International Journal of Chemical Studies

P-ISSN: 2349–8528
E-ISSN: 2321–4902
IJCS 2019; 7(3): 3655-3658

Received: 13-03-2019
Accepted: 15-04-2019

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A Facile synthesis of 1, 2-disubstituted 4-arylmethylene- 2-imidazolin-5-ones via 2-substituted 2-oxazolin-5-ones

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Abstract
In view to synthesize some bioactive 1,2-Disubstituted 4-arylmethylene-2-imidazoline-5-ones (6) through a disciplined route, a modified eco-friendly method has been designed, because 2-imidazolin-5-one derivatives are reported to have a wide range of pharmacological profile. 2-Substituted 2-oxazolin-5-ones (2) which are also known as saturated azlactones and are unstable,were generated *in situ* fromα-N-acylglycines (1) using p-toluenesulphonyl chloride or tosyl chloride as cyclizing agent in dry benzene in presence of triethylamine base at room temperature. Subsequent addition of aromatic aldehydes (3) and refluxing the mixture for 10 minutes, 2-Substituted 4-arylmethylene-2-oxazolin-5-ones (4) were obtained, which are also known as unsaturated azlactones and are stable. On aminolysis of 2-Substituted 4-arylmethylene-2-oxazolin-5-ones (4) in acidic medium say in glacial acetic acid by primary amines N-Substituted 2-acylamino-2-alkenamides (5) were obtained within 5-10 minutes. The reaction seems to proceed by the cleavage of 1,5-bond of 2-Substituted 4-arylmethylene-2-oxazolin-5-ones (4) by the nucleophiles i.e. primary amines. On continuous heating for 4.0 hours in the presence of catalytic amount of sodium acetate, 1,2-Disubstituted 4-arylmethylene-2-imidazoline-5-ones (6) were the product. There are four steps in total for the conversion of α-N-acylglycines (1) to 1,2-Disubstituted 4-arylmethylene-2-imidazoline-5-ones (6). In this present investigation, all the steps can be carried out in one flask by designing a facile modified route.

Keywords: α-N-acylglycine, *p*-toluenesulphonyl chloride, alkenamides, 1, 2-disubstituted 4-arylmethylene-2-imidazolin-5-ones, Stereospecific

1. Introduction
2-oxazolin-5-ones, continue to attract the attention of chemists because of their usefulness as due to the presence of vulnerable 1, 5-bond. Most of the 2-imidazolin-5-one derivatives are potentially important to have remarkable pharmacological profile which includes anticancer [1], anticonvulsant [2], antiparkinson [3], antibacterial [4, 5], CVS active [6] and anti-inflammatory [7] agents. Some of them may be useful in polymer chemistry [8]. There are large varieties of imidazolones and their derivatives which exhibit different types of pharmacological and biological activities. They are developed for different therapeutic actions [8]. In light of green chemistry methodology, chemists of synthetic organic chemistry are always in search of new routes utilizing minimum chemicals, optimum use of energy and maximum productivity of the targeted compounds. In view of minimum disposal of chemicals and by-products to the environment, some modified eco-friendly disciplined routes have been designed to synthesize 1, 2–Disubstituted 4-arylmethylene-2-imidazolin -5- ones using α-N-acylglycines via 2-substituted 2-oxazolin-5-ones.
The conversion of α-N-acylglycine (1) to unstable 2-substituted 2-oxazolin-5-one (2) was carried out at room temperature by using cyclizing agent, followed by the condensation with aromatic aldehydes with 2. The stable 2-substituted 4-arylmethylene-2-oxazolin-5-ones (4) were obtained. On aminolysis in acidic medium alkenamides (4) were obtained within 5-10 min. If heating was continued for 4 hours in the presence of catalytic amount of sodium acetate, 1, 2-disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) were the product. All the steps were carried out in one flask (Figure-1).

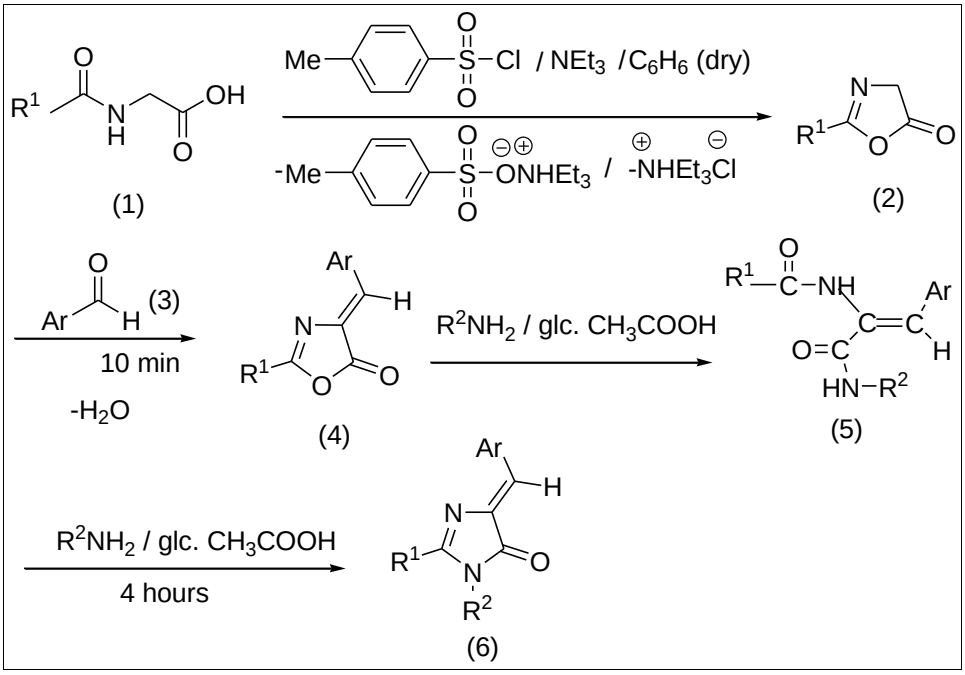

Fig 1: Synthesis of 1, 2-disubstituted 4-arylmethylene-2-imidazolin-5-ones starting from α-N-acylglycines

4, 5, 6	R^1	R^2	Ar
a	Ph	Ph	Ph
b	Ph	Ph	3- $C_6H_4NO_2$
c	Ph	Ph	4- $C_6H_4NMe_2$
d	Ph	*n*- C_4H_9	Ph
e	Ph	CH_2Ph	Ph
f	Me	Ph	Ph
g	Ph	Ph	3-MeO,4-OHC_6H_4
h	PhCH=CH	Ph	Ph

2. Materials and Methods

All the prepared compounds are known in the literature [10-14]. The purity of the compounds was verified by TLC (silica gel /benzene) and their melting points. Melting point was recorded by metal block melting point apparatus and is uncorrected. The IR spectra of the compounds were recorded on IR Affinity-1, Shimadzu.

One flask synthesis of 1,2-disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) using aromatic aldehydes and primary amines

2.1 Method A

To a stirred suspension of α-N-acylglycine (1, 1.0mol) in dry benzene (50mL/g of 1) containing triethylamine (2.5 mol), *p*-toluenesulphonyl chloride (1.0 mol) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The aromatic aldehyde (3, 1.0 mol) was added to the mixture which was then heated under reflux for about 10 min. The triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL). The benzene solution and washing were combined and concentrated to dryness under reduced pressure. To the residue, primary amine (1.0 mol) and glacial acetic acid (20 mL/g of 1) were added and the mixture was heated under reflux for 5-10 min. To the solution mixture of glacial acetic acid, a catalytic amount of sodium acetate (0.2g) were added and heated under reflux for about 4 hours. The mixture was concentrated to dryness in steam bath. The residue was triturated with ethanol. The solid material was isolated by suction, washed twice with ethanol and recrystallized with 95% ethanol.

Yields are calculated based on α-N-acylglycine (1) taken.

2.2 Method B

To a stirred suspension of α-N-acylglycine (1, 1.0mol) in dry benzene (50mL/g of 1) containing triethylamine (2.5 mol), *p*-toluenesulphonyl chloride (1.0 mol) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The aromatic aldehyde (3, 1.0 mol) was added to the mixture which was then heated under reflux for about 10 min. The triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL). To the filtrate, primary amine (1.0 mol) and glacial acetic acid (5 mL/g of 1) were added and the mixture was heated under reflux for 5-10 minutes. On cooling, a solid was separated out which was filtered under suction and the intermediate is subjected to reflux for 4 hours in glacial acetic acid medium after adding a catalytic amount of Sodium acetate (0.2 g). The mixture was concentrated to dryness in steam bath. The residue was triturated with ethanol. The solid material was isolated by suction, washed twice with ethanol and recrystallized with 95% ethanol.

Yields are calculated based on α-N-acylglycine (1) taken. The typical IR absorption band for imidazolone lactam is observed at 1708- 1711 cm^{-1}.

5a: Yield, 50% (method A), 62% (method B), m.p. 178^{O}C (reported[12]: 180^{O}C), IR (KBr): 3053, 1709, 1637 cm^{-1}

5b: Yield, 56% (method A), 48% (method B), m.p. 196^{O}C (reported[12]: 198-199^{O}C), IR(KBr): 3074, 1708, 1637, 1530 cm^{-1}

5c: Yield, 45% (method A), 57% (method B), m.p. 248^{O}C (reported[12]: 250-252^{O}C), IR(KBr) : 3053, 1709, 1610 cm^{-1}

5d: Yield, 50% (method A), 47% (method B), m.p. 99^{o}C (reported[12]: 99^{O}C), IR(KBr) : 3053, 1711, 1638 cm^{-1}

5e: Yield, 60% (method A), 52% (method B), m.p. 141°C (reported[12]: 143-144°C), IR(KBr) : 3021, 1711, 1637 cm^{-1}
5f: Yield, 38% (method A), 50% (method B), m.p. 143°C (reported[13]: 144°C), IR(KBr) : 3021, 1708, 1621, 1493 cm^{-1}
5g: Yield, 40% (method A), 50% (method B), m.p. 190°C (reported[12]: 190°C), IR(KBr) : 3500, 3021, 1709, 1621 cm^{-1}
5h: Yield, 42% (method A), 60% (method B), m.p. 240°C (reported[12]: 240-241°C), IR (KBr): 3020, 1710, 1621, 1490 cm^{-1}

3. Results

The saturated azlactone i.e. 2-substituted 2-oxazolin-5-one (2) generated by cyclodehydration of α-N-acylglycine (1) with *p*-toluenesulphonyl chloride and triethylamine as base in dry benzene is treated with an aromatic aldehyde (3) and heated with under reflux for 10 min. The unsaturated azlactone i.e. 2-substituted 4-Arylmethylene-2-oxazolin-5-ones (4) obtained, is directly subjected to 1,5-bond cleavage. The compound 4 is heated with primary amine in the presence of glacial acetic acid for 5-10 min. On cooling, the crystals of the product N-substituted 2- acylamino-3-arylpropenamides (5) separate out. It follows the attack of lone pair of electron on the nitrogen atom of the primary amine which leads to the cleavage of 1, 5-bond of the compound 4. If the heating is continued for 4 hours in the presence of catalytic amount of freshly fused sodium acetate, 1,2–disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) are directly obtained as major products.

4. Discussions

With a view to converting the unstable 2-oxazolin-5-one (2), obtained by *p*-toluenesulphonyl chloride-mediated cyclization of α-N-acylglycines (1), into more stable 4-arylmethylene-2-oxazolin-5-one (4), a suitable aromatic aldehyde (3) is added. Further, the propenamide (5) is obtained through the 1, 5-bond cleavage of 4 by primary amine in acidic medium and recyclization of 5, produces the product 6. It is found that the products 1,2-disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) were obtained from α-N-acylglycine (1) through the intermediate 2, 4 and 5 subsequently, where the intermediates 4 and 5 can be isolated if the reaction is carried out in stepwise fashion. In the present procedure, 2-imidazolin-5-one derivatives (6) are synthesized in one flask. The products are recrystallized from ethanol and the purity of the compounds is verified by TLC. The compounds are characterized by IR spectra and melting points.

The typical IR absorption band for 2-imidazolin-5-one lactam (6) is observed at 1710 cm^{-1}.

Yields of the pure products are based on the amounts of α-N-acylglycines (1).

It is noteworthy that the intermediate unsaturated azlactone (4) obtained by this method have (*Z*)–configuration[5] and it is known that the cleavage of the 1, 5-bond in such compounds does not change the stereochemistry of the olefinic center at the C-4 position. Further, cyclization of N-substituted 2-acyl-aminoprop-2-enamides (5) produce (*Z*)-imidazolones (6) without affecting the stereochemistry at C-4 center. Therefore, the conversion of 4 to 6 is highly stereospecific. The present procedure does not have some of the drawbacks of the earlier methods. For example, the Erlenmeyer azlactone synthesis[15] employs acetic anhydride for cyclization and it affords a mixture of (*E*) and (*Z*)–isomers of the unsaturated azlactone which have to be separated by fractional crystallization before using them for aminolysis and subsequent recyclization to imidazolones. This is rather time consuming and it lowers the overall yields of the products. Other methods involve the preparation of anilides in several steps whereas the generation of unsaturated azlactone 4 by the present procedure is quite convenient ; the crude product is subjected to aminolysis and subsequent recyclization to imidazolones without isolation of intermediates, so that the reaction can be carried out in the same flask. The steric integrity of the products is maintained at the same time.

5. Conclusion

2-Substituted 2-oxazolin-5-ones (2) remain very important starting materials for the construction of various heterocycles and therefore can be used as synthons. A disciplined route for the facile and convenient one flask synthesis of 1,2–disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) were developed and steric integrity of the products were maintained simultaneously. The reaction can be terminated even at any stage depending on need to get either stable2-Substituted 4-arylmethylene-2-oxazolin-5-one (4) or N-Substituted 2-acylamino-2-alkenamides (5). In view of the ready availability of the starting materials, the milder experimental conditions, and the simplicity of the work-up with good overall yields, the present proposed route appears to be potentially useful for the synthesis of 1,2–disubstituted 4-arylmethylene-2-imidazolin-5-ones (6) using the concept of green chemistry.

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