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A Facile Synthesis of (*Z*)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl) amino) Substituted Acid Using Microwave Irradiation and Conventional Method

Dattatraya N. Pansare, Devanand B. Shinde*

Department of Chemical Technology, Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, India.

Abstract: A new effective approach to the synthesis of some new (Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid 6a-l is reported under microwave irradiation as well as conventional conditions.

Keywords: Amino acids, Knoevenagel condensation, Microwave irradiation, Rhodanine.

INTRODUCTION

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules have fascinated organic and medicinal chemists. In recent years, 4-thiazolidinones (Rhodanine) have been extensively investigated as class of compounds. Rhodanine have many interesting activity profiles namely COX-1 inhibitors [1] inhibitors of the bacterial enzyme MurB [2]. The rhodanine scaffold is a central part of biologically active compounds with various applications and uses [3, 4] such as anti-microbial [5, 6] anti-malarial [7] anti-HIV agents [8 - 11] anti-inflammatory [12, 13] anti-fungal [14] anti-cancer [15] antidiabetic [16] and antitubercular [17, 18]. For the discovery of new lead structures in drug discovery, based on high throughput screening, synthetic methodologies are required which deliver highly diverse derivatives in a timely manner. Under these circumstances, microwave-assisted chemistry appears to be a promising synthetic method [19]. Utility of microwave irradiation [20] (MW) to carry out organic reaction has now become a regular feature. The main benefits of performing the reaction under microwave conditions are the significant rate enhancements and the higher product yields in minimum time requirement. Here, we wish to mention the development and implementation of a methodology, allowing for the synthesis of some new (*Z*)-2- ((5-(4-fluorobenzylidene) -4-oxo-4,5-dihydrothiazol- 2-yl)amino) substituted acid (**6a-l)** derivatives. The rhodanine has been known for over 50 years, so there have been several attempts to design antimicrobial agents based on this heterocycle. There are various reports available on rhodanine derivatives as antimicrobial agents [21 - 25]. These reports suggested that a chain containing free carboxyl group at rhodanine nucleus was important to the observed as levels of antimicrobial activity [26, 27]. The reported reactions under microwave irradiation as well as conventional method proceed in short reaction times and are good to excellent yields. With this in mind, we initiated a program by using microwave irradiation and conventional method to synthesized rhodanine derivatives, having amino acids chain as antimicrobial agent by preparing hybrid molecules having the similar features of reported potent antimicrobial agents (Fig. **1**).

In continuation of our work [28], on the synthesis of bioactive compounds, we have synthesized some rhodanine analogues. The synthetic protocols employed for the synthesis of rhodanine derivatives **3** and **4** are presented in Scheme **1**.

RESULT AND DISCUSSION

The first part of the study was aimed at optimizing the reaction conditions. The screening of model reaction of (*Z*)-2-((5- (4-fluorobenzylidene) -4-oxo-4,5-dihydrothiazol-2 -yl)amino)propanoic acid **6a** (Scheme **2**, Table. **1**). We have developed the protocol for the synthesis of compound **6a** by condensation of compounds **4** and **5a**. After the initial success in ethanol, we screened various solvents, bases, time and yield; the results are shown in Table. **1**. The reaction of compound **4** (1 mmol) and compound **5a** (1.2 mmol), catalyzed by

* Address correspondence to this author at the Department of Chemical Technology, Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, India; Tel No.:+91 0240-2403308; Fax No.: +91 0240-2400413; E-mail: dbsdattatraya10@rediffmail.com

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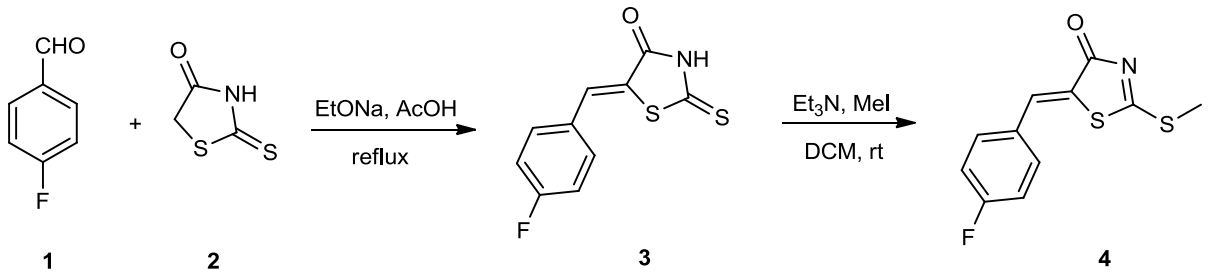
various bases and various solvents were selected as a model reaction to optimize the reactive conditions. In terms of the effect of solvents and bases on the condensation reaction, potassium carbonate was found to be the better base and ethanol was found to be the best solvent for the reaction (Table. **1**, entry 11); other solvents, including dichloromethane (DCM), acetic acid, methanol and toluene were less efficient (Table. **1**, entries 2–5, 7–10 and 12–15). Nevertheless, all of these yields were generally low before further optimizations. Ethanol gave the corresponding product in a 50–90% yield, which was the best among these solvents (Table. **1**, entries 1, 6 and 11). To increase the efficiency of the condensation reaction, the effects of different bases were investigated (Table. **1**, entries 1–15). Potassium carbonate exhibited the best performance with used solvents and gave better yield, (Table. **1**, entries 11–15). Diethylamine and triethylamine gave lower yields with other solvents, but gave better yield in combination with ethanol as a solvent (Table. **1**, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of ethanol turned out to be the best choice with yields of 50%, 65% and 90% (Table. **1**, entries 1, 6 and 11). We would like to mention here that ethanol as a solvent with potassium carbonate as base was the best choice with a yield of 90% and less time required for the completion of the reaction (Table. **1**, entry 11). Thus we decided to carry out the reactions in ethanol with potassium carbonate. Simultaneously, we also performed microwave-assisted reactions. In addition the reaction time for microwave-assisted reactions was much shorter than the same reactions in all of our studied substrates. As a result the reaction time was shortened, thermal decomposition also minimized, resulting in higher isolated yields (Table. **2**).

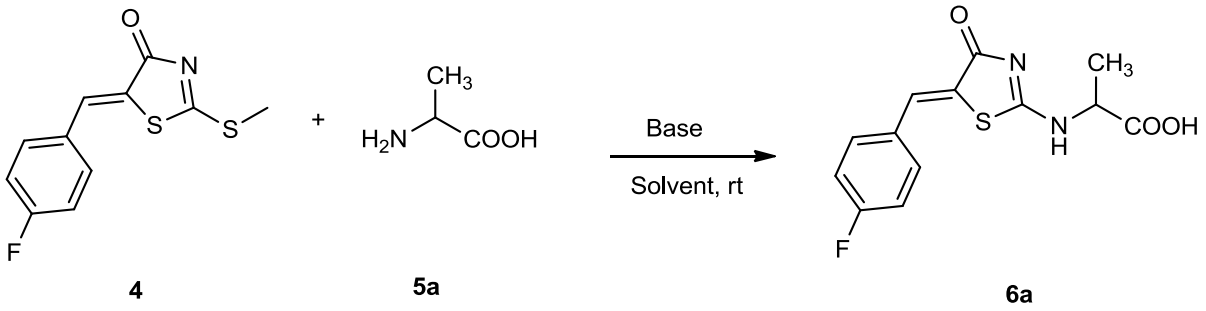
Table 1. Screening of bases, solvents, reaction time and yield for the synthesis (6a)[a].

Entry	Base	Solvent	Time (min)	Yield[b] (%)
1	Diethylamine	Ethanol	120	50
2	Diethylamine	Methanol	130	30
3	Diethylamine	Acetic acid	150	35
4	Diethylamine	DCM	110	40
5	Diethylamine	Toluene	140	30
6	Triethylamine	Ethanol	100	65
7	Triethylamine	Methanol	110	40
8	Triethylamine	Acetic acid	130	30
9	Triethylamine	DCM	120	45
10	Triethylamine	Toluene	125	35
11	Potassium carbonate	Ethanol	30	90
12	Potassium carbonate	Methanol	40	80
13	Potassium carbonate	Acetic acid	60	80
14	Potassium carbonate	DCM	50	85
15	Potassium carbonate	Toluene	70	75

[a] All the reaction was carried out in 1:1.2 molar amounts of each compound in 1 mL of solvent.
[b] Isolated yield.



Scheme. 1. Synthesis of (*Z*)-5-(4-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (**4**).



[a] Reaction condition: compound (**4**)(1 mmol), L-Alanine(**5a**)(1.2 mmol), base(1 mmol), solvent 1mL, rt. 30-150 min.

Scheme. 2. Screening of model reaction (Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**)[a].

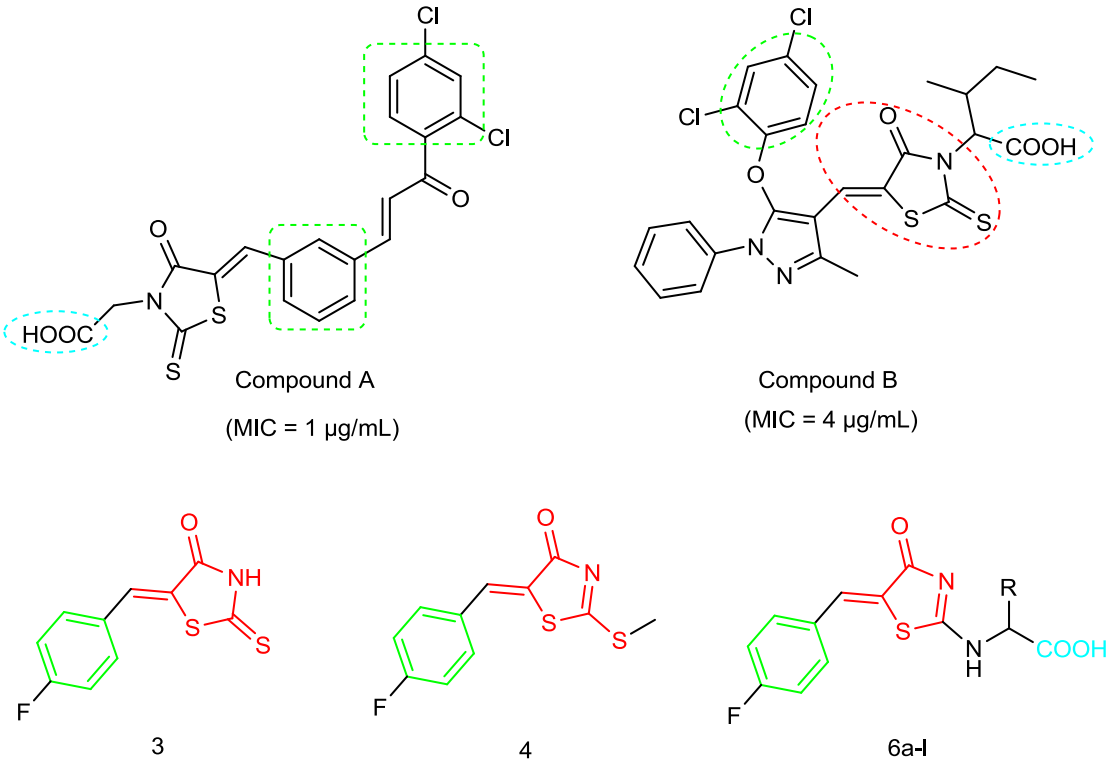


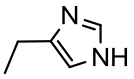
Fig. (1). Previously reported antibacterial agents and synthesized compounds.

The synthesized rhodanine derivatives by using microwave irradiation and conventional method **6a-l** (Scheme **3**, Table. **2**). The compound 5-(4-fluorobenzylidene)-2-thioxothiazolidin- 4-one **3** was prepared *via* a Knoevenagel condensation between 4-fluorobenzaldehyde **1** and rhodanine **2**. The compound 5-(4-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** was obtained *via* reaction of 5-(4-fluorobenzylidene)-2-thioxothiazolidin-4-one (**3**) with iodomethane in dichloromethane using triethylamine as catalyst [29]. Further, to expand the series, 2-((5-(4-fluorobenzylidene)- 4-oxo-4, 5-dihydrothiazol -2-yl)amino) acid derivatives **6a-l** were synthesized reacting 5-(4-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** with various amino acids **5a-l** in ethanol using K_2CO_3 as catalyst [30].

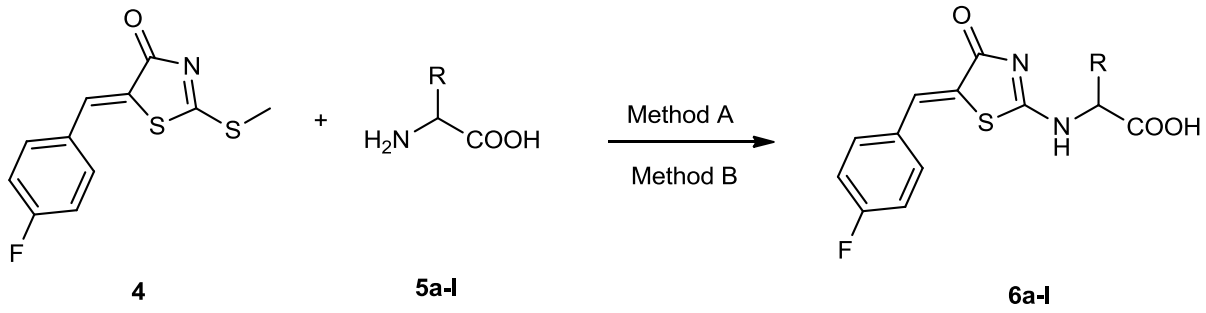
In this reaction, there was displacement of a methyl sulfinyl group by amino acids from the C2 position of the thiazolone ring.

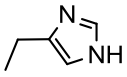
Rhodanine based compounds were synthesized by microwave irradiation (MW) as well as conventional heating with potassium carbonate and ethanol.

Table 2. Physical data for synthesized rhodanine derivatives 6(a-l)[a].

Sr. No.	Substituent (R)	Time (min)		Yield[b] (%)		Melting point (°C)
		MW[c]	Con[d]	MW[c]	Con[d]	
6a	-CH3	4	30	96	90	230-232
6b	-CH(CH3)2	4	40	96	80	202-204
6c	-CH(CH3)CH2CH3	3	35	94	82	140-142
6d	-CH2C6H5	3	45	93	80	170-172
6e	-CH2CH2SCH3	3	45	94	82	156-158
6f	-CH2CH(CH3)2	4	35	94	84	233-235
6g	-CH2OH	3	30	95	82	201-203
6h	-CH2SH	4	35	94	84	206-208
6i	-CH2COOH	4	50	96	80	182-184
6j		3	50	92	76	192-194
6k	-CH2C6H4OH	3	45	92	72	150-152
6l	-CHOHCH3	3	35	94	78	170-172

[a] Reaction condition (**6a-l**). Compound (**4**) (1 mmol), amino acids (**5a-l**) (1.2 mmol),
Method A: Microwave-assisted synthesis: potassium carbonate, ethanol, 70 ºC, 3-4 min.
Method B: Conventional synthesis: potassium carbonate, ethanol room temperature, 30-50 min.
[b] Isolated yields.
[c] Microwave-assisted.
[d] Conventional condition.



R = 5a = 6a = -CH_3
5b = 6b = -$CH(CH_3)_2$
5c = 6c = -$CH(CH_3)CH_2CH_3$
5d = 6d = -$CH_2C_6H_5$
5e = 6e = -$CH_2CH_2SCH_3$
5f = 6f = -$CH_2CH(CH_3)_2$
5g = 6g = -CH_2OH
5h = 6h = -CH_2SH
5i = 6i = -CH_2COOH
5j = 6j = 
5k = 6k = -$CH_2C_6H_4OH$
5l = 6l = -$CHOHCH_3$

[a]Reaction condition:
Method A: Microwave-assisted synthesis: potassium carbonate, ethanol, 70 ºC, 3-4 min.
Method B: Conventional synthesis: potassium carbonate, ethanol room temperature, 30-50 min.

Scheme. 3. Synthesis of (*Z*)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl) amino) substituted acid (**6a-l**)[a].

The physical data of the synthesized compounds are presented in (Table. **2**). All the reactions proceeded well in 3-4 min. in microwave irradiation to give products in very good yields (92–96%) and 30-50 min at conventional method to give products in very good yields (72–90%). The purity of the synthesized compounds was checked by TLC and melting points were recorded on SRS Optimelt, melting point apparatus

and are incorrected. The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

EXPERIMENTAL

General Procedure for the Synthesis of Compounds (3)

In a 100 ml round bottom flask, equimolar amounts of 4-fluorobenzaldehyde 1 (1 mmol), 2-thioxothiazolidin -4-one 2 (1 mmol), anhydrous sodium acetate (1 mmol) were added in glacial acetic acid (1 mL). The mixture was stirred under reflux condition for 7 h. The progress of reaction was monitored by TLC (20% ethyl acetate: n-hexane). After completion of the reaction, the reaction mixture was poured into the icecold water. The precipitate was filtered off and washed with water (3×15 mL), dried and purified by recrystallization in ethanol as solvent to give 85% yield.

(Z)-5-(4-fluorobenzylidene)-2-thioxothiazolidin-4-one (3)

Yellow solid. Yield: 85%. mp 226–228 ºC; ES-MS m/z: 239. IR νmax/cm^{-1}: 3034 (NH), 2837 (CH–Ar), 1687 (C=O), 1574 (C=C), 1444 (C=N), 1229 (C=S), 1069 (C–N). ^{1}H NMR: äppm = 6.90–7.10 (d, 2H, Ar–H), 7.50–7.60 (d, 2H, Ar–H), 8.10 (s, 1H, =CH), 7.90 (s, 1H, NH). ^{13}C NMR: δppm = 115.3, 116.3, 130.4, 130.8, 143.4, 162.3, 168.3, 193.6.

General Procedure for the Synthesis of Compounds (4)

In a 100 mL round bottom flask, the compound 3 (1 mmol), iodomethane (1.2 mmol) triethylamine (1.2 mmol) were added to dichloromethane (1 mL) at room temperature, stirred reaction mixture for 1 h at room temperature. The progress of the reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction the reaction mixture was concentrated in vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 75%.

(Z)-5-(4-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (4)

Yellow solid. Yield: 75%. mp 143–145 ºC; ES-MS m/z: 253. IR νmax/cm^{-1}: 3015 (CH–Ar), 1700 (C=O), 1594 (C=C), 1483 (C=N), 1153 (C-S), 824 (C–N). ^{1}H NMR: äppm = 2.80 (s, 3H, SCH_3), 7.50–7.75 (m, 4H, Ar–H), 7.90 (s, 1H, =CH). ^{13}C NMR: δppm = 14.2, 115.4, 130.4, 132.3, 132.4, 133.5, 152.2, 162.1, 167.2.

General Procedure for the Synthesis of Compounds (6a-l)

Method A: Microwave-Assisted Synthesis

In a 100 ml round bottom flask, the compound **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonates (1.2 mmol), were added to ethanol (1 mL) was added and this mixture subjected to MW irradiation (800 W), at 70 ºC temperature for 3-4 min. The progress of reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction, the reaction mixture was concentrated in vacuo. The resulting solid was extracted with ethyl acetate for column chromatography. The column chromatography was performed using silica gel (200–300 mesh), eluted with ethyl acetate and petroleum ether (1:1, v/v) to give product **6a-l** (Yield: 92-96 %).

Method B: Conventional Synthesis

In a 100 ml round bottom flask, the compound **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonates (1.2 mmol), were added to ethanol (1 mL) stirring 30-50 min. at room temperature. The progress of the reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction, the reaction mixture was concentrated in vacuo. The resulting solid was extracted with ethyl acetate for column chromatography. Column chromatography was performed using silica gel (200–300 mesh), eluted with ethyl acetate and petroleum ether (1:1, v/v) to give product 6a-l (Yield: 72-90 %).

(Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol- 2-yl)amino)propanoic acid (6a)

Yellow solid. Yield: 96%. mp 230–232 ºC; ES-MS m/z: 294. IR νmax/cm^{-1}: 3342 (OH), 2966 (CH–Ar), 1723 (C=O), 1593 (C=C), 1504 (C=N), 1158 (C-S), 893 (C–N). ^{1}H NMR: äppm = 1.40–1.45 (d, 3H, CH_3), 4.60–4.80 (q, 1H, CH), 7.36–7.65 (m, 4H, Ar-H), 7.86 (s, 1H, =CH), 10.20 (s, 1H, NH), 12.65 (s, 1H, OH). ^{13}C NMR: δppm = 16.9, 53.7, 115.4, 130.3, 130.7, 132.6, 152.2, 158.3, 167.2, 174.7.

(Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol- 2-yl)amino)-3-methylbutanoic acid (6b)

Yellow solid. Yield: 96%. mp 202–204 ºC; ES-MS m/z: 322. IR νmax/cm^{-1}: 3366 (OH), 3175 (NH), 2997 (CH–Ar), 1724 (C=O), 1677 (C=C), 1505 (C=N), 1235(C-S), 1160 (C–N). ^{1}H NMR: äppm = 0.90–1.10 (d, 6H, CH_3), 2.11–2.25 (m, 1H, CH), 4.47–4.55 (d, 1H, CH), 7.35–7.65 (m, 4H, Ar-H), 7.80 (s, 1H, =CH), 9.90 (s, 1H, NH), 13.00 (s, 1H, OH). ^{13}C NMR: δppm = 18.9,

30.2, 61.3, 115.3, 130.4, 130.8, 132.6, 152.2, 158.3, 162.2, 167.2, 174.3.

(Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methylpentanoic acid (6c)

Yellow solid. Yield: 94%. mp 140–142 ºC; ES-MS m/z: 336. IR νmax/cm^{-1}: 3523 (OH), 3180 (NH), 2964 (CH–Ar), 1703 (C=O), 1554 (C=C), 1503 (C=N), 1228 (C-S), 1158 (C–N). ^{1}H NMR: äppm = 1.01–1.15 (t, 3H, CH_3), 1.23–1.31 (d, 3H, CH_3), 1.83–2.03 (m, 3H, CH_2, CH), 3.45–3.55 (d, 1H, CH), 7.45–7.65 (m, 4H, Ar-H), 7.80 (s, 1H, =CH), 10.15 (s, 1H, NH), 12.80 (s, 1H, OH). ^{13}C NMR: δppm = 11.2, 15.3, 25.2, 37.3, 58.6, 115.3, 130.2, 130.8, 132.6, 152.2, 158.3, 162.2, 167.3, 174.6.

CONCLUSION

In conclusion, we have successfully developed an easy access to a new series of 2-((5-(4-fluorobenzylidene) -4-oxo-4, 5-dihydrothiazol -2-yl)amino) acid derivatives **6a-l**. The mild reaction conditions, good to excellent yields, easy workup, and easily available substrates make the reactions attractive for the preparation of compounds **6a-l**. Efforts towards the synthesis of other important drug molecules with a rhodanine moiety by microwave irradiation as well as conventional method are ongoing in our laboratory. Besides, the technique has the advantage of being simple and allows the synthesis of rhodanine moiety in minimum time.

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