

Synthesis of 5-arylalkylidenerhodanines catalyzed by tetrabutylammonium bromine in water under microwave irradiation

Jian-Feng Zhou,^{a,b*} Feng-Xia Zhu,^b Yuan-Zhi Song,^b and Yu-Lan Zhu^{a,b}

^a*Department of Chemistry, Huaiyin Teachers College, Huaian 223300, P. R. China*

^b*Jiangsu Key Laboratory for Chemistry of Low-Dimensional Materials,*

Huaian 223300, P. R. China

E-mail: jfzhou@163.com

Abstract

A series of benzylidenerhodanine derivatives were synthesized by the crossed Aldol condensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide (TBAB) as phase transfer catalyst in water under microwave irradiation. The reactions were completed in 8~10 min with 71~96% yield, short reaction times, environmentally benign conditions and easy work-up.

Keywords: Rhodanine, benzylidenerhodanines, aromatic aldehyde, microwave irradiation

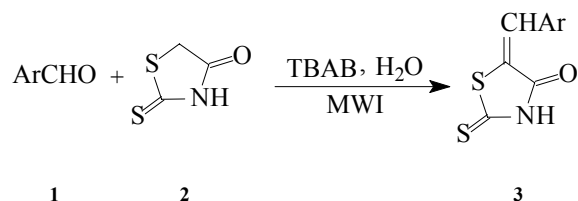
Introduction

Rhodanine derivatives have proven to be attractive compounds due to their outstanding biological activities and have undergone rapid development as anticonvulsant, antibacterial, antiviral and antidiabetic agents.¹ At the same time, rhodanine derivatives have been reported also as Hepatitis C Virus (HCV) protease inhibitors² and used as inhibitors of uridine diphospho-N-acetylmuramate/L-alanine ligase.³ Therefore, the synthesis of these compounds is of considerable interest. The rhodanine (2-thiono-4-thiazolidinone) moiety has been synthesized by various methods such as the addition of isothiocyanate to mercaptoacetic acid followed by acid-catalyzed cyclization, or the reaction of ammonia or primary amines with carbon disulfide and chloroacetic acid in the presence of bases.⁴ Condensation of aromatic aldehydes at the nucleophilic C-5 active methylene has been performed using piperidinium benzoate in refluxing toluene⁵ or sodium acetate in refluxing glacial acetic acid.⁴ Recently, Sim *et al.*⁶ reported the synthesis of 5-arylalkylidene rhodanines in 60-82% yields by heating the reactants suspended in toluene at 110°C for 3 days. Sing *et al.*⁷ reported the condensation of rhodanine with an aldehyde (0.1 mmol) by heating in anhydrous EtOH (200 mL) for 6 h at 80°C. Alternatively, rhodanine

(0.1 mmol), ketone (0.1 mmol) and NH_4OAc (0.2 mmol) were refluxed in toluene (500 mL) for 3 days (61-92% yields). Obviously, these methods involve long reaction times, high temperatures, use large quantities of organic solvents and some give unsatisfactory yields. Therefore, it is useful to develop new methods, which are simple and environmentally friendly for the synthesis of 5-arylalkylidene rhodanines.

The wide applicability of microwave irradiation in chemical reaction enhancement is due to high reaction rates, formation of cleaner products, and operational simplicity.^{8, 9, 10} Zhang, Alloum *et al.* reported the successful synthesis of some 5-arylalkylidene rhodanines on solid inorganic supports in dry media under microwave irradiation.^{11, 12} Since then, Toda *et al.*¹³ have reported the first examples of aldol condensation in the absence of solvent. Due to stringent and growing environmental regulations, organic chemists have endeavored to develop clean, economical, and environmentally safer methodologies. One of the most promising approaches is to utilize water as reaction medium.^{14, 15} The use of microwave irradiation to carry out organic reactions is a well-established procedure since the reactions are clean, rapid and economical. Application of phase-transfer catalysis (PTC) instead of traditional technologies for industrial processes provides substantial benefits to the environment. The combination of these techniques has shown excellent results.¹⁶

We have reported previously a high yield synthesis of *bis*(benzylidene)cycloalkanones by the aldol condensation in an aqueous medium under phase-transfer catalysis and microwave irradiation.¹⁷ This paper reports an efficient and clean synthesis of 5-arylalkylidenerhodanines by the aldol condensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide (TBAB) as phase-transfer catalyst in an aqueous medium under microwave irradiation (Scheme 1). This reaction requires only 8-10 minutes, proceeds in 71~96% yields, is environmentally benign, with low energy consumption and easy work-up.



a) Ar = C_6H_5 , b) 2- ClC_6H_4 , c) 4- ClC_6H_4 , d) 4- $\text{NO}_2\text{C}_6\text{H}_4$, e) 3- $\text{NO}_2\text{C}_6\text{H}_4$, f) 4- $\text{CH}_3\text{C}_6\text{H}_4$, g) 4- $\text{CH}_3\text{OC}_6\text{H}_4$, h) 4- $(\text{CH}_3)_2\text{NC}_6\text{H}_4$, i) 2-furyl, j) 2- HOC_6H_4 , k) 3,4- $(\text{OCH}_2\text{O})\text{C}_6\text{H}_3$, l) 3-HO-4- $\text{CH}_3\text{OC}_6\text{H}_3$

Scheme 1

Results and Discussion

The reaction of *m*-nitrobenzaldehyde (**1e**) with rhodanine was tested as a model reaction and was explored initially without any catalyst using water as a solvent under microwave irradiation for 20 min. Unfortunately, the target compound could not be obtained (*Table 1, entry 1*) presumably due to the fact that the reactants exist as a non-miscible mixture of oil and water. Therefore, TBAB as phase-transfer catalyst, was applied for this reaction. The results showed that when the molar ratio of TBAB, aromatic aldehyde and rhodanine was 0.3:1:1, the reaction proceeded efficiently (*Table 1, entry 2*). An attempt to maximize the yield and shorten the reaction time, by increasing the amounts of TBAB, did not increase the rate of the reactions nor the yield of **3e** (*Table 1, entry 3-4*). At the same time, various phase-transfer catalysts such as tetraethylammonium bromine (TEAB), triethylbenzylammonium chloride (TEBAC), PEG-400 and PEG-600 were also investigated for this reaction. The reaction proceeded with TBAB, TEAB and TEBAC as phase-transfer catalyst and gave **3e** in 96, 74 and 63% yield, respectively (*Table 1, entries 2, 5, 7*). However, with PEG-400 and PEG-600 as phase-transfer catalysts, compound **3e** was not obtained after microwave irradiation for 20 minutes (*Table 1, entry 8, 9*).

Table 1. Influence of type and amount of catalyst on the reaction of **3e** with rhodanine ^a

Entry	Phase transfer Catalyst (mol.)	Time (min)	Yield (%)
1	TBAB	0	0
2	TBAB	0.3	96
3	TBAB	0.6	77
4	TBAB	0.9	55
5	TEAB	0.3	74
6	TBAB	0.3	240 ^b
7	TEBAC	0.3	63
8	PEG-400	0.3	0
9	PEG-600	0.3	0

^a *m*-Nitrobenzaldehyde (1mmol), rhodanine (1mmol), catalyst and 5mL water; microwave power 195W, pulsed irradiation.

^b Carried out under conventional reflux heating instead of microwave irradiation.

It is believed that $Q_4N^+ X^-$ (TBAB) serves both as a phase-transfer catalyst and as a base because the reactants would exist as a non-miscible mixture of oil and water in the absence of $Q_4N^+ X^-$, and $5-CH_2$ of rhodanine cannot be removed by the alkali effectively. Therefore, the carbanion or enolate ions would not be formed in the reaction, which would explain why the reaction does not take place in the presence of polyethylene glycol, or in the absence of TBAB. It

is also obvious that the rates of the reactions were accelerated by microwave irradiation. For instance, in the case of **3e**, the yield is only 65% after refluxing for 4 hrs (*Table 1, entry 6*).

In addition to our study in an aqueous medium, the aldol condensations of aromatic aldehydes with rhodanine in acetic acid using sodium acetate as catalyst under microwave irradiation was investigated. The results show that the reaction requires long times and proceeds in low yields in organic media when compared with the aqueous medium (*Table 2*).

Table 2. Reaction times, yields of **3a-3m** in organic medium and in water medium

Products	In Organic Medium		In Aqueous Medium		Mp (°C)	Lit. mp (°C)
	Time min	Yields (%) ^a	Time (min)	Yields (%) ^b		
3a	8	76	8	86	205-206	199-202 ¹⁸
3b	10	45	8	77	177-178	179.5-180.5 ¹¹
3c	10	81	8	75	242-243	224-230 ¹⁸
3d	10	89	8	85	255-256	180.5-181.5 ¹¹
3e	10	94	8	96	269-270	263-264 ¹¹
3f	15	43	8	83	233-234	219-223 ¹⁸
3g	10	40	8	80	261-262	240-246 ¹⁸
3h	10	60	8	78	283-284	266-270 ¹⁸
3i	10	74	8	70	228-229	228-229 ¹¹
3j	15	71	8	72	221-222	200-202 ¹⁹
3k	15	61	10	71	278-279	>300 ²⁰
3l	15	60	10	77	223-225	231-231.5 ¹¹

^aAromatic benzaldehyde (1mmol), rhodanine (1mmol), NaOAc (1.2 mmol) and 5mL AcOH; microwave power 195W, pulsed irradiation. ^bAromatic benzaldehyde (1m mol), rhodanine (1mmol), TBAB (0.3 mmol) and 5mL water; microwave power 195W, pulsed irradiation.

Experimental Section

General Procedures. All compounds prepared were characterized by ¹H NMR, IR and elemental analyses and are described in the experimental section. Melting points were determined in a XT-5 digital melting point instrument and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ¹H NMR spectra were measured at 400 MHz on a Burke-400 spectrometer using TMS as internal standard and DMSO-d₆ as solvent. MS spectra were obtained on a LCQ Advanbabe instrument. Elemental analyses were determined using a Perkin-Elmer 240C Elemental Analyzer. The reactions were carried out with a modified commercial microwave oven (Sanle WP650D 650w) under atmospheric pressure. All the reagents are commercially available.

General experimental procedure. A mixture of the aromatic aldehyde (1mmol), rhodanine (1mmol), TBAB (0.3 mmol) and water (5 mL) in an Erlenmeyer flask (25ml) equipped with a reflux condenser were irradiated in a microwave oven at 195 watts at 100°C for 8~10 minutes. After the completion of the reaction was monitored by TLC, the reaction mixture was allowed to stand at room temperature to solidify. The solid obtained was collected, washed with 2-3 mL water. It was dried and recrystallized from 3 mL DMF-H₂O (50:50 by v/v) to give **3a~l**. For example, **3l**: yellow solid; mp. 223~225°C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H: 13.71(s, 1H, NH), 10.09 (s, 1H, OH), 7.59 (s, 1H, CH=), 7.17(s, 1H, aromatic H), 7.14 (d, 1H, *J* = 8.4Hz, aromatic H), 6.95 (d, 1H, *J* = 8.4Hz, aromatic H), 3.84 (s, 3H, CH₃O); IR (KBr) ν: 3340, 3266, 3007, 2934, 1714, 1591, 1181 cm⁻¹; MS *m/z*: 266.4 (M-H)⁻; Anal. Calcd for C₁₁H₉NO₃S₂: C, 49.42; H, 3.39; N, 5.24. Found: C, 49.67; H, 3.32; N, 5.15

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20571029) and Jiangsu Key Laboratory for Chemistry of Low-Dimensional Materials for financial support.

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