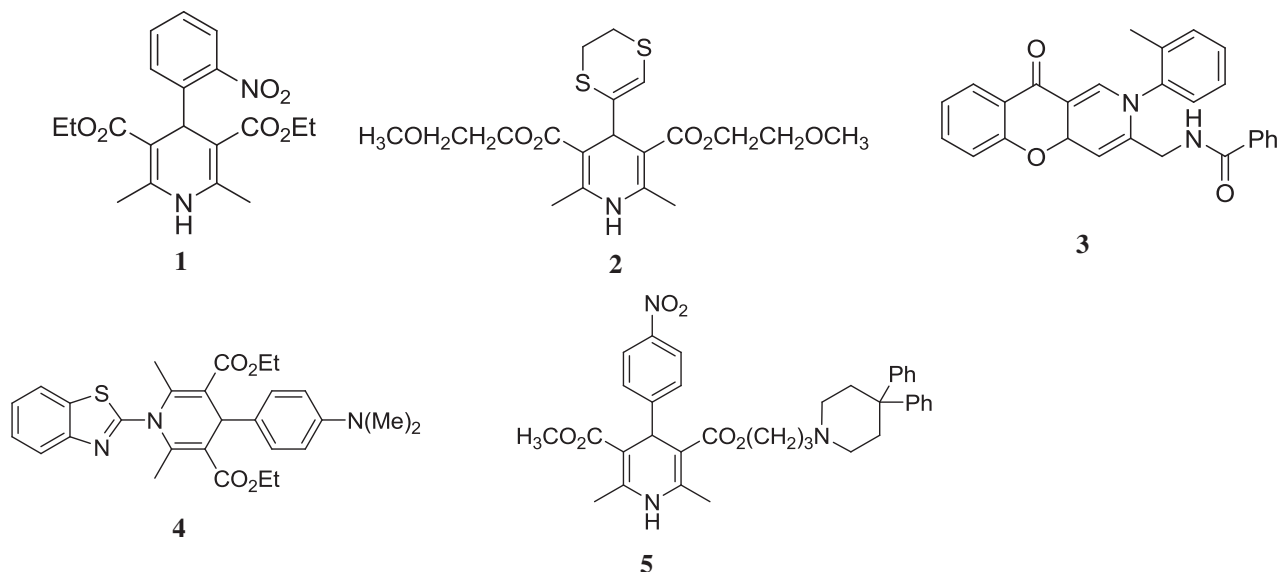
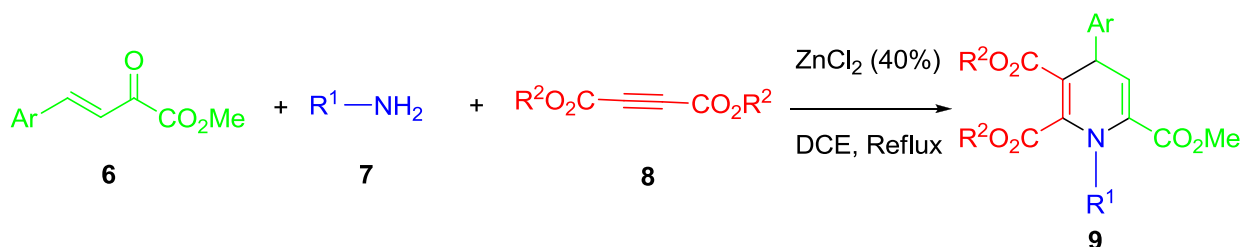


Fig. 1. Bioactive compounds with dihydropyridine core structure.



Scheme 1. Synthesis of *N*-substituted 1,4-dihydropyridines via three-component reaction in the presence of ZnCl_2 .

according to the known procedure by reaction of aromatic aldehydes and pyruvic acid in an aqueous MeOH solution of KOH.¹²

Typically, the addition of amines to dialkyl acetylenedicarboxylate has been extensively studied and the desired DMAD-primary amine adducts (enaminone) as a mixture of *E* and *Z* isomers have been used as efficient starting materials for the synthesis of heterocyclic skeletons.¹³

We began our investigation with methyl (phenylmethylidene) pyruvate **6a**, which was synthesized according to the reported procedure.¹² The reaction of **6a** with benzylamine and dimethyl acetylenedicarboxylate was selected as the model reaction. Heating of the mixture in toluene for 72 h did not provide our goal and a mixture of *E* and *Z* of enaminones was obtained. After this failure, we tried various Lewis acids, such as ZrO_2 , ZrCl_4 , CuI, but the desired product was not formed. We only got satisfactory results with ZnCl_2 and FeCl_3 . The best result was obtained with ZnCl_2 . According to this result, ZnCl_2 was selected as the best Lewis acid for the synthesis of desired *N*-substituted 1,4-dihydropyridine **9a**. Then the amount of this Lewis acid was examined in the model reaction. The reaction was checked without the presence of ZnCl_2 and FeCl_3 as Lewis acids, and we did not get any product. In the presence of 20, 30, and 40% of ZnCl_2 , the yield of **9a** was obtained 38, 47, and 61%, respectively. This confirmed the important role of ZnCl_2 in this reaction. The optimum reaction condition used of 40% ZnCl_2 and boiling toluene as reaction medium (Table 1).

The amount of reactants was further optimized and, finally, the best ratio of **6a**, **7a**, and **8a** (1.3:1.3:1) was selected. In an attempt to investigate the range of solvents compatible with this reaction, methyl (phenylmethylidene) pyruvate **6a** and enaminone from reaction of benzylamine and dimethyl acetylenedicarboxylate in the

Table 1

The effect of the amount of different Lewis acids on the synthesis of *N*-substituted 1,4-dihydropyridine **9a**

Lewis acid	(mol %)	Yield ^a [%]
CuI	20	—
ZrO_2	20	—
ZrCl_4	20	—
CuBr_2	20	30
$\text{Zn}(\text{OAc})_2$	20	—
FeCl_3	20	50
ZnCl_2	20	38
ZnCl_2	30	47
ZnCl_2	40	61

^a Yield of isolated product.

presence of 40% ZnCl_2 were chosen for a model system, and this reaction was performed in various solvents. A change in the solvent to trifluoroethanol, ethanol, acetonitrile, toluene, 1,4-dioxane, THF, and dichloroethane gave the desired *N*-substituted 1,4-dihydropyridine **9a** in 8–68% yield. The results summarized in Table 2. The best yield for reaction model was obtained in dichloroethane.

After finding suitable conditions, the three-component reaction of methyl (arylmethylidene) pyruvates, dialkyl acetylenedicarboxylates, and also different primary amines for the synthesis of 1,4-dihydropyridines **9a–n** were studied. The results summarized in Table 3. The scope of the reaction with regard to a substitution pattern in primary amines was investigated. Some aniline derivatives were used as primary amines and the best result was obtained with 4-methoxyaniline (**9e**, 84%). Our investigation showed that the existence of substituents on the aromatic ring in

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