

Utilisation of enols of mono- and dicarbonyl compounds in 1,3-dipolar cycloaddition reactions

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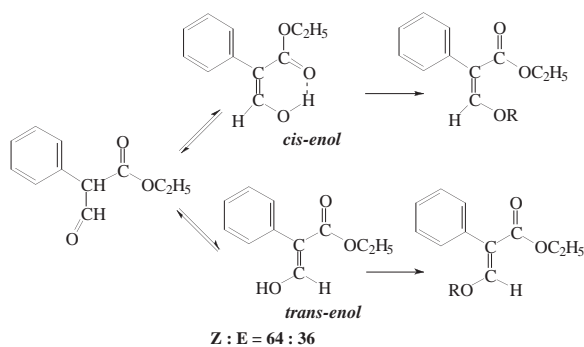
2-Isoxazolines were obtained from substituted enols or their ester or ether derivatives in 1,3-dipolar cycloaddition reactions with aliphatic or aromatic nitrile oxides.

Keywords: 2-isoxazoline, enol, ether derivatives, synthesis

The formation of 2-isoxazolines from substituted ethers of mono and dicarbonyl compounds enols in 1,3-dipolar intermolecular cycloaddition reactions is not a subject often cited in the literature. Compounds of this type, according to literature data, are usually utilised in cyclisation reactions with hydroxylamine hydrochloride.¹

The present work concerns the formation of 2-isoxazolines from substituted enols or their ester or ether derivatives in 1,3-dipolar cycloaddition reactions with aliphatic or aromatic nitrile oxides.²⁻⁴ The effect of the type and number of substituents (H, CH₃, C₂H₅, COOC₂H₅, OH, OCH₃, OCOCH₃) present at the dipolarophile's double bond on the cycloaddition reaction course – yield, regioselectivity, and possibility of water or methanol molecule elimination from the cycloaddition product, leading to the formation of isoxazole as the final reaction product, has been investigated. The present work is a continuation of the search for new 2-isoxazoline derivatives.⁵⁻¹⁰

Ethyl acetylacacetate, ethyl α -phenylformylacetate and ether derivatives of enols of these compounds as examples of β -dicarbonyl compounds, as well as *n*-butylvinyl ether and isopropenylmethyl ether as monocarbonyl compounds derivatives, were selected for the study.



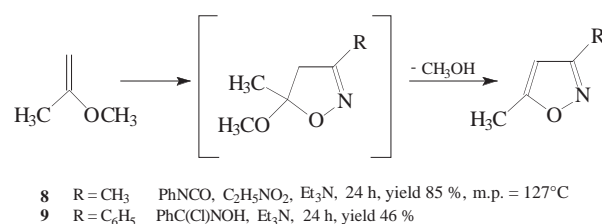
Scheme 1

Ether **1** and ester **2** derivatives of ethyl α -phenylformylacetate enol were obtained in satisfactory yields in etherification or esterification reactions (Scheme 1). The etherification of ethyl formylacetate and ethyl acetoacetate was carried out with dimethyl sulfate in an analogous way to that of ethyl α -phenylformylacetate.

The studies were started with the reaction with *n*-butylvinyl ether, as an example of a monocarbonyl compound enol.

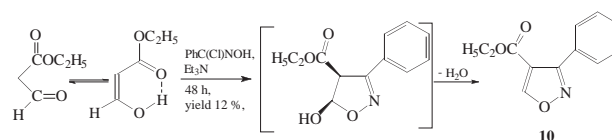
The reactions were performed by standard methods of Mukayama² – with an aliphatic nitrile oxide and of Torsel³ – with an aromatic oxide. In both cases 2-isoxazolines with a butyl substituent at position 5 were obtained. Consecutive syntheses consist in the addition of isopropenyl-methyl ether

also to an aliphatic and aromatic nitrile oxide (Scheme 4). Attempts to stop these reactions at the 2-isoxazolines step failed, since in the reaction medium immediate elimination of a methanol molecule from the initial addition products took place. This synthesis is a new method of obtaining the product isoxazole.



Scheme 4

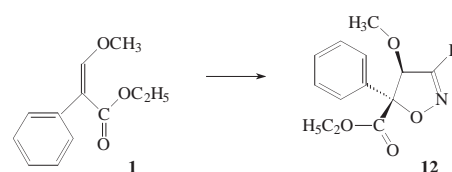
During the cycloaddition of aromatic nitrile oxide to ethyl formylacetate carried out in toluene one regioisomer with an ester group at position 4 was obtained. Elimination took place, similarly as for isopropenyl-methyl ether, but here of a water molecule, and 4-ethoxycarbonyl-3-phenylisoxazole **10**, a stable aromatic heterocyclic system was obtained (Scheme 5). It seems that the fact that the percentage content of the starting material enol form in the solvent used is *ca* 90% is not of negligible importance.¹⁸



Scheme 5

Ethyl α -phenylformylacetate was one of the more interesting selected starting materials used in the 1,3-dipolar cycloaddition reaction. It exists in three tautomeric forms with a clear presence of the *trans* enol form, whereas the equilibrium is shifted towards the *cis* form, even for the pure liquid compound.²²

The ethyl α -phenylformylacetate enol methyl ether **1** showed much greater reactivity under the reaction conditions applied. The product, ethyl-3-methyl-4-methoxy-5-phenyl-2-isoxazoline-5-carboxylate **12**, was obtained in a 22% yield by the Mukayama method and 35% yield by the Kwiatkowski²³ method (Scheme 7).



Scheme 7

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Conclusions

The studies concerned the synthesis of 2-isoxazolines with the utilisation of enols of mono- and dicarbonyl compounds in 1,3-dipolar cycloaddition reactions. It was observed that the structure of the starting material capable of enolisation and not the degree of enolisation has an essential effect on the reaction course and product structure. A substituted isoxazole as the product of water or methanol elimination from the intermediate 2-isoxazoline is obtained in the case of using isopropenyl-methyl ether, ethyl acetocetate, ethyl formylacetate and their ether derivatives as dipolarophiles for the synthesis. Also, only one reaction product – ethyl-3-methyl-4-methoxy-5-phenyl-2-isoxazoline-5-carboxylate **12** is formed in the case of ethyl α -phenylformylacetate methyl ether **1** and acetonitrile oxide for the 1,3-dipolar cycloaddition.

Techniques used: IR, ^1H and ^{13}C NMR spectroscopy, TLC, elemental analysis.

Schemes: 7

Tables: 2

References: 23

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