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Features of two- and multicomponent heterocyclization reactions involving 3,4-disubstituted 5-aminopyrazoles and alkyl pyruvates

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ABSTRACT

Three-component heterocyclizations of pyruvic acids and their esters with 5-aminopyrazoles and aromatic aldehydes, in addition to the sequential versions of these reactions, under different activating conditions were studied. Under conventional heating, pyrazolopyrimidine derivatives containing a hydroxyl group in the 6-position were formed in both two- and three-component treatments. Whereas the application of an inert atmosphere did not influence the outcome of these reactions, the use of ultrasonic irradiation led to the formation of 7-hydroxy-tetrahydropyrazolopyrimidines in multi-component reactions and 6-hydroxy-dihydropyrazolopyrimidines in the case of a step-by-step approach. The products of the latter treatment were further transformed into heteroaromatized 6-hydroxy-pyrazolopyrimidines by conventional heating.

1. Introduction

The reactions of pyruvic acid derivatives have been used for the synthesis of various heterocyclic compounds since the beginning of the twentieth century. Among these processes, the most thoroughly studied were those dealing with benzylidene- and acetylpyruvic acids.[1–18] A series of our previous publications was also devoted to two- and multicomponent reactions (MCRs) involving pyruvic acids and different aminoazoles, such as 5-amino-1,2,4-triazoles,[1,19–23] 5-aminotetrazole,[2,19] 5-amino-3-methylisoxazole,[24] 5-aminopyrazoles[7,8,10,25] and tuning the selectivity of these heterocyclizations.[7,10,20,25]

Interest in the mechanism and outcome of these reactions arose due to the proven biological activity of the final products[21,25,26] and their multi-vector character.[19–25] In particular, in the case of pyruvic acid heterocyclizations with different aminopyrazoles, the approach based on the application of specific catalytic systems and non-classical activation methods (microwave and ultrasonic irradiation), gave the opportunity to develop selective synthetic procedures to afford various classes of heterocyclic compounds.[7,8,10,19–25] For instance, pyrazolopyridine acids **IV** were formed when 3-aryl-5-aminopyrazole was used as a reagent in the MCRs with aromatic aldehydes **II** and pyruvic acid **III** (Scheme 1).[8] However, applying benzylidenepyruvic acid and its substituted derivatives **V** and 3-aryl-5-aminopyrazole in two-component reactions resulted in a mixture of dihydropyrazolopyrimidines **VI** and dihydopyrazolopyridines **VII** and heteroaromatic pyrazolopyridines **VIII** (Scheme 1). Application of ultrasonication in a two-component reaction yielded dihydropyrazolopyrimidines **VI** selectively (Scheme 1).[7] On the other hand, the introduction of a carboxamide substituent in the 4-position of 5-aminopyrazole led to exclusively pyrimidine acids **IX** both in two-component and three-component reactions with pyruvic acid derivatives (Scheme 1). Tetrahydropyrazolopyrimidines **X** were formed when ultrasonic irradiation was applied in a three-component reaction of 5-amino-4-ethyl-3(4′-fluorophenyl)pyrazole, pyruvic acid, and aromatic aldehydes (Scheme 1).[21]

It should be noted that using alkyl pyruvates as starting reagents in the three-component reaction with substituted aminopyrazoles **I**

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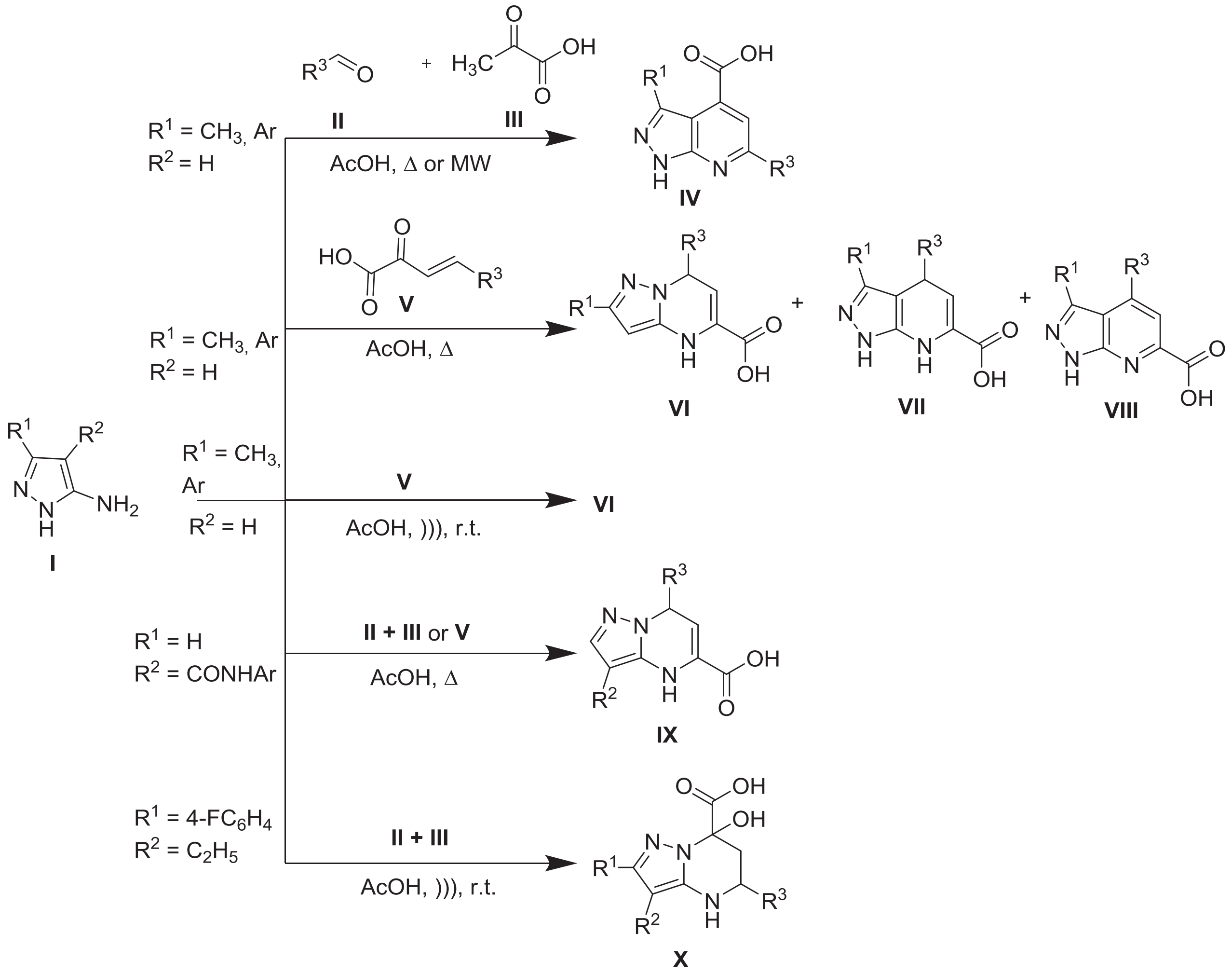

Scheme 1. Some sequential and multicomponent reactions involving pyruvic acids and different 5-aminopyrazoles.

(R^2 = H), and aldehydes led to the formation of a set of reaction products which were similar to the compounds isolated from the MCRs involving pyruvic acid with aminoazoles and aromatic aldehydes.[8,27–29]

The sequential and multicomponent reactions of aromatic anilines with pyruvic acid based β,γ-unsaturated ester or with pyruvates and aromatic aldehydes yielding 2- or 4-substituted quinolines and pyrrol-2-ones have been studied. The formation of different reaction products was described depending on whether the reaction is sequential or a multicomponent, and on specific reaction conditions.[30–32]

2. Results and discussion

The present paper is devoted to the study of some features of MCRs between 3-aryl-4-alkyl-substituted 5-aminopyrazoles, aromatic aldehydes, and alkyl pyruvates as well as of the sequential version of these treatments under conventional heating and ultrasonication.

In particular, it was established that the three-component reaction of an equimolar mixture of 5-aminopyrazoles **1a-c**, aromatic aldehydes **2a-e**, and pyruvic acid esters **3a,b** under conventional heating at reflux in acetic acid for 7 h led to the formation of a pyrimidine ring followed by an oxidative heteroaromatization process which finally gave alkyl 6-hydroxy-2,7-diphenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylates **4a-s,** (Scheme 2, Table 1, Method A). It is worth noting that the same treatment under an inert atmosphere also yielded compounds **4a-s** while neither dihydropyrazolopyrimidine nor the compound without a hydroxyl-group were observed. This experimental fact shows that the oxidation occurs irrespective of the presence of oxygen in the reaction mixture and may be connected with more complex processes such as disproportionation.[8,21] Indeed, the yields of pyrimidine derivatives were always lower than 50%, both under atmospheric and inert conditions.

On the other hand, MCR of the same reagents **1a-c**, **2a-e** and **3a,b** under ultrasonication in acetic acid at room temperature for 6 h redirected the reaction towards the formation of alkyl 7-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylates **5a-e** (Scheme 2, Table 1). Replacement of ultrasonication by mechanical stirring at room temperature allowed us to obtain compounds **5a-e** in a much longer reaction time (20 h) and with lower yields and purity (TLC and NMR control). It is believed, that the cavitation effect and the specific influence of ultrasonication on the mass transfer enhance the reaction and its overall efficiency.[33–37] Compounds **5** were transformed into substances **4** upon boiling in acetic acid for 9 h. The same transformations for similar compounds had been described in our previous publications.[10,20,25]

In our previous work[8] it was found that three-component reactions of 5-amino-3-methylpyrazole or 5-amino-3-arylpyrazole (R^2 = H) with aromatic aldehydes and ethyl pyruvate under