Synthesis of 5-arylidene-3-methylrhodanines catalyzed by 1-butyl-3-methylimidazolium chloride in water under microwave irradiation condition

- **Le Hoang Giau**
- **Ngo Thi Thuy Duong**
- **Thach Ut Dong**
- **Nguyen Kim Phi Phung**
  University of Science, VNU-HCM
- **Fritz Duus**
  Roskilde University, Denmark

(Received on August 7th 2015, accepted on April 14 th 2016)

ABSTRACT

Six 5-arylidene-3-methylrhodanine derivatives were synthesized by the crossed aldolization of aromatic aldehydes with 3-methylrhodanine using 1-butyl-3-methylimidazolium chloride ([BMI]Cl) as phase transfer catalyst in water. The reactions, under microwave irradiation (160 watts) during 10 minutes, afforded the yield of 59–83 %. This is the first time [BMI]Cl was used as phase transfer catalyst in the aldol condensation.

Keywords: *3-Methylrhodanine, 5-arylidene-3-methylrhodanine, ionic liquid, microwave irradiation condition, aldol condensation*

INTRODUCTION

Rhodanine derivatives have showed a wide range of biological activities which include anticonvulsant, antibacterial, antiviral and antidiabetic effects [1]. These have also been reported as Hepatitis C virus (HCV) protease inhibitors [2] and used as inhibitors of uridine diphospho-*N*-acetylmuramate/L-alanine ligase [3]. Recently, substituted rhodanines were investigated for tau aggregation inhibitor properties [4]. Rhodanines, classified as nonmutagenic and a long-term study on the clinical effects of the rhodanine-based Epalrestat as an anti-diabetic showed that it was well tolerated [5]. Due to various possibilities the rhodanine derivatives, these compounds will probably remain a privileged scaffold in drug discovery. Therefore, the synthesis of these compounds is of considerable interest.

Condensation of aldehydes at the active methylene C-5 of 3-methylrhodanine has been performed using piperidinium benzoate in toluene or sodium acetate in glacial acetic acid [6, 7]. Recently, Sim *et al.* [8] reported the synthesis of 5-arylidenerhodanines in 60–82 % yields by heating the reactants suspended in toluene at 110 ^{o}C for 3 days. Sing *et al.* [9] reported the condensation of rhodanine with an aldehyde (0.1 mmol) by heating in anhydrous EtOH (200 mL) at 80 ^{o}C for 6 hours. Obviously, these methods involve long reaction times, high

temperatures, using large quantities of organic solvents. Therefore, it is useful to develop new methods, which are simple and friendly with the environment to synthesize rhodanine derivatives. Jian-Feng Zhou *et al.* [10] had reported the synthesis of 5-arylidenerhodanines by the aldol condensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide as phase transfer catalyst in an aqueous medium under microwave irradiation.

Microwave (MW) activation provides a valuable tool for organic synthesis. MW-assisted reactions have emerged as green methods which promote much faster, cleaner reactions than conventional heating [11-14]. MW-assisted organic syntheses in green media or in the absence of solvent have received significant interest due to the simple and environmentally benign procedures [15–17].

In the present paper, we report the synthesis of seven 5-arylidene-3-methylrhodanines by the crossed aldol condensation of substituted benzaldehydes with 3-methylrhodanine using 1-butyl-3-methylimidazolium chloride ([BMI]Cl) as phase transfer catalyst in an aqueous medium under microwave irradiation (Fig. 1). These reactions required only 10 minutes and proceeded in 59–83 % yields. Especially, this is the first time [BMI]Cl was used as phase transfer catalyst in this reaction.

MATERIALS AND METHOD

Materials

Melting points were determined in a Wagner & MunzPolytherm A melting point apparatus. The ^{1}H NMR spectra were run on a Bruker Ultrashield 500 Plus spectrometer operating at 500 MHz for ^{1}H using $CDCl_3$ as solvent. The mass spectra were scanned on a GC Agilent Technologies 7890 A spectrometer with detector MS Agilent Technologies 5975 C.

General experimental procedure

In a 5 mL test tube, a solution containing the studied aromatic aldehyde (x mmol), 3-methylrhodanine (0.14 mmol), [BMI]Cl (0.14 mmol), base (0.14 mmol) and water (1 mL) was irradiated in a microwave oven at 160 watts for 10 minutes. After the reaction, the mixture was allowed to stand at room temperature to solidify. The solid was filtered, dried and recrystallized from $CHCl_3$. The obtained compound was dried in a desiccator up to the moment the weight of the residue did not change. Then this compound was weighed for the calculation of the yield of the reaction.

5-Benzylidene-3-methyl-2-thioxothiazolidin-4-one (3a)

Orange solid; yield: 74 %; mp 169–170 ^{o}C. ^{1}H NMR δ_H 3.52 (3H, s, NCH_3), 7.42–7.51 (5H, m, ArH) and 7.74 (1H, s, C=CH). MS (ESI) *m/z* = 235 $[M]^+$.

3-Methyl-5-(4-methylbenzylidene)-2-thioxothiazolidin-4-one (3b)

Orange solid, yield: 62 %, mp: 160–162 ^{o}C. ^{1}H NMR δ_H 2.41 (3H, s, $ArCH_3$), 3.53 (3H, s, NCH_3), 7.29 (2H, d, J = 8.0 Hz, ArH), 7.40 (2H, d, J = 8.0 Hz, ArH) and 7.74 (1H, s, C=CH). MS (ESI) *m/z* = 249 $[M]^+$

5-(4-Methoxybenzylidene)-3-methyl-2-thioxothiazolidin-4-one (3c)

Orange solid, yield: 59 %, mp: 164-165 ^{o}C. ^{1}H NMR δ_H 3.45 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 6.92 (2H, d, J = 8.5 Hz, ArH), 7.40 (2H, d, J = 8.5 Hz, ArH) and 7.64 (1H, s, C=CH). MS (ESI) *m/z* = 265 $[M]^+$

5-(4-Chlorobenzylidene)-3-methyl-2-thioxothiazolidin-4-one (3d)

Orange solid, yield: 70 %, mp: 194–195 ^{o}C. ^{1}H NMR δ_H 3.56 (3H, s, NCH_3), 7.45–7.50 (4H, m, ArH) and 7.72(1H, s, C=CH). MS (ESI) *m/z* = 269 $[M]^+$

5-(4-Trifluoromethylbenzylidene)-3-methyl-2-thioxothiazolidin-4-one (3e)

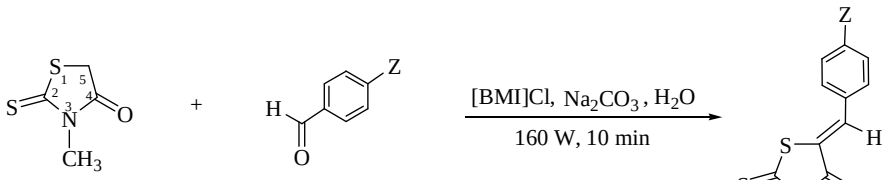
Orange solid, yield: 83 %, mp: 164-165 ^oC. ^1H NMR δ_H 3.46 (3H, s, NCH_3), 7.53 (2H, d, J = 10.0 Hz, ArH), 7.66–7.67 (3H, m, ArH and C=CH). MS (ESI) *m/z* = 303 $[M]^+$

5-(4-Nitrobenzylidene)-3-methyl-4-oxo-2-thionothiazolidine (3f)

Orange solid, yield: 76 %, mp: 194–195 ^oC. ^1H NMR δ_H 3.50 (3H, s, NCH_3), 7.59 (2H, d, J = 10.0 Hz, ArH), 7.68 (1H, s, C=CH) and 8.26 (2H, d, J = 10.0 Hz, ArH). MS (ESI) *m/z* = 280 $[M]^+$

RESULTS AND DISCUSSION

In order to optimize the reaction condition, we examined the influences of contributing parameters such as reaction times, molar ratios of reactants, catalytic amounts and types of base catalysts. The crossed aldol condensation of 3-methylrhodanine with benzaldehyde was chosen as the model reaction and NaOH, [BMI]Cl were selected as the base and phase-transfer catalyst, respectively in an aqueous medium under microwave irradiation (Table 1). In the first series of studies, the effect of different molar ratios (from 1:1 to 1:5) of 3-methylrhodanine and benzaldehyde was investigated. The results showed that the optimal ratio for maximum yield was observed at a ratio of 1:3 (Table 1, entry 3). The high usage of benzaldehyde could be explained by its evaporation under the *microwave irradiation condition* in a domestic microwave oven.



1

2a Z = H **2d** Z = Cl
2b Z = CH_3 **2e** Z = CF_3
2c Z = OCH_3 **2f** Z = NO_2

3a-f

Fig. 1. Synthesis of 5-arylidene-3-rhodanine from 3-methylrhodanine and substituted benzaldehydes

Next, we compared the catalytic activity of NaOH with other bases as shown in Table 2. Under the same experimental conditions, the inorganic bases (NaOH, KOH, Na_2CO_3 and $Na_2B_4O_7.10H_2O$) gave better results than organic bases [pyridine and $(CH_3)2NH$]. Among these inorganic bases, Na_2CO_3 was the best base catalyst (Table 2, entry 3) to give the highest yield. It was found that in the absence of base, the reaction did not proceed to desired products (Table 3, entry 6).

The result in Table 3 showed that Na_2CO_3 was a suitable base for this type of aldol condensation. The molar ratio between 3-methylrhodanine: Na_2CO_3: [BMI]Cl was further investigated and the high yield was achieved at the ratio of 1:1:1 (Table 3, entry 4).

The optimized condition of this reaction was applied to synthesize various 5-arylidene-3-methylrhodanine from various benzaldehydes possessing different substituents (Table 4). The results of the aldol condensation of aromatic compounds with 3-methylrhodanine showed that substituted benzaldehydes with electron withdrawing groups (Table 4, entries 5, 7) were more reactive than the ones bearing electron donating groups (Table 4, entries 1–4). The much electrophilic the aldehydic carbon of benzaldehyde, the much reactive it is. In general, the aldolisation of several aromatic aldehydic

substrates with 3-methylrhodanine proceeded smoothly to give the corresponding 5-arylidene-3-methylrhodanines in good to excellent yields within short reaction times.

Finally, in an investigation of the influence of microwave irradiation, a similar yield was obtained in the case of aldolisation of 3-methylrhodanine with *p*-trifluoromethyl benzaldehyde under conventional heating, however, this reaction required much reaction time (Table 4, entry 6).

Table 1. Effect of 3-methylrhodanine:benzaldehyde molar ratio in the crossed aldol condensation[a]

Entry	3-Methylrhodanine: benzaldehyde (mol : mol)	Yield[b] (%)
1	1:1	54
2	1:2	61
3	1:3	65
4	1:4	65
5	1:5	66

[a] Reagents and conditions: **1** (0.14 mmol), NaOH (0.14 mmol, 1 eq.), [BMI]Cl (0.14 mmol, 1 eq.) H_2O (1 mL), MW: 160 W, 10 min. [b] Isolated yield *after recrystallization*

Table 2. Effect of various base catalysts on the crossed aldol condensation of 3-methylrhodanine (**1**) with benzaldehyde (**2a**)[a]

Entry	Base catalyst	Yield[b] (%)
1	NaOH	65
2	KOH	71
3	Na_2CO_3	77
4	$Na_2B_4O_7.10H_2O$	74
5	CH_3COONa	66
6	$(CH_3)_2NH$	35
7	Pyridine	35

[a] Reagents and conditions: **1** (0.14 mmol), **2a** (0.42 mmol, 3eq), base (0.14 mmol, 1 eq), [BMI]Cl (0.14 mmol, 1 eq), H_2O (1 mL), MW: 160 W, 10 min. [b] Isolated yield *after recrystallisation*

Table 3. Effect of molar ratio of 3-methylrhodanine : Na_2CO_3: [BMI]Cl in the crossed aldol condensation with benzaldehyde[a]

Entry	3-Methylrhodanine : Na_2CO_3 : [BMI]Cl (mol : mol : mol)	Yield[b] (%)
1	1.00 : 1.00 : 0.25	53
2	1.00 : 1.00 : 0.50	63
3	1.00 : 1.00 : 0.75	73
4	1.00 : 1.00 : 1.00	74
5	1.00 : 1.00 : 1.25	71
6	1.00 : 0.00 : 1.00	0
7	1.00 : 0.50 : 1.00	68
8	1.00 : 0.15 : 1.00	66

[a] Reagents and conditions: **1** (0.14 mmol), **2a** (0.42 mmol, 3eq), H_2O (1 mL), MW: 160 W, 10 min. [b] Isolated yield after recrystallisation

Table 4. Effect of various substituted benzaldehydesin the crossed aldol condensation of 3-methylrhodanine[a]

Entry	Product	Yield[b] (%)		Entry	Product	Yield[b] (%)
1	3a	74		5	3e	83
2	3b	62		6	3e*	78
3	3c	59		7	3f	76
4	3d	70				

[a]Reagents and conditions: 1 (0.14 mmol), substituted benzaldehydes (0.42 mmol, 3eq), Na_2CO_3(0.14 mmol, 1 eq), [BMI]Cl (0.14 mmol, 1 eq), H_2O (1 mL), MW: 160 W, 10 min. [b]Isolated yield after recrystallization. *Carried out under conventional reflux heating (80 ^oC, 300 minutes) instead of microwave irradiation.

CONCLUSION

We reported a straightforward and effective method for the synthesis of 5-arylidene-3-methylrhodanine with the assistance of microwave irradiation from 3-methylrhodanine and substituted benzaldehydes based on crossed aldol condensation in water using [BMI]Cl as phase-transfer catalyst. The microwave irradiation was prominent with slightly higher yield 83 % in a short time 10 min compared with conventional heating method.

Acknowledgements: *The authors would like to thank Prof. Fritz Duus, Department of Science, Systems and Models, Roskilde University, Denmark for the gift of 3-methylrhodanine.*

Tổng hợp 5-arylidene-3-methylrhodanine sử dụng 1-butyl-3-methylimidazolium chloride trong nước dưới sự chiếu xạ vi sóng

- **Lê Hoàng Giàu**
- **Ngô Thị Thùy Dương**
- **Thạch Út Đồng**
- **Nguyễn Kim Phi Phụng**
  Trường Đại học Khoa học Tự nhiên, ĐHQG-HCM
- **Fritz Duus**
  Đại học Roskilde, Đan Mạch

TÓM TẮT

Tổng hợp 6 dẫn xuất 5-arylidene-3-methylrhodanine dựa trên phản ứng ngưng tụ aldol chéo của aldehyde thơm và 3-methylrhodanine, sử dụng 1-butyl-3-methylimidazolium chloride ([BMI]Cl) làm xúc tác chuyển pha trong dung môi nước. Phản ứng được thực hiện dưới sự chiếu xạ vi sóng (160 watts) trong thời gian 10 phút cho hiệu suất 59–83 %. Lần đầu tiên chất lỏng ion [BMI]Cl được sử dụng làm chất xúc tác chuyển pha trong phản ứng ngưng tụ aldol.

Từ khóa: *3-Methylrhodanine, 5-arylidene-3-methylrhodanine, chất lỏng ion, chiếu xạ vi sóng, phản ứng ngưng tụ aldol*

REFERENCES

[1]. K. Bourahla, A. Derdour, M. Rahmouni, F. Carreaux, J.P. Bazureaua, A practical access to novel 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones via sulfur/nitrogen displacement under solvent-free microwave irradiation, *Tetrahedron Lett.*, 48, 5785 (2007).

[2]. J.H. Ahn, S.J. Kim, W.S. Park, S.Y. Cho, J.D. Ha, S.S. Kim, S.K. Kang, D.G. Jeong, S.K. Jung, S.H. Lee, H.M. Kim, S.K. Park, K.H. Lee, C.W. Lee, S.E. Ryu, J.K. Choi, Synthesis and biological evaluation of rhodanine derivatives as PRL-3 inhibitors, *Bioorg. Med. Chem. Lett.* 16, 2996 (2006).

[3]. M.M. Sim, A.D. Buss, S.C. Crasta, K.L. Goh, S.K. Lee, Benzylidenerhodanines as novel inhibitors of UDP-N-acetylmuramate/L-alanine ligase, *Bioorg. Med. Chem. Lett.*, 12, 697 (2002).

[4]. B. Bulic, M. Pickhardt, I. Khilstunova, J. Biernat, E.M. Mandelkow, E. Mandelkow, H. Waldmann, Rhodanine-based tau aggregation inhibitors in cell models of tauopathy, *Angew. Chem. Int. Ed. Engl.*, 46, 9215 (2007).

[5]. N. Hotta, Y. Akanuma, R. Kawamori, K. Matsuoka, Y. Oka, M. Shichiri, T. Toyota, M. Nakashima, I. Yoshimura, N. Sakamoto, Y. Shigeta, Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative aldose reductase inhibitor-diabetes complications trial, *Diabetes Care*, 29, 1538 (2006).

[6]. F.C. Brown, 4-Thiazolidinones, *Chem. Rev.*, 61, 463 (1961).

[7]. S.P. Singh, S.S. Parmar, K.V. Raman, I. Stenberg, Chemistry and biological activity of thiazolidinones, *Chem. Rev.*, 81, 175 (1981).

[8]. C.L. Lee, M.M. Sim, Solid-phase combinatorial synthesis of 5-arylalkylidene rhodanine, *Tetrahedron Lett.*, 41, 5729 (2000).

[9]. A.B. Alloum, S. Bakkas, K. Bougrin, M. Soufiaoui, Synthèse de nouvelles spiro-rhodanine-pyrazolines par addition dipolaire-1,3 de la diphénylnitrilimine sur quelques 5-arylidènerhodanines en 'milieu sec' et sous irradiation micro-onde, *J. New.Chem.*, 22, 809 (1998).

[10]. J.F. Zhou, Synthesis of spiro-fused pyrazolidoylisoxazolines, *Org. Prep. Proced. Int.*, 37, 75 (2005).

[11]. H. Koshima, M. Kubota, Microwave-assisted Friedel-Crafts reactions, *Synth. Commun.*, 33, 3983 (2003).

[12]. C.R. Trauss, J. Varma, Microwave methods in organic synthesis, *Green Chem. Lett. Rev.*, 1, 37 (2007).

[13]. W. Su, J. Li, C. Jin, Microwave assisted, $Yb(OTf)_3$ /TfOHCocatalyzedsynthesis of xanthones and thioxanthones by intramolecular Friedel-Crafts reaction under solvent-free conditions, *Heterocycles*, 83, 855 (2011).

[14]. A. Majumder, R. Gupta, A. Jain, Microwave-assisted synthesis of nitrogen-containing heterocycles, *Green Chem. Lett. Rev.*, 6, 151 (2013).

[15]. P. Sunitha, K.S. Kumar, B.R. Rao, G. Venkateshwarlu, Microwave assisted efficient synthesis of β-keto-sulfones in aqueous medium, *Green. Chem. Lett. Rev.*, 1, 179 (2008).

[16]. J. Andraos, A.P. Dicks, Green chemistry teaching in higher education: a review of effective practices, *Green Chem. Lett. Rev.*, 2, 87 (2009).

[17]. A.P. Dicks, R.A. Batey, Greening the organic curriculum: Development of an undergraduate catalytic chemistry course, *Green Chem. Lett. Rev.*, 2, 9 (2009).