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# An expedient synthesis strategy to the 1,4-dihydropyridines and pyrido[1,2-a]quinoxalines: iodine catalyzed one-pot four-component domino reactions

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ABSTRACT

Another aspect concerning enaminone chemistry leading to the one-pot synthesis of functionalized novel 1,4-dihydropyridines and pyrido[1,2-*a*]quinoxalines has been described. By highly efficient, one-pot, iodine-catalyzed four-component reactions, combining one set of enamine intermediates and arylidene pyruvic acid (APA) in two procedures, heterocyclic skeletal diversity can be achieved. The synthesis involves reaction of the intermediates formed by the 1:1 interaction between primary amines (or *o*-phenylenediamine) and dialkyl acetylenedicarboxylate with pyruvic acid and benzaldehyde through an iodine-catalyzed Knoevenagel/Michael/cyclization sequence. The reaction is particularly attractive due to the following advantages: atom economy, optimum convergence, high bond-forming efficiency, and avoidance of tedious workup and purification of products. Significantly, the presence of an acidic group at the 9-position on the products make these compounds excellent precursors for further synthetic modifications to meet the need for diverse chemical inputs.



## 1. Introduction

1,4-Dihydropyridines (1,4-DHPs) present ubiquitous structural motifs, which are frequently found in natural products and in compounds for the pharmaceutical, agrochemical, and other chemical industries.[1,2] 1,4-DHPs are a very important class of heterocyclic compounds due to a variety of biological activities[3] such as antihypertensive,[4] antianginal,[4,5] *anti*-inflammatory,[6,7] antitubercular,[8] analgesic,[9] antithrombotic,[10,11] vasodilation,[12] anticonvulsant,[13] stress protective effect,[14] and cardio depressant activity.[15] It is shown that the presence of ester groups in the structure of 1,4-DHPs and their positions of substitution has an important role in antihypertensive activity.[4,16] Researchers have long been fascinated by the biological activity of 1,4-dihydropyridines (**I**), tacrine (**II**) and their derivatives (Fig. 1). Initially, these compounds were found to be calcium channel modulators, and were developed as cardiovascular and antihypertensive drugs, which include felodipine, amlodipine, nifedipine (**III**) and nicardipine.[17]

Quinoxalines belong to a class of excellent heterocyclic scaffolds owing to their wide biological properties and diverse therapeutic applications in medicinal research. Recent updates showed that the chemistry of quinoxaline has attracted considerable attention[18] due to its diverse chemical reactivities,[19–21] application in materials science[22,23] and wide spectrum of biological activities.[24,25] The quinoxaline motif is known to represent a class of medicinally important compounds which are effective as antibacterial,[18] antifungal,[22] anticancer,[25] antitumor,[26] antiamoebic,[27] antiepileptic,[28] anticonvulsant,[29] antitubercular,[30] antiproliferative,[31] *anti*-HCV[32] and *anti*-inflammatory[33] agents among others. Compounds with quinoxaline cores are used as allosteric dual Akt1 and Akt2 inhibitors, human cytomegalovirus polymerase inhibitors[34] SRPK-1 inhibitors[35] and monoamine oxidase A inhibitors.[36] Reports have shown recently that pyrrolo[1,2-*a*]quinoxaline derivatives are potent and selective 5-HT3 ligands.[22] Furthermore, the quinoxaline nucleus is a common substructure of many biologically and pharmacologically active compounds.[37] In view of this, some coded quinoxaline derivatives such as CNQX and YM872 (Fig. 1) have been reported as potent AMPA receptor antagonists and were projected as good candidates for neuro-pharmacological screening.[29] The known biological properties and the huge potential in drug discovery of these heterocyclic compounds necessitate the development of facile and efficient methodologies for their selective and diverse synthesis.

Multicomponent reactions (MCRs) offer a wide range of possibilities for the construction of pre-defined highly complex molecules in a single step with high atom economy, minimum time, labor, cost, and straight forward experimental procedures.[38] These

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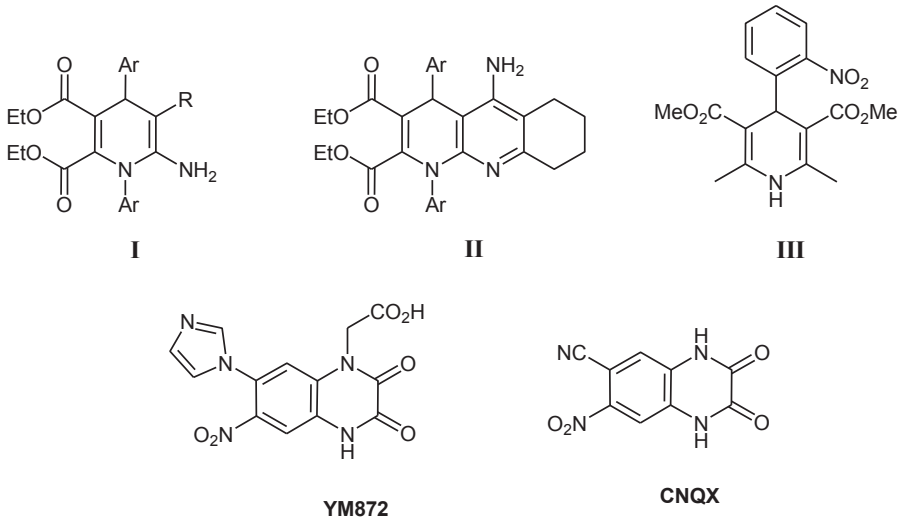



**Fig. 1.** Some biologically important 1,4-dihydropyridines and quinoxalines.

benefits are highlights for multicomponent cascade reactions, which involve in situ production of an intermediate with a strategic reactive site for subsequent transformations.[39] In the past decade, a lot of multicomponent reactions have been reported,[40] yet developing novel MCRs that meet almost all of advantages above is still in the burgeoning phase.

## 2. Results and discussion

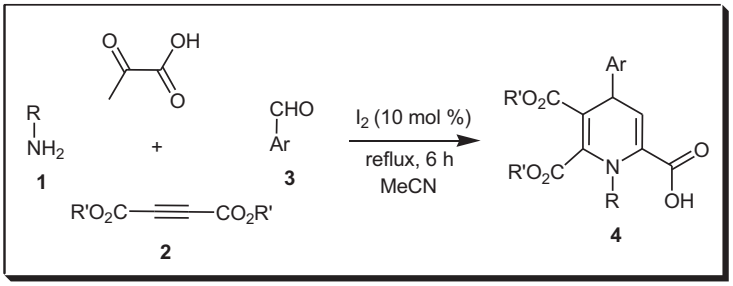
As part of our ongoing research program for the development of new environmentally benign methodologies for the synthesis of useful precursors in the field of biology, industry, and key intermediates for multistep synthesis,[41] during a previous investigation[41a] it was discovered that molecular iodine can be applied as a good catalyst for the activation of the carbonyl group of benzaldehyde.[42] Utilising this result imidazo[1,2-*a*]pyridines were successfully prepared based on the reaction of nitro ketene aminals (NKAs) and the Knoevenagel adduct from pyruvic acid and benzaldehyde in the presence of a catalytic amount of molecular iodine.

Accordingly, and in continuation of this study, it was questioned whether this Knoevenagel adduct could be trapped by the enaminone generated in situ from a primary amine and a dialkyl acetylenedicarboxylate to give a cascade reaction product. The addition of amines to dialkyl acetylenedicarboxylates has been extensively studied and the desired dialkyl acetylenedicarboxylate-primary amine adducts (enaminones) as a mixture of *E* and *Z* isomers have been used as efficient starting materials for the synthesis of heterocyclic skeletons.[43] It is believed that the two ester groups pendent to the enaminone decrease its nucleophilicity.

At first, the reaction was evaluated in a four-component manner according to the previously reported procedure.[41a] The reaction was carried out by the sequential addition of reagents: alkylamine **1**, dialkyl acetylenedicarboxylate **2**, pyruvic acid and benzaldehyde **3** in one flask under the same reaction conditions (Scheme 1). Thus, in a pilot reaction, propylamine and dimethyl acetylenedicarboxylate (DMAD) under solvent-free conditions at room temperature were combined. The resultant reaction mixture was stirred to complete the reaction as monitored by thin-layer chromatography (TLC). After the formation of enaminone (10 min), pyruvic acid and 4-chlorobenzaldehyde with catalytic amount of $I_2$ (10 mol %) were introduced and the reaction was heated at reflux in acetonitrile for 6 h. After workup, the expected 1,4-dihydropyridine **4a** was obtained in excellent yield.

Once the feasibility of the proposed pathway had been validated, the scope and robustness of this one-pot, four-component 1,4-dihydropyridine synthesis was evaluated by employing a range of the primary amines **1**, dialkyl acetylenedicarboxylates **2** and benzaldehydes **3** component (Table 1, entry 1–9). A variety of electron-poor and electron-rich aromatic aldehydes and amines were found to react very smoothly to provide the analogous 1,4-dihydropyridines **4** in satisfactory yields (85–70%) as shown in Table 1.

After this successful endeavor with the synthesis of 1,4-DHPs **4** using the enaminone intermediate and Knoevenagel adduct, our attention turned to the use of dihydroquinoxalines derived from *o*-phenylenediamine and dialkyl acetylenedicarboxylates to evaluate the formation of pyrido[1,2-*a*]quinoxalines. For this aim, initially the reaction of *o*-phenylenediamine and dimethyl acetylenedicarboxylate was performed in acetonitrile at room temperature. As expected, the reaction produced dihydroquinoxaline **5** in excellent




**Scheme 1.** Iodine-mediated 4-component reaction for the synthesis of 1,4-DHPs.