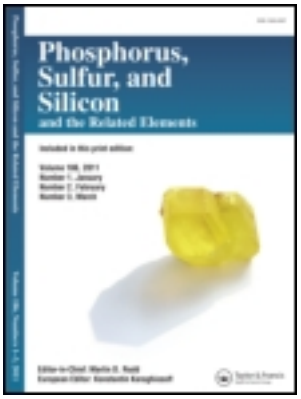


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Facile and Convenient Synthesis of 5-Arylalkylidenerhodanines by Electrocatalytic Crossed Aldol Condensation

Hojat Veisi [a], Zahra Vafajoo [b], Behrooz Maleki [c] & Malek Taher Maghsoodlou [b]

[a] Department of Chemistry, Payame Noor University, Tehran, Iran

[b] Department of Chemistry, The University of Sistan and Baluchestan, Zahedan, Iran

[c] Department of Chemistry, Hakim Sabzevari University, Sabzevar, Iran

Accepted author version posted online: 09 Aug 2012.Published online: 31 May 2013.

To cite this article: Hojat Veisi, Zahra Vafajoo, Behrooz Maleki & Malek Taher Maghsoodlou (2013): Facile and Convenient Synthesis of 5-Arylalkylidenerhodanines by Electrocatalytic Crossed Aldol Condensation, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:6, 672-677

To link to this article: http://dx.doi.org/10.1080/10426507.2012.717134

Phosphorus, Sulfur, and Silicon, 188:672–677, 2013

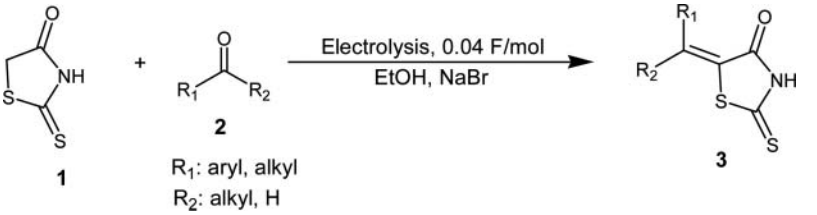
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.717134

FACILE AND CONVENIENT SYNTHESIS OF 5-ARYLALKYLIDENERHODANINES BY ELECTROCATALYTIC CROSSED ALDOL CONDENSATION

Hojat Veisi,[1] Zahra Vafajoo,[2] Behrooz Maleki,[3] and Malek Taher Maghsoodlou[2]

[1]*Department of Chemistry, Payame Noor University, Tehran, Iran*
[2]*Department of Chemistry, The University of Sistan and Baluchestan, Zahedan, Iran*
[3]*Department of Chemistry, Hakim Sabzevari University, Sabzevar, Iran*

GRAPHICAL ABSTRACT



Abstract *An electrochemically induced catalytic crossed Aldol condensation of one equivalent of rhodanine with various aromatic aldehydes and ketones in ethanol in an undivided cell in the presence of sodium bromide as an electrolyte results in the formation of the corresponding 5-arylalkylidenerhodanines in 80–96% yield with reactions in 40 min.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Electrocatalysis; aldol condensation; rhodanine; aldehydes; ketones

INTRODUCTION

The discovery of novel synthetic methodologies to facilitate the efficient preparation of compounds of prominent utility is a pivotal focal point of research in modern organic chemistry.[1] The continual upsurge in facile, convenient, and nonpolluting synthetic procedures urges chemists to increase the tools of their arsenal. One approach to address this challenge involves the development of tandem reactions, which are defined as a one-pot combination of two or more reactions that occur in a specific order.[2] In addition to the intrinsic atom economy and selectivity underlying such protocols, the tandem reaction strategy

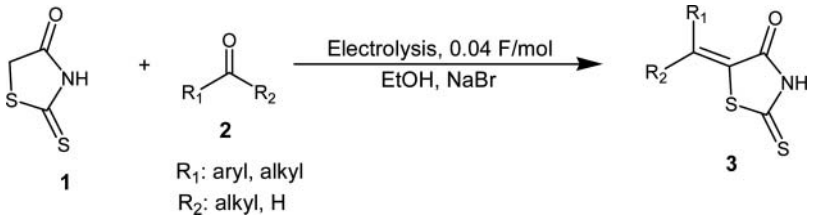
Received 27 April 2012; accepted 27 July 2012.
We are thankful to the Payame Noor University (PNU) for partial support provided for this work.
Address correspondence to Hojat Veisi, Department of Chemistry, Payame Noor University, 19395-4697 Tehran I.R. of Iran. E-mail: hojatveisi@yahoo.com

offers significant advantages over conventional linear-type synthesis due to its flexible and convergent nature.[3]

Compounds containing the 2-thioxothiazolidin-4-one ring (rhodanine, pKa 5.52) have showed a wide range of pharmacological activities, which includes antimicrobial,[4–9] anticonvulsant,[10] antibacterial,[10] antiviral,[11] anti-diabetic,[12] and anticonvulsant effects.[13] In addition, rhodanine-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV NS3 protease,[15] aldose reductase,[16] β-lactamase,[17] UDP-N-acetylmuramate/L-alanine ligase,[18] antidiabetic agents,[19] cathepsin D,[20] and histidin edecarboxylase.[21] The rhodanine moiety has been synthesized by various methods such as the addition of isothiocyanate to mercaptoacetic acid followed by acidcatalyzed cyclization, or the reaction of ammonia or primary amines with carbon disulfide and chloroacetic acid in the presence of bases.[22] Condensation of aromatic aldehydes or ketones at the nucleophilic C-5 active methylene has been performed using piperidinium benzoate in refluxing toluene,[22] under microwave conditions in the presence of K_2CO_3/Al_2O_3,[23] NH_4OH/NH_4Cl,[24] or sodium acetate in refluxing glacial acetic acid.[25] Recently, Sim et al.[26] reported the synthesis of 5-arylalkylidene rhodanines in 60–82% yield by heating the reactants suspended in toluene at 110 °C for 3 days. Sing et al.[27] 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% yield). 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 environment friendly for the synthesis of 5-arylalkylidene rhodanines. Also, rhodanine derivatives have attracted considerable pharmaceutical interest. Therefore, the preparation of this heterocyclic core unit has attracted the attention of many organic chemists.

RESULTS AND DISCUSSION

Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of electrochemical procedures is often limited on account of their technical complexity, and the recently developed electrochemically induced Knoevenagel[28] and Michael[29] reactions are in compliance with this thesis. In the course of our study on the synthesis of organic compounds,[30] we applied this electrocatalytic procedure to the synthesis of a number of medicinally relevant rhodanine derivatives. In the present study we report our results on electrocatalytic tandem chain transformation of rhodanine **1** and arylaldehydes **2** into **3** under neutral and mild conditions by electrolysis in an undivided cell. The reaction was performed in ethanol in the presence of sodium bromide as an electrolyte (Scheme 1).



Scheme 1

Table 1 Electrocatalytic transformation of rhodanine (**1**) and benzaldehyde (**2**) into (**3**)[a]

I (mA)	Current density (mA/cm^2)	Time (min)	Electricity passed (F/mol)	Yield (%)[b]
5	1	180	0.04	67
10	2	90	0.04	75
20	4	40	0.04	92
50	10	15	0.04	72

[a]Using **1** (10 mmol), **2a** (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm_2), graphite anode (5 cm^2), 20 °C.
[b]Yield of isolated product.

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic tandem transformation of one equivalent of rhodanine and benzaldehyde into **3** was studied (Table 1).

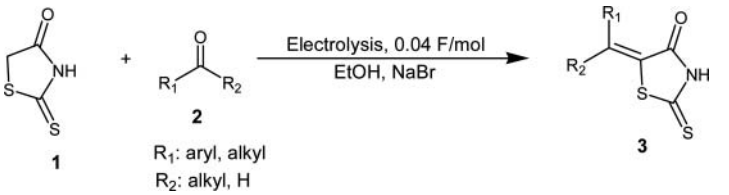
Excellent conversions of the starting compounds were obtained under 4 mA/cm^2 and 10 mA/cm^2 current densities after 0.04 F/mol of electricity was passed. The current density of 4 mA/cm^2 ($I = 20$ mA, electrodes surface 5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of **3**. An increase in the current density up to 10 mA/cm^2 ($I = 50$ mA) resulted in a slight decrease in the reaction yield, and this is perhaps as a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material.

After electrolysis, **3** were directly crystallized from the reaction mixture without any further purification. Under the optimal conditions (current density 4 mA/cm^2, 0.04 F/mol passed) the electrolysis of one equivalent of **1** and arylaldehydes **2** in ethanol in an undivided cell affords substituted **3** in 80–96% yield at ambient temperature over a 40-min reaction period (Table 2).

The following mechanism[28b] for the electrocatalytic chain transformation of **1** and arylaldehydes **2** into **3** is proposed. The initiation step of the catalytic cycle begins with the deprotonation of a molecule of alcohol at the cathode, which leads to the formation of an ethoxide anion. The subsequent reaction between the ethoxide anion and **1** gives rise to the corresponding rhodanine anion **4** (Scheme 2). The following process in the solution represents a typical tandem reaction. The Knoevenagel condensation of anion **4** with arylaldehyde **2** takes place with the elimination of a hydroxide anion and formation of **3**. This novel electrocatalytic chain process offers an efficient and convenient way to create rhodanine derivatives, the prominent compounds with approved practical utilities and different biomedical applications. We have used a catalytic amount of EtONa for entry 1 in Table 2 to compare results with the electrochemical procedure. We could not obtain good results as an electrochemical procedure.

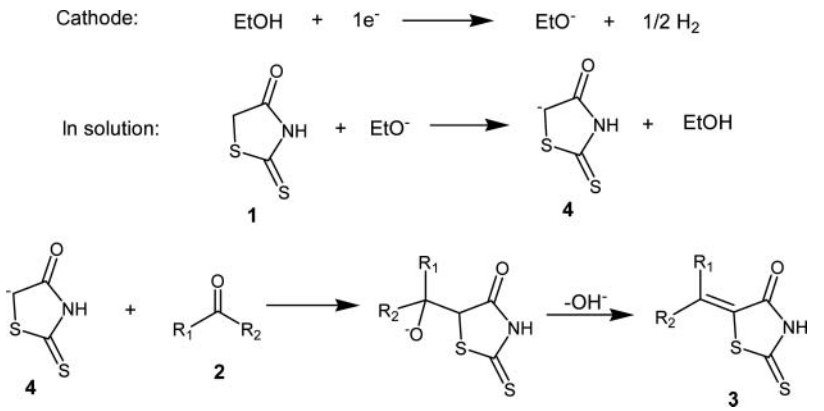
In addition, to evaluate the chemoselectivity of this method, a control experiment was allowed to proceed under the developed condition utilizing 1 mmol of *p*-methoxybenzaldehye and 1 mmol of acetophenone. It was found that rhodanine only reacts with *p*-methoxybenzaldehye and leads to the formation of 4-methylbenzylidene rhodanine as final product and no adduct was obtained from the condensation of rhodanine with ketone (Scheme 3).

Table 2 Electrocatalytic transformation of rhodanine (**1**) and arylaldehydes (**2**) into (**3**)[a]

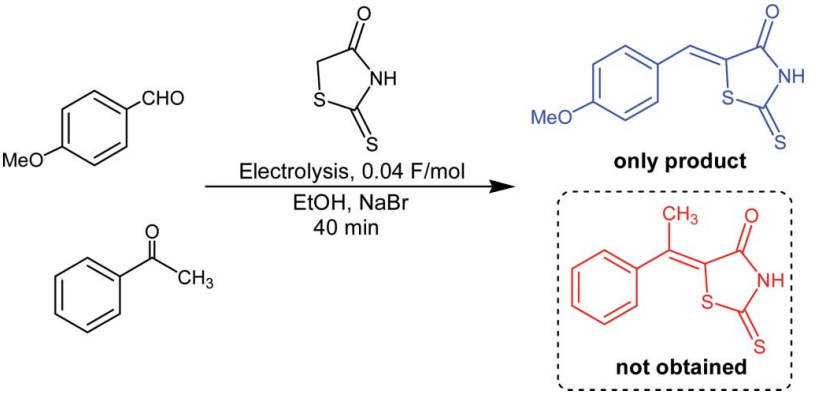


Entry	Carbonyl compounds (1)	Time (min)	Yield (%)[b]	mp (°C)	Lit-mp (°C)
1.	R_1: C_6H_5-R_2: H	40	92	202–204	199–202[31]
2.	R_1: 2-MeO-C_6H_5-R_2: H	40	96	248–250	245–247[32]
3.	R_1: 4-OH-3-MeO-C_6H_5-R_2: H	40	90	232	231–231.5[24]
4.	R_1: 4-MeO-C_6H_5-R_2: H	40	95	250–253	250–252[32]
5.	R_1: 4-Me-C_6H_5-R_2: H	40	90	220–223	219–223[31]
6.	R_1: 2,4-dichloro-C_6H_5-R_2: H	40	85	230–232	231.5–232.5[32]
7.	R_1: 2-Cl-C_6H_5-R_2: H	40	90	191–192	192[32]
8.	R_1: 4-Cl-C_6H_5-R_2: H	40	85	225–227	224–230[32]
9.	R_1: 3-NO_2-C_6H_5-R_2: H	40	90	261–263	263–264[23]
10.	R_1: 4-NO_2-C_6H_5-R_2: H	40	92	251–252	249–250[31]
11.	R_1: 2-Furyl R_2: H	40	92	229–230	228–229[23]
12.	R_1: 2-Furyl R_2: CH_3	60	85	242–244	243.5–244.5[24]
13.	Cyclohexylidene	60	80	171–174	172–173[24]
14.	Cyclopentylidene	60	85	196–198	195–196[24]
15.	R_1: C_6H_5-R_2: CH_3	60	90	165–166	165–166[24]
16.	R_1: 4-Cl-C_6H_5-R_2: CH_3	60	85	203–205	204[24]

[a]Using **1** (10 mmol), **2** (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C, current density 4 mA/cm^2, 40 min, electricity passed: 0.04 F/mol.
[b]Yield of isolated product.



Scheme 2



Scheme 3

CONCLUSIONS

In conclusion, the simple electrocatalytic system can produce, under neutral and mild conditions, a fast and selective tandem crossed Aldol condensation of one equivalent rhodanine with various aromatic aldehydes and ketones into **3** in excellent yields. This novel electrocatalytic chain process offers an efficient and convenient way to create rhodanine derivatives, the prominent compounds with approved practical utilities and different biomedical applications.

EXPERIMENTAL

General Procedure

A solution of rhodanine (**1**, 3.48 g, 10 mmol), arylaldehyde or ketone **2** (10 mmol), and NaBr (0.1 g, 1 mmol) in EtOH (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an iron cathode at 20 °C under a constant current density of 4 mA/cm^2 (I = 20 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.04 F/mol of electricity was passed. After the electrolysis was finished, the solution was filtered to isolate the solid product, which was then rinsed with an ice-cold EtOH–H_2O (9:1, 3 mL), and dried under reduced pressure.

The products are all known compounds; their spectroscopic data was compared with the original characterization data.[23,24,31,32] Selected NMR spectra for compounds 1 and 5 are presented in the Supplemental Materials (Figures S1–S4).

REFERENCES

1. (a) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, 4, 324-327; (b) Nefzi, J.; Ostresh, M.; Houghten, R. A. *Chem. Rev.* **1997**, 97, 449-472.
2. (a) Ho, T. L. *Tandem Organic Reactions*, John Wiley: New York, **1992**; (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, 248, 2365-2379 (for recent reviews).
3. Weber, L. *Drug Discov. Today* **2002**, 7, 143-147.
4. (a) Desai, K. G.; Desai, K. R. *J. Saudi Chem. Soc.* **2006**, 9, 631-635; (b) Wu, Y.; Karna, S.; Hee Choi, C.; Tong, M.; Tai, H.-H.; Hee Na, D.; Jang, C. H.; Cho, H. *J. Med. Chem.* **2011**, 54, 5260-5264.

5. Desai, K. G.; Desai, K. R. *J. Sulfur Chem.* **2006**, 27, 315-328.
6. Abdel-Halim, A. M.; Abdel-Aziz, R. M.; El-Dein, H. S.; El-Kafrawy, A. F. *Indian J. Heterocycl. Chem.* **1994**, 4, 45-51; *Chem. Abstr.* **1995**, 122, 105795d.
7. Pachhamia, V. L.; Parikh, A. R. *Acta Cienc. Indica Chem.* **1991**,17, 67-71; *Chem. Abstr.* **1992**, 117, 26399w.
8. Ashour, F. A.; Habib, N. S.; Soliman, R.; El-Taibbi, M. *Bull. Fac. Pharm.* (Cairo Univ.) **1993**, 31, 381-388; *Chem. Abstr.* **1993**, 123, 198651n.
9. Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, 6, 306-313.
10. Foye, W. O.; Tovivich, P. *J. Pharm. Sci.* **1977**, 66, 1607-1611.
11. Sudo, K.; Matsumoto, Y.; Matsushima, M. *Biochem. Biophy. Res. Comm.* **1997**, 238, 643-647.
12. Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1-21.
13. Troutman H. D.; Long, L. M. *J. Am. Chem. Soc.* **1948**, 70, 3436-3439.
14. Captan, G.; Ulusoy, N.; Ergenc, N.; Ekinic, A. C.; Vidin, A. *Il Farmaco.* **1996**, 51, 729-736; *Chem. Abstr.* **1996**, 126, 157436q.
15. Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem.Lett.* **2001**, 11, 91.
16. Fujishima, H.; Tsuboto, K. *J. Ophthalmol.* **2002**, 86, 860-865.
17. Grant, E. B.; Guiadeen, D.; Baum, E. Z.; Foleno, B. D.; Jin, H.; Montenegro, D. A.; Nelson, E. A.; Bush, K.; Hlasta, D. *J. Bioorg. Med. Chem. Lett.* **2000**, 10, 2179-2182.
18. Sim, M. M.; Ng, S. B.; Buss, A. D.; Crasta, S. C.; Goh, K. L.; Lee, S. K. *J. Bioorg. Med. Chem. Lett.* **2002**, 12, 697-699.
19. Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, 39, 1440-1445.
20. Whitesitt, C. A.; Simon, R. L.; Reel Jon, K.; Sigmund, S. *J. Bioorg. Med. Chem. Lett.* **1996**, 6, 2157-2162.
21. Free, C. A.; Majchrowicz, E.; Hess, S. M. *Biochem. Pharmacol.* **1971**, 20, 1421-1428.
22. Lohray, B. B.; Bhushan, V.; Rao, P. B.; Madhavan, G. R.; Murali, N.; Rao, K. N.; Reddy, K. A.; Rajesh, B. M; Reddy, P. G.; Chakrabarti, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **1997**, 7(7), 785-788.
23. Zhang, M.; Wang, C. D.; Yu, S. L.; Tian Z. B.; Zhang, L. *Chem. J. Chin. Univ*. **1994**, 15, 1647-1650; *Chem. Abstr.* **1995**, 122, 213992z.
24. Brown, F. C.; Bradsher, C. K.; McCallum, S. G.; Potter, M. *J. Org. Chem.* **1950**, 15, 174-176.
25. (a) Brown, F. C. *Chem. Rev.* **1961**, 61(5), 463-521; (b) Singh, S. P.; Parmar, S. S.; Raman, K. V.; Stenberg, I. *Chem. Rev.* **1981**, 81(2), 175-203.
26. Lee, C. L.; Sim, M. M. *Tetrahedron Lett.* **2000**, 41(30), 5729-5732.
27. Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001**, 11(2), 91-94.
28. (a) Feroci, M.; Orsini, M.; Palombi, L.; Inesi, A. *Green Chem.* **2007**, 9, 323-325; (b) Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin, G. I. *Synthesis* **2008**, 1933-1937.
29. (a) Caruso, T.; Feroci, M.; Inesi, A.; Orsini, M.; Scettri, A.; Palombi, L. *Adv. Synth. Catal.* **2006**, 348, 1942-1947; (b) Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A. *Chem. Commun.* **2004**, 1846-1847.
30. (a) Veisi, H. *Synthesis* **2010**, 2631-2635; (b) Veisi, H. *Tetrahedron Lett.* **2010**, 51, 2109-2114; (c) Veisi, H. *Curr. Org. Chem.* **2011**, 15, 2438-2468.
31. Sun, J.; Jiang, Y.; Yan, C. G. *Chem. J. Int.* **2001**, 032009ne; *Chem. Abstr.* **1995**, 122, 213992z.
32. Luo, J.; Li, Y.; Zhou, M. *J. Chem. Int.* **2006**, 8, 17-23.