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Cyanamide: a convenient building block to synthesize 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine systems via a multicomponent reaction

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Abstract

4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine derivatives were prepared using a multicomponent reaction by reacting a mixture of arene or heteroarenecarbaldehyde, 1,3-dicarbonyl compounds, and cyanamide under acidic conditions. The novelty of this approach derives from its use of cyanamide as a building block in a four-component Biginelli-type reaction. Varying the reaction conditions led to the formation of either *N*-(2-imino-6-phenyl-1,3,5-oxadiazinan-4-ylidene) cyanamide or 3,4-dihydropyrimidin-2(1*H*)-one. The type of heterocycle skeleton synthesized depends on the nature of the acid catalyst as well as the reaction conditions employed.
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1. Introduction

In recent years, multicomponent reactions (MCRs) have emerged as a powerful strategy to construct structurally complex molecules from simple starting materials.[1] Molecules synthesized by this method continue attracting the attention of medicinal and synthetic chemists.[2] One of the most cited MCRs is the Biginelli reaction, which leads to the formation of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives using benzaldehyde, ethyl acetoacetate, and urea as starting materials.[3] This reaction has been widely extended to include variations in all of its components,[4] allowing access to a large number of multifunctionalized DHPM derivatives. For example, an interesting reaction is the four-component approach, recently reported by Orru and et al., to synthesize DHPMs that are properly functionalized at the N-3 position, providing a pool of structurally diverse compounds of biological interest.[5] Many of these derivative compounds have emerged as a class of therapeutic drugs with important pharmacological roles in medicinal chemistry, such as hexahydrotriazaacenaphthalenes (**1**),[6] SQ 32926 (**2**),[7] and HAP-1 (**3**).[8]

Although this reaction has been intensely explored, the construction of 4-aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine (aryl-CIDHPM) compounds (**4**) that are chemically analogous to the Biginelli compounds has not yet been reported. Interestingly, the above molecules possess the *N*-cyanoguanidinyl moiety in their structure, which is found in other biologically active molecules such as the potentially antimycotic agent *N*-cyanoiminopyrimidine (**5**),[9] pinacidil (**6**), a K_{ATP} channel activator[10] (Fig. 1), and other compounds containing the cyanoimino

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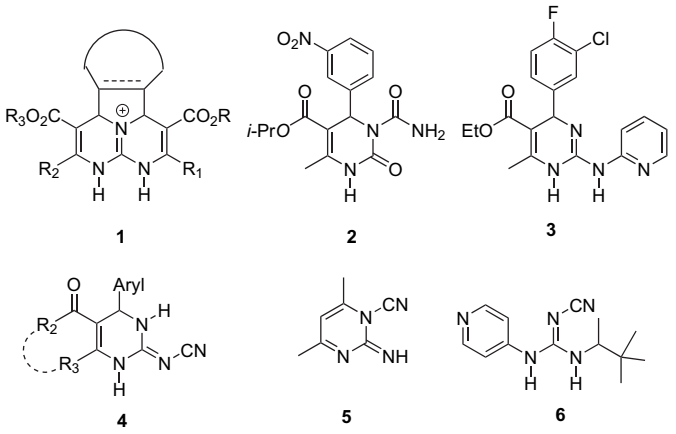
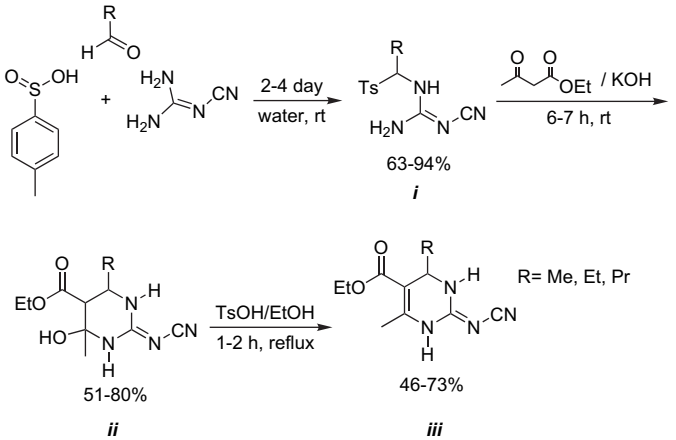


Figure 1. Biginelli-type and cyanoguanidine compounds with pharmacological activity.

functional group that have been found in pharmacologically active products.[11]

The most promising method to construct aryl-CIDHPMs is through the synthesis reported by Shutalev et al. for the obtention of 4-alkyl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidines (alkyl-CIDHPMs).[12] This approach implies the preparation of α-tosyl-substituted *N*-cyanoguanidines **i**. A subsequent reaction with potassium enolates of ethyl acetoacetate results in 5-ethoxycarbonyl-2-cyanimino-4-hydroxyhexahydropyrimidines **ii**, which yield the alkyl-CIDHPMs **iii** after dehydration under acidic conditions (Scheme 1). However, some of the drawbacks of this approach involve a relatively long synthetic pathway, lengthy reaction times, and purification steps that considerably reduce the efficiency of the reaction and overall yields of these compounds.



Scheme 1. Shutalev synthesis of alkyl-CIDHPMs.

More relevant to the present work is the novel methodology employed to synthesize aryl-CIDHPMs by a four-component Biginelli-type reaction based on replacing the cyanoguanidine with 2 equiv of cyanamide. It is worth mentioning that this protocol explored the use of cyanamide as a precursor of new urea-type building blocks to obtain structurally diverse Biginelli compounds, whereas most of the previously reported Biginelli reactions involve urea, thiourea, isourea, or guanidine as building blocks.[13] Therefore, the application of this approach to prepare aryl-CIDHPMs, its scope and limitations via systematic variation of arene or heteroarenecarbaldehyde and 1,3-diketone components, and the influence of catalyst nature in the absence or presence of solvents are reported.

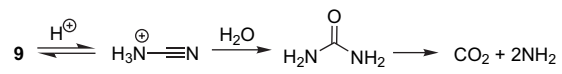
2. Results and discussion

The initial efforts to synthesize aryl-CIDHPMs were based on the preparation of *N*-arylidenecyanoguanidine, a Michael acceptor that was chemically convenient to replace α-tosyl-substituted *N*-cyanoguanidines, the key intermediate in the synthesis of alkyl-CIDHPMs. In agreement with the accepted Biginelli mechanism,[14] this species may form in situ under the Biginelli three-component reaction (B-3CR) conditions through the initial reaction of a mixture of arenecarbaldehyde and cyanoguanidine. The subsequent formation of the aryl-CIDHPMs theoretically could have been achieved by reacting the *N*-arylidenecyanoguanidine with an appropriate 1,3-dicarbonylic compound. Unfortunately, we were unable to prepare this compound using this method.

However, recently Fischer et al. reported the synthesis of 2-arylaminopyrimidine derivatives through *N*-arylguanidine. This intermediate was appropriately synthesized from a mixture of cyanamide and aryl amines under strongly acidic conditions.[15] The chemical explanation behind this process led us to attempt to form *N*-arylidenecyanoguanidine under similar conditions by replacing cyanoguanidine with 2 equiv of cyanamide in the presence of 1 equiv of arenecarbaldehyde, yielding the title compound after a subsequent reaction with a 1,3-dicarbonyl compound. The result was the development of a novel one-pot multicomponent reaction via a four-component approach to prepare aryl-CIDHPMs.

In this multicomponent approach, an exploratory reaction composed of benzaldehyde **7a**, ethyl acetoacetate **8a**, and cyanamide **9** (50% in water) were reacted in a 1:1:2 molar ratio, respectively, in the presence of concd hydrochloric acid (pH ~2) at reflux conditions (EtOH, 4 h). The desired 2-cyanoimino-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidine **10a** was obtained, although in very low yields (5%, Scheme 2, method a).

The result may be rationalized by considering the substantial formation of cyanamidium cations and its corresponding hydrolysis to urea, according to the following equation:[16]



This reaction is known to occur at pH <8.[17] Therefore, weak acidic conditions that shift the equilibrium toward the cyanamide would inhibit ureide formation and probably improve the yield.

Thus, the next catalytic system explored was a mixture of AcONa (1 equiv) and concd hydrochloric acid (in catalytic amount) at pH ~5, which substantially improved the overall yield (40%, Scheme 2, method b). Since this process implies the in situ formation of AcOH, the possibility of better yields

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