Asian Journal of Chemistry; Vol. 29, No. 3 (2017), 623-625

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20279

Organocatalytic Synthesis of *N*-Substituted 5-Arylidene Rhodanines

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Received: 1 September 2016; *Accepted*: 29 November 2016; *Published online*: 30 December 2016; AJC-18214

A simple and efficient synthesis of *N*-substituted 5-arylidene rhodanines has been developed *via* aldol condensation of *N*-substituted rhodanines with aromatic aldehydes using L-proline as the catalyst in water at room temperature. The attractive features of this protocol are simple experimental procedures, cleaner reactions, column free, high yield and avoid the use of toxic solvents.

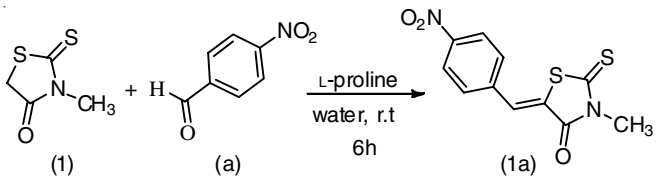
Keywords: *N*-Substituted 5-arylidene rhodanines, L-Proline, Aldol condensation, Room temperature.

INTRODUCTION

The importance of *N*-functionalized 5-arylidene rhodanines are known to exhibit outstanding biological activities such as anti-inflammatory [1], antiviral [2] and anti-HIV [3]. Moreover, they are found to be inhibitor of many targets such as aldose reductase [4], dynamin GTPase [5] and hepatitis C virus (HCV) [6]. In view of their unique bioactivities, various methods have been developed for their synthesis, which include (i) condensation of *N*-substituted-rhodanines with aromatic aldehyde in presence of alumina [7] or in presence of base [8], (ii) heating the reaction mixture of *bis*(carboxymethyl)trithiocarbonate, primary amines and aromatic aldehyde using triethylamine as the base [9], (iii) a multicomponent reaction of primary amines, aldehydes, ethyl chloroacetate and carbon disulfide in presence of potassium hydroxide or 1-butyl-3-methyl imidazolium acetate [10] and (iv) reaction of amines, carbon disulfide and arylpropiolates in the presence of tributylphosphine under an argon atmosphere [11].

Although the above reported methods are valuable, most of them suffer from one or more drawbacks like the use of environmentally unfavourable solvents, heating at high temperature, tedious work-up procedures, non-recovery of the catalysts, column purification for product, limited substrate scope and low yields of the desired products. Therefore, the development of a simple, mild, economic and environmentally friendly method for the synthesis of *N*-substituted 5-arylidene rhodanine is highly desirable.

Water has been emerging as potential "greener" alternatives to volatile organic solvents and used for many important organic reactions as it is low-cost, safe, non-toxic and most abundant solvent [12]. On the other hand, L-proline has been used as catalyst in different organic reactions due to its experimental simplicity, non toxicity, ease of handling, cost effectiveness and recyclability [13-15]. Inspired by the unique reactivity of L-proline, we explore the synthesis of *N*-substituted 5-arylidene rhodanine *via* aldol condensation reaction of *N*-substituted rhodanine and aromatic aldehyde in aqueous media using L-proline as catalyst (**Scheme-I**).



Scheme-I: Aldol condensation reaction of 3-methyl-2-thioxothiazolidin-4-one and 4-nitrobenzaldehyde

EXPERIMENTAL

All the compounds were commercial grade and were used without further purification. ^{1}H NMR spectra were recorded on 400/600 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100/150 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded in KBr. High-resolution mass spectral analysis (HRMS) data were recorded using ESI mode (Q-TOF type Mass Analyzer).

General procedure for the synthesis of *N*-substituted 5-arylidene rhodanines (1-3)(a-k): A mixture of 3-methyl-2-thioxothiazolidin-4-one (1) (0.5 mmol), 4-nitro benzaldehyde (**a**) (0.6 mmol), L-proline (30 mol %) and water (3 mL) was taken in a 10 mL round bottom flask. The heterogeneous reaction mixture was stirred for 6 h at room temperature. After completion of the reaction (monitored by TLC), the crude solid

product was collected by filtration and recrystallized from ethanol to give the corresponding (*Z*)-3-methyl-5-(4-nitrobenzylidene)-2-thioxothiazolidin-4-one (**1a**) in 90 % yield. Spectral and analytical data of selected compounds are given below.

(*Z*)-3-Methyl-5-(4-nitrobenzylidene)-2-thioxothiazolidin-4-one (1a): Yellow solid; m.p. 210-211 °C; yield 90 %; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.5 (s, 3H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.73 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 35.9, 124.7, 127.8, 129.2, 131.1, 139.4, 148.2, 167.6, 191.9; IR (KBr, ν_{max}, neat): 1715, 1574, 1377, 1191 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_8N_2O_3S_2$ $[M+H]^+$: 280.9986; found: 280.9990.

(*Z*)-3-Benzylidene-2-thioxothiazolidin-4-one (2c): Yellow solid; m.p. 155-156 °C (Lit. [11] m.p. 156 °C); yield 90 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.30 (s, 2H), 7.24-7.32 (m, 3H), 7.45-7.47 (m, 7H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6, 123.0, 128.2, 128.6, 129.0, 129.4, 130.7, 130.9, 133.4, 133.5, 134.9, 167.9, 193.3; IR (KBr, ν_{max}, neat): 1706, 1595, 1343, 1190 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NOS_2$ $[M+H]^+$: 312.0511; found: 312.0514.

(Z)-5-(2,6-Dichlorobenzylidene)-3-benzyl-2-thioxothiazolidin-4-one (2e): Yellow solid; m.p. 113-114 °C; yield 96 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.28 (s, 2H), 7.25-7.37 (m, 6H), 7.48 (d, *J* = 6.6 Hz, 2H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.8, 128.2, 128.3, 128.5, 128.6, 129.1, 131.0, 131.3, 131.6, 134.1, 134.4, 166.5, 193.3.

(Z)-3-(2-(1H-Indol-3-yl)ethyl)-5-((furan-2-yl)-methylene)-2-thioxothiazolidin-4-one (4f): Grey solid; m.p. 186-187 °C; yield 75 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13-3.17 (m, 2H), 4.36-4.00 (m, 2H), 6.55–6.59 (m, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.12-7.20 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.69 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 45.2, 53.5, 111.0, 111.9, 113.4, 118.1, 118.7, 119.0, 119.8, 122.1, 122.2, 127.4, 136.1, 146.9, 150.1, 167.5, 194.7.

(Z)-3-Benzyl-5-[(pyridine-2-yl)methylene]-2-thioxothiazolidin-4-one (2g): Light green solid; m.p. 194-195 °C; yield 83 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (s, 2H), 7.25-7.34 (m, 4H), 7.44-7.53 (m, 3H), 7.61 (s, 1H), 7.73-7.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.1, 123.5, 127.4, 128.0, 128.1, 128.5, 128.6, 129.0, 135.1, 135.7, 149.6, 151.8, 168.0, 199.9.

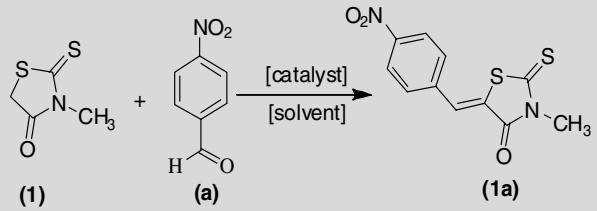
(5Z)-5-(3-[(Z)-(3-Benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)methyl]benzylidene)-3-benzyl-2-thioxothiazolidin-4-one (2h): Yellow solid; m.p. 174-175 °C; yield 60 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (s, 4H), 7.30-7.33 (m, 6H), 7.45-7.52 (m, 8H), 7.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7, 125.0, 128.3, 128.7, 129.1, 130.4, 131.4, 131.8, 132.1, 134.6, 134.7, 167.7, 192.4.

RESULTS AND DISCUSSION

With the above expectation, a trial reaction was carried out by treating *N*-substituted rhodanine (**1**) with 4-nitrobenzaldehyde (**a**) in the presence of L-proline (20 mol %) in water at room temperature. After 6h stirring, a yellow precipitate was observed, separated by filtration and the product was isolated (70 % yield) by recrystallization from ethanol. On the basis of spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR, HRMS), the structure of the isolated product was determined as (*Z*)-3-methyl-5-(4-nitrobenzylidene)-2-thioxothiazolidin-4-one (**1a**) (**Scheme-I**).

To optimize the reaction condition, the effect of catalyst loading was screened. Increasing L-proline to 30 mol % led to a higher yield of 90 % (Table-1, entry 2); further increasing it to 35 mol % did not improve the yield. Different catalysts such as L-histidine and L-leucine (Table-1, entries 3-4) were tested for this transformation, from which L-proline (Table-1, entry 2) was found to be the most effective catalyst. Next, various solvents were screened for their influence on this reaction. In water, the reaction proceeded efficiently and gave the desired product (**1a**) in highest yield (90 %); while using ethanol, yield was reduced to 85 % (Table-1, entry 5). Other solvents such as CH_3CN (70 %), dioxane (68 %) and THF (65 %) were less effective compared to water (Table-1, entries 6-8).

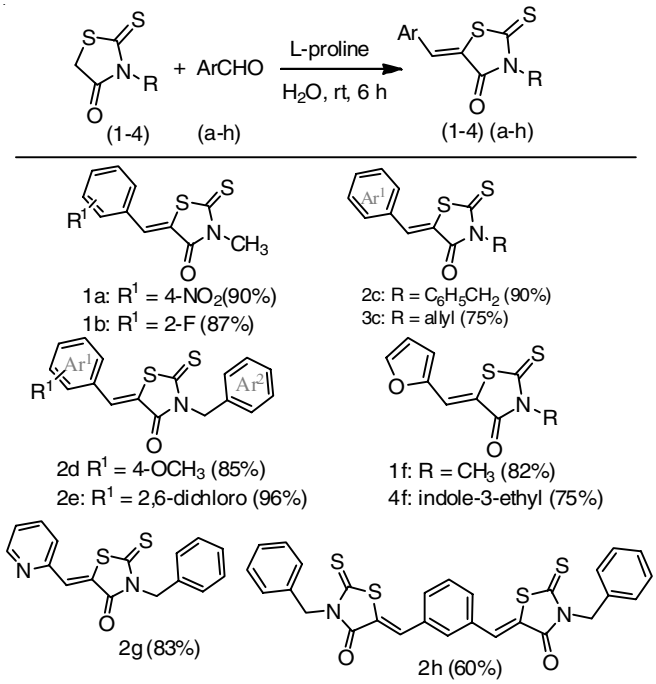
TABLE-1
OPTIMIZATION OF REACTION CONDITIONS



Entry	Catalyst	Solvent	Yield[b] (%)
1	L-proline[c]	H_2O	70
2	L-proline	H_2O	90
3	L-histidine	H_2O	65
4	L-leucine	H_2O	70
5	L-proline	EtOH	85
6	L-proline	CH_3CN	70
7	L-proline	1,4-Dioxane	68
8	L-proline	THF	65

[a]Reaction conditions: (1) (0.5 mmol), (a) (0.6 mmol), catalyst (30 mol %) and solvent (3 mL) at room temperature for 6 h; [b]Isolated yield. [c]Catalyst (20 mol %).

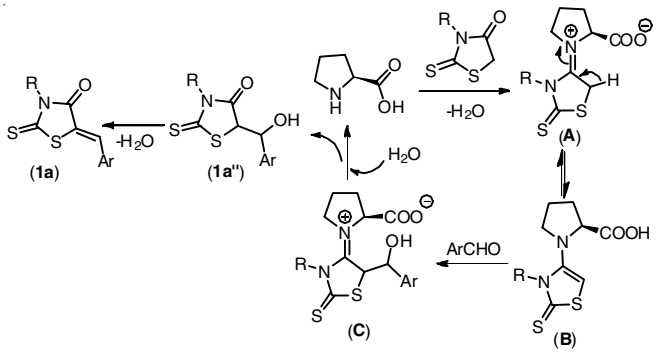
Having established the appropriate reaction conditions, we next explored the substrate scope of *N*-substituted 5-arylidene rhodanines using various *N*-substituted rhodanines and aromatic aldehydes (**Scheme-II**). The *N*-substituted rhodanines (**1**) condensed with aromatic aldehydes possessing electron withdrawing group such as 4-NO_2 (**a**) and 2-F (**b**) giving desired *N*-substituted 5-arylidene rhodanines (**1a**) and (**1b**) in 90 % and 87 % yields respectively. Here, highly electron withdrawing group gave higher yield of the product irrespective of their position. The *N*-substituted rhodanines (**2**) and (**3**) were smoothly condensed with benzaldehyde (c) to give their corresponding *N*-substituted 5-arylidene rhodanines (**2c**, 90 %) and (**3c**, 78 %), respectively. The *N*-substituted rhodanine (**2**) reacted with aromatic aldehydes having electron donating substituent 4-OCH_3 (**d**) giving its respective *N*-substituted 5-arylidene rhodanines (**2d**, 85 %), but gave lesser yield as compared to (**2e**, 96 %) which were obtained from aromatic aldehyde having electron withdrawing substituent 2,6-dichloro (**e**). The condensation reaction is also successfully applied to heterocyclic aldehyde (**f**) and (**g**). The use of dialdehyde (**h**) gave molecule containing two differently space rhodanine rings (**2h**) in good yield.



Scheme-II: Substrate scope of *N*-substituted 5-arylidene rhodanines[a,b] ([a]Reaction conditions: (1-4) (0.5 mmol), (a-h) (0.6 mmol), L-proline (30 mol %), H_2O (3 mL), rt. [b]Isolated yields)

Subsequently, we investigated the recyclability of the catalyst. The L-proline is highly soluble in water whereas the product is insoluble. The products can be directly separated by filtration. The filtrate containing L-proline can be directly reused for up to three times without noticeable decrease in catalytic activity.

A plausible mechanistic pathway is outlined in **Scheme-III**. Initially, rhodanine and L-proline formed iminium ion (**A**). The nucleophilic attack of enamine (**B**) to aromatic aldehyde forming intermediate (**C**) which upon hydrolysis give aldol product (**1a″**) with the release of catalyst, L-proline. The aldol product (**1a″**) undergoes a dehydration process to afford product (**1a**).



Scheme-III: A plausible mechanism for the synthesis of *N*-substituted 5-arylidene rhodanines

Conclusion

In summary, we have developed a simple, efficient and novel method for the synthesis of rhodanine derivatives. The reaction proceeded under mild condition and the desired products can be obtained by simply recrystallization from ethanol in good to high yields.

ACKNOWLEDGEMENTS

This study was financially supported by Department of Science and Technology (DST) (SB/FT/CS-170/2013), New Delhi, India.

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