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L-Proline catalyzed three component one-pot efficient synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones

H.R.Sonawane[1], S.P.Patil[1], S.V.Goswami[1], V.L.Deshmukh[2], S.R.Bhusare[1]*

[1]Department of Chemistry, Dnyanopasak College, Parbhani-431401, MS, (INDIA)

[2]Department of Biotechnology, Dnyanopasak College, Parbhani-431401, MS, (INDIA)

E-mail : bhusare71@yahoo.com

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ABSTRACT

L-Proline is used as an efficient catalyst for the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones via condensation of aromatic aldehydes, substituted anilines, and 2-mercaptoacetic acid. The easy work-up, higher yields and shorter reaction time, are the advantages of the method is presented. The result of the in *vivo* tests showed that some of them have effective antibacterial activity.

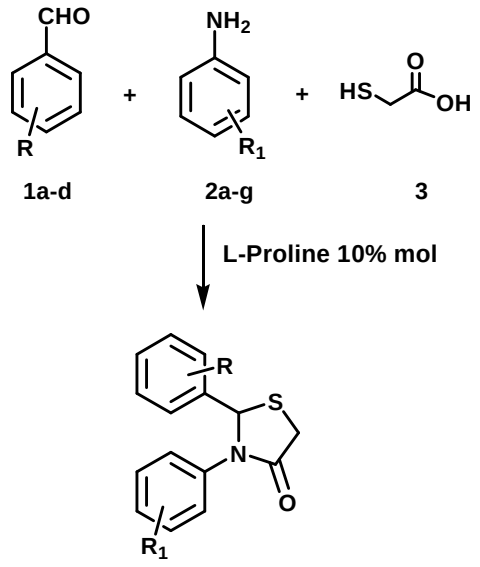
KEYWORDS

Aniline;
Aromatic aldehydes;
L-proline;
2-mercaptoacetic acid;
Thiazolidin-4-ones.

INTRODUCTION

Some ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. Among these type of molecules, thiazolidin-4-ones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostasic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory and analgesic properties[1-4]. It also has effect on the CNS and has been reported as novel inhibitors of the bacterial enzyme Mur-B which is precursor acting during the biosynthesis of peptidiglycon[5,6]. Some of these compounds were screened for their antibacterial and antituberculostatic activities, and it has been found that some of them have moderate to good biological properties[7].

We have already reported some of our work on the synthesis and biological properties of various 2,3-diaryl-1,3-thiazolidin-4-ones[8,9]. The biological significance of this class of compounds impelled us to continue working on the synthesis of new thiazolidin-4-one derivatives. *L*-proline is an efficient bi-functional abundant chiral organo-catalyst which is inexpensive and available in both enantiomeric forms[10]. These two functional groups can both act as acid or base and



Scheme 1

can also facilitate chemical transformations in concert, similar to enzymatic catalysis. It has been extensively used in the synthesis of various heterocycles[11] as well as in Aldol, Mannich and Michael reactions[12]. As the mechanism of multi-component Hantzsch reaction originally involves Aldol related reactions such as Knoevenagel condensation and Michael addition, the use of *L*-proline for the same reaction will be a useful and attractive modification for the same. Herein, we report first time the use of *L*-proline as an organo-catalyst for the synthesis of novel 2,3-diaryl-1,3-thiazolidin-4-ones derivative starting from various substituted anilines, aromatic aldehydes and 2-mercaptoacetic acid in one-pot synthesis method with the aim of investigating their biological properties. Our results demonstrate that *L*-proline is a very effective, environmentally friendly catalyst for the three component condensations of aromatic aldehyde, anilines and 2-mercaptoacetic acid to form 2,3-diaryl-1,3-thiazolidin-4-ones in excellent yields (Scheme 1).

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on Varian FTIR-640 spectrometer; ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard.

General procedure for the synthesis of thiazolidin-4-ones

A mixture of aniline (10 mmol) and aromatic aldehydes (10 mmol) were stirred in 1,4-dioxane (10ml) in an ice bath for 5 min, followed by addition of 2-mercaptoacetic acid (12 mmol). After 5 minutes *L*-proline (10 % mol) as catalyst was added at 0°C and the reaction mixture was stirred till completion of reaction at room temperature as indicated by TLC (ethyl acetate: petroleum ether; 1: 9). Reaction mixture was poured into crushed ice (50ml) to get the precipitated solid. The solid separated out was filtered, washed with sodium-bi-carbonate solution to remove excess of 2-mercaptoacetic acid and crystallized from ethyl alcohol to give 4-thiazolidinones (TABLE 1; **(4a-j)**).

ANTIBACTERIAL ACTIVITY

The compounds synthesized were screened for their antibacterial activity using *Staphylococcus species* and *Candida albicans* as bacteria. The activities of these compounds were tested using disc diffusion method[13] at 100ppm concentration using 5 mm filter papers disc. Control experiment was carried out under similar condition by using tetracycline as a standard for comparison. The inhibition zone measured in mm showed that compounds **(4a)**, **(4e)**, **(4f)** and **(4h)** were more active then other compounds tested against the above microbes, but none showed better or comparable activity to tetracycline (TABLE 1).

TABLE 1 : Analytical and antibacterial data of synthesized thiazolidin-4-one (4a-j)

Entry	R	R_1	Reaction Time (h)	Yield (%)[a]	Zone of inhibition in mm	
					Ss	*Ca*
4a	3,4,5-OCH_3	4-Cl	3	89	16	15
4b	3,4,5-OCH_3	4-OC_2H_5	4	86	14	13
4c	3,4,5-OCH_3	2-NO_2, 4-Cl	4	83	12	12
4d	3,4,5-OCH_3	4-OC_6H_5	4	81	10	12
4e	3,4,5-OCH_3	4-CH_3	4	88	15	16
4f	3,4,5-OCH_3	4-OCH_3	4	91	16	17
4g	3,4,5-OCH_3	3-OC_6H_5	4	85	12	12
4h	2-OH, 5-Br	4-Cl	5	92	17	16
4i	4-(CH_3)N-	4-Cl	5	83	12	13
4j	3-NO_2	4-Cl	4	80	10	12
			Tetracycline		20	20

[a]**All the products exhibited the expected analytical and spectral data. *Ss*= *Staphylococcus species* and *Ca* = *Candida albicans***

RESULT AND DISCUSSION

In a typical experimental procedure, a mixture of aniline (10 mmol), benzaldehyde (10 mmol) and 2-mercaptoacetic acid (12 mmol) in 1,4-dioxane was stirred at room temperature in the presence of *L*-proline (10 mol %) as a catalyst for appropriate time (TABLE 1). After completion of the reaction mixture was poured into crushed ice thus solid product separated was filtered, washed with sodium-bi-carbonate and crystallized from ethyl alcohol to get desired product. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields of thiazolidin-4-ones. The products were obtained were isolated in satisfactory yields by conventional workup. Both analyti-

cal and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures.

We have shown that a high level of activity was associated with the presence of an electron donating groups present on phenyl ring at C-2. Moreover, we found that an increase in antibacterial activity was dependent on the presence of a 2-hydroxy-5-bromophenyl group at N-3.

In conclusion, a new series of 2,3-diaryl-1,3-thiazolidin-4-ones was synthesized in one-pot reaction method by the use of *L*-proline as an efficient catalyst and some of them proved to have potent antibacterial activity. The results confirm that the antibacterial activity is strongly dependent on the nature of the substituents at C-2 and N- 3 of the thiazolidinone ring.

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