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A Facile Preparation of 4-Arylidene-4,5-dihydrooxazol-5-ones using Zeolite as a Cyclodehydrating Agent†

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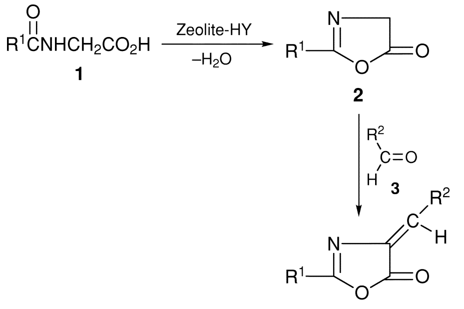
An efficient new method for the azlactonisation of acylamino acids using zeolite under mild conditions is described; the method is fairly general as well as providing high yields.

4,5-Dihydrooxazol-5-ones (2-oxazolin-5-ones) are important intermediates in organic synthesis and there is continuing interest in the exploration of their chemistry.[1] The 5-oxazolone derivatives are reported to exhibit biological activity such as anticancer activity[2] and the dehydropeptides, *N*-substituted amides obtained by their aminolysis, are claimed to have antitumour[3] and central nervous system inhibiting[4] properties.

There are several chemical methods reported for the cyclodehydration of *N*-acylamino acids, *e.g.* acetic anhydride–sodium acetate, acetic anhydride–lead acetate,[5] polyphosphoric acid,[6] perchloric acid[7] and carbodiimides.[8] All these methods have several drawbacks, *i.e.* the need for a large amount of dehydrating agent, and poor yields caused by the formation of undesirable side products. In addition, side products are formed by the reaction of the reagents used with other functional groups in the substrate: *e.g.* amino and phenolic groups are acetylated when acetic anhydride is used in this azlactonization. Also, these methods are not so environment friendly. Moreover, in recent years there has been increased interest in the area of zeolite induced organic transformations[9] in view of their remarkable catalytic properties. Several methods using such catalysts, *e.g.* thioacetalization of carbonyl compounds, sulfoxidation of thioethers, deketalisation, tetrahydropyranylation of alcohol, oxidative cleavage of tosylhydrazones and methoxymethylation of alcohols, have been investigated.[10] However, the cyclodehydration of α-acylamino acids in Erlenmeyer azlactone synthesis has not been reported. We disclose here a new mild, convenient and heterogeneous catalytic procedure for the synthesis of various 4,5-dihydrooxazol-5-ones. The reaction is fairly general, facile and efficient and is devoid of any side products emanating from functional groups present as formed in the known methods employing anhydrides.



Typically, HY-zeolite was impregnated with melted hippuric acid (heated under microwave oven operating at 2450 MHz frequency for 6 min) to incipient wetness and then a hydrocarbon solvent was added to extract the lactone products out of the zeolite cavities as the amino acid is insoluble in hydrocarbon but the lactone **3** is soluble. The catalyst was separated by filtration and the hydrocarbon solvent was evaporated to dryness. To the residue, benzaldehyde (10 mmol) was added and then triethylamine (30 mmol) in dichloromethane (10 ml) was added dropwise. The resulting mixture was stirred at room temperature for 6 h (monitored with TLC), washed with water and the organic solvent was dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallisation of the residue from ethanol yielded the corresponding 4-arylidene-4,5-dihydrooxazol-5-one **4a** in 80% yield. Similarly other 4,5-dihydrooxazol-5-ones were prepared; see Table 1. It is remarkable that the above reaction did not proceed when performed in the absence of the catalyst under microwave irradiation, also the reaction is not as effective when conventional heating is employed without microwave energy the conversion is only 50% after 6–7 h of heating.

Table 1 Preparation of 4-arylidine-2-oxazolin-5-one **4**[a]

Entry	R^1	R^2	Yield (%)[b]	Mp/°C Found	Mp/°C Lit.
4a	Ph	Ph	80	166–167	165–166[11a]
4b	Me	Ph	73	149–150	147–148[11b]
4c	Ph	4-NMe_2Ph	85	214–215	213–214[11c]
4d	Ph	3-OMe,4-HOC_6H_4	72	158–159	158[11d]
4e	Ph	2-Furyl	73	170-171	171[11e]
4f	PhCH=CH	Ph	75	132–133	133–134[11f]
4g	Me	4-$AcOC_6H_4$	70	136–138	138–139[11g]
4h	Me	3-OMe, 4-$AcOC_6H_4$	72	143–145	144–148[11h]
4i	Me	3-OMe, 4-OMe	78	164–165	167[11i]

[a]All products were characterised by their IR and ^1H NMR spectroscopic data and also by comparison with authentic samples. [b]Yields refer to isolated pure products.

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In conclusion, the results described herein demonstrate the novelty of zeolite catalysts which exercises unique selectivity in the lactonisation of hippuric acid to 4,5-dihydrooxazol-5-ones. The present method also offers significant improvements over the existing procedures and constitutes a useful and important addition to the present methodologies.

Experimental

Melting points were recorded in open capillary tubes on a Buchi apparatus and are uncorrected. All chemicals were purified by distillation or crystallisation prior to use.

General procedure for the preparation of 4-*arylidene*-4,5-*dihydro*-5-*ones using zeolite-HY under microwave irradiation*—In a typical procedure, about 1 g of zeolite-HY was impregnated with the melted hippuric acid (1.8 g, 10 mmol) in a commercial microwave oven (operating at 2450 MHz) for 6 min and then benzene (20 ml) was added to extract the lactone. The catalyst was separated by filtration and the benzene was evaporated to dryness. To the residue, benzaldehyde (1.06 ml, 10 mmol) was added and then dry triethylamine (4.03 ml, 30 mmol) in dichloromethane (10 ml) dropwise. The resulting mixture was stirred at room temperature for 6 h, washed with water (2 × 50 ml) and the organic solvent was dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallisation of the residue from ethanol yielded the 2-phenyl-4-phenylmethylene-4,5-dihydrooxazol-5-one **4a** in 80% yield. Similarly other acylamino acids and aldehydes were reacted and the corresponding 4,5-dihydrooxazol-5-ones were obtained in 75–85% yields. All the products obtained were characterised by IR and ^{1}H NMR spectroscopy and finally by comparison with authentic samples.

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