A solvent-free protocol for the green synthesis of arylalkylidene rhodanines in a task-specific ionic liquid

Abdolhamid Alizadeh, Mohammad M. Khodaei, and Ali Eshghi

Abstract: 2-Hydroxyethylammonium formate acts as a task-specific ionic liquid (TSIL) for the Knoevenagel condensation of carbonyl compounds with rhodanine to afford arylalkylidene rhodanines under solvent-free conditions and in good-to-excellent yields. Additionally, compared with those in organic solvents, the yields obtained in the presence of our ionic liquid (IL) were significantly increased. The detailed mechanism of the catalytic effect of TSIL is also reported for the first time.

Key words: 2-Hydroxyethylammonium formate, task-specific ionic liquids (TSILs), Knoevenagel condensation, arylalkylidene rhodanines.

Résumé : Dans des conditions n'impliquant aucun solvant, le formiate de 2-hydroxyéthylammonium agit comme liquide ionique pour une tâche spécifique (LITS) pour la condensation de Knoevenagel des composés carbonylés avec la rhodanine qui conduit aux arylalkylidènes de rhodanine avec des rendements allant de bons à excellents. De plus, par comparaison avec les rendements obtenus dans des solvants organiques, ceux obtenus en présence de notre liquide ionique sont nettement plus élevés. On propose pour la première fois un mécanisme détaillé de l'effet catalytique du LITS.

Mots-clés : formiate de 2-hydroxyéthylammonium, liquide ionique pour une tâche spécifique (LITS), condensation de Knoevenagel, arylalkylidènes de rhodanine.

[Traduit par la Rédaction]

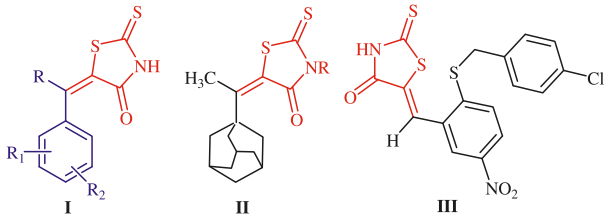
Introduction

Rhodanine derivatives, especially arylalkylidene rhodanines (**I**) (Fig. 1), have proven to be attractive compounds because of their outstanding biological activities and have undergone rapid development as anticonvulsant, antibacterial, and antidiabetic agents.[1] A series of arylalkylidene rhodanines have also been reported as Hepatitis C Virus (HCV) protease inhibitors (**II**)[2] (Fig. 1) or as novel inhibitors of UDP *N*-acetylmuramate/L-alanine ligase (**III**) (Fig. 1).[3]

For the preparation of 5-arylalkylidene rhodanines, various methods have been developed from acyclic building blocks or by functionalization of the thiazolone core.[4] In the second case, the Knoevenagel condensation of aldehydes at the nucleophilic C-5 position of rhodanine leads to the desired arylalkylidene rhodanine adducts. This reaction has been performed using sodium acetate in refluxing glacial acetic acid[5a] or piperidinium benzoate in refluxing toluene.[5b] Recently, Lee and Sim reported the synthesis of 5-arylalkylidene rhodanines by heating the reactants suspended in toluene at 110 °C for 3 days.[6] Also, Sing et al. reported the condensation of rhodanine with an aldehyde by heating in anhydrous EtOH for 6 h at 80 °C.[7]

The use of microwave irradiation (MW) as a clean and operationally simple technique has also been employed with solid inorganic support (Al_2O_3 or montmorillonite KSF clay)[8,9] but without control of the reaction temperature. Recently, Zhou et al. reported the use of MW and tetrabutylammonium bromide (TBAB) as phase-transfer catalyst in water.[10] In addition, despite their promising biological features, the synthesis of ketone derivatives of arylalkylidene rhodanine adducts has not been subjected to detailed investigations, and only a 60-year-old study of Brown and coworkers has reported the Knoevenagel condensation reaction of rhodanine with ketones in the presence of ammonium hydroxide and ammonium chloride in refluxing ethanol.[11] Similar to most conventional chemical transformations, all of the above-mentioned procedures involve harsh reaction conditions, large quantities of toxic solvents, long reaction

Fig. 1. Biologically active compounds bearing a 5-arylalkylidene rhodanine moiety.

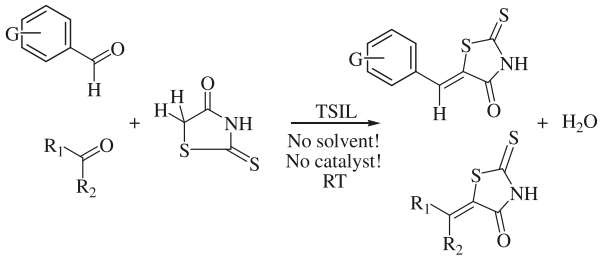


Received 15 October 2009. Accepted 4 January 2010. Published on the NRC Research Press Web site at canjchem.nrc.ca on 29 April 2010.

A. Alizadeh,[1] M.M. Khodaei,[2] and A. Eshghi. Faculty of Chemistry and Nanoscience & Nanotechnology Research Center (NNRC), Razi University, Kermanshah 67149, Iran.

[1]Corresponding author (e-mail: ahalizadeh2@hotmail.com).
[2]Corresponding author (e-mail: mmkhoda@razi.ac.ir).

Scheme 1. TSIL-catalyzed synthesis of 5-arylalkylidene rhodanines.



times, and unsatisfactory yields. Therefore, facile and green routes to arylalkylidene rhodanines would be of great interest.

Currently, ionic liquids (ILs) are being used as green solvents for laboratory as well as industrial use because of their desirable properties, such as good solvating ability, variable polarity, negligible vapor pressure, and ease of recyclability.[12] A literature survey revealed that ILs have not been utilized extensively for the Knoevenagel condensation of aldehydes or ketones with rhodanine, and only a study by Liu and co-workers utilizing a functionalized imidazolium-based IL has been reported.[13]

While considering ILs as reaction media and their use in industrial processes, one major concern is cost. The cost of the IL would be directly dependent on the price of the cations and anions that are used for their production.[11] Thus, the popular ILs incorporating expensive cations, such as alkyl methyl imidazolium and dialkyl imidazolium, are likely to remain expensive. Similarly, the anions that are frequently used in ILs, such as tetraflouro borate and hexaflouro phosphate, are also expensive. This indicates that there is a need to develop and explore simple and cost-effective ILs.

Herein, we wish to report for the first time, a solvent-free and green procedure for the Knoevenagel condensation of aromatic aldehydes and ketones with rhodanine promoted with a low cost and task-specific IL (2-hydroxyethylammonium formate)[14] as an effective catalyst and reaction medium (Scheme 1).

To our knowledge, literature only shows one recent publication[15] related with the application of this new potential IL, but no further information is available about its application in chemical processes and organic syntheses. This IL can easily be synthesized from commercially available low cost chemicals (ethanolamine and formic acid) and has high conductivity and powerful solvating ability. Also, its low melting point (–82 °C) makes it an appropriate solvent for low temperature chemical transformations.

Results and discussion

Our investigations on the Knoevenagel condensation reaction of rhodanine with carbonyl compounds began with the optimization of reaction conditions. Initially, the reaction of 1 mmol benzaldehyde with 1 mmol rhodanine in acetonitrile was tested in the absence of IL at room temperature. The reactants remained unchanged even after stirring for 20 h. Upon addition of only 1 mL of IL, condensation occurred and the reaction lead to the desired product immediately after only 2 min in 94% yield without using any solvent or catalyst at room temperature (Table 1, entry 1). Further increase in the reaction temperature did not result in a decrease in the reaction time or in an increase in the yield. Also, using 2 mmol of aldehyde (and 1 mmol of rhodanine) showed no change in the final product structure, and again, 5-benzylidene-2-thioxothiazolidine-4-one (Table 1, entry 1) was obtained as the final product.

Thus, under this optimized mild condition, various structurally diverse aromatic aldehydes and ketones were tested with rhodanine, and the corresponding results are listed in Tables 1 and 2.

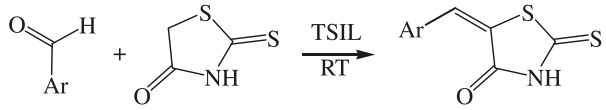
As shown in Table 1, the aryl aldehydes bearing electron-releasing and electron-withdrawing groups are effective for the aforementioned reaction and gave the desired products in excellent yields in the reaction time ranging from 1 to 6 min. For instance, aryl aldehydes such as 4-nitrobenzaldehyde and 4-fluorobenzaldehyde required relatively short reaction times (Table 1, entries 4 and 6), and in contrast, aryl aldehydes with electron-releasing groups required nearly longer reaction times (Table 1, entries 11 and 13).

In examining the scope and generality of the developed protocol as well as the influence of structural variation of carbonyl compounds on their reactivity toward rhodanine enolate, we studied the Knoevenagel condensation reaction of rhodanine with ketones in the conditions similar to that of aldehydes. It was found that the reaction proceeds in a similar fashion to that of aryl aldehydes except that ketones undergo nucleophilic attack of rhodanine enolate more slowly with relatively low yields. Entries 1–4 in Table 2 show that both cyclic and acyclic ketones can react with rhodanine enolate. In contrast, any effort to obtain Knoevenagel condensation adducts from the reaction of rhodanine enolate with benzophenone, benzamide, and 2,4-dimethyl-3-pentanone (diisopropylketone) was unsuccessful. We believe that benzophenone and benzamide do not participate in the condensation, presumably because of the resonance of the carbonyl moiety with the phenyl groups and nitrogen lone-pair electrons. Also, diisopropylketone has a steric hindrance around the carbonyl group, and hence, it does not react with rhodanine. The results are listed in Table 2.

A control experiment was also allowed to proceed under the developed conditions utilizing 1 mL of TSIL, 1 mmol of *p*-methylbenzaldehye, and 1 mmol of acetophenone to evaluate the chemoselectivity of the TSIL. It was found that in the presence of 1 mL of the IL, rhodanine only reacts with *p*-methylbenzaldehye, which leads to the formation of 4-methylbenzylidene rhodanine as the final product, and no adduct was obtained from the condensation of rhodanine with ketone (Scheme 2).

The obtained results allow us to propose a tentative mechanism for the TSIL-catalyzed Knoevenagel condensation reaction of aldehydes and ketones with rhodanine as depicted in Scheme 3. The structure of the IL used in this study (2-hydroxyethylammonium formate) has a specific feature bearing both acidic and basic sites. We believe that the acidic part of the IL (ammonium moiety) protonates the oxygen of the carbonyl group; this is a very suitable condition in nucleophilic additions to carbonyl compounds. On the other hand, rhodanine is a CH-acidic nucleophile and the anionic part of the IL (formate anion) is basic and easily deprotonates rhodanine at the C-5 position and causes the

Table 1. TSIL-catalyzed reaction of rhodanine with aromatic aldehydes.



			Mp (°C)		
Entry	Ar	Time (min)	Found	Reported	Yield (%)[a,b]
1	C_6H_5	2	205	204[16]	94
2	4-MeC_6H_4	2	221	220[16]	95
3	4-$MeOC_6H_4$	2	251	251[16]	96
4	4-$NO_2C_6H_4$	1	255	250[16]	98
5	4-ClC_6H_4	2	232	232[16]	96
6	4-FC_6H_4	1	226	226[17]	98
7	4-BrC_6H_4	1	230.5	231[17]	97
8	2,4-ClC_6H_3	1	230	231[16]	95
9	2,4-$MeOC_6H_3$	3	275[c]	—	92
10	2-Furyl	2	230	229[16]	95
11	4-$N(Me)_2C_6H_4$	3	272	270[18]	90
12	2-ClC_6H_4	4	191	192[16]	94
13	2-OHC_6H_4	6	223	222[18]	91
14	Cinammyl	1	227[c]	—	98

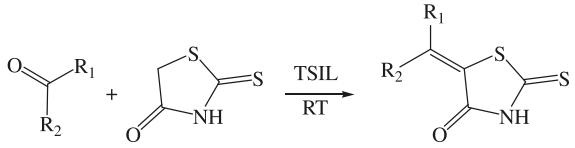
Note: Reaction conditions: aldehyde (1 mmol), rhodanine (1 mmol), ionic liquid (1 mL), and RT.

[a]The products were characterized by comparison of their spectroscopic and physical data with those reported in the literature.

[b]Yields refer to pure isolated products.

[c]New compounds.

Table 2. TSIL-catalyzed reaction of rhodanine with ketones.



			Time	Mp (°C)		
Entry	R_1	R_2	(min)	Found	Reported	Yield (%)[a]
1	$(–CH_2–)_5$	$(–CH_2–)_5$	20	175	173[11]	87
2	$(–CH_2–)_4$	$(–CH_2–)_4$	15	195	195[11]	90
3	C_6H_5	CH_3	70	167	166[11]	92
4	$4ClC_6H_4$	CH_3	72	205	204[11]	90
5	C_6H_5	C_6H_5				NR[b]
6	*i*-Pro	*i*-Pro				NR
7	C_6H_5	NH_2				NR

Note: Reaction conditions: ketone (1 mmol), rhodanine (1 mmol), ionic liquid (1 mL), and RT.

[a]Yields refer to pure isolated products.

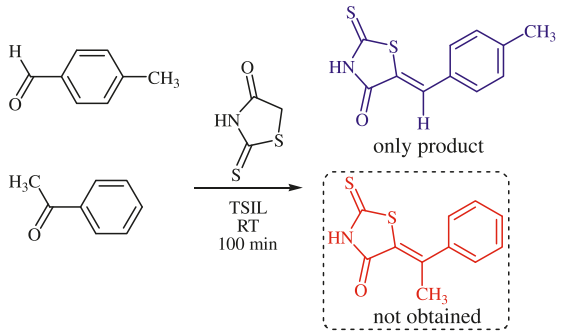
[b]NR: No reaction.

formation of nucleophilic rhodanine enolate. Subsequently, this enolate attacks the protonated aldehyde or ketone and gives an intermediate alcohol. Eventually, protonation of this alcohol, followed by a dehydration process, gives the desired products, recovered catalyst, and water as the only byproduct of the reaction.

The ionic liquid was recovered and reutilized four times without the addition of extra ionic liquid; the results are shown in Fig. 2.

In conclusion, we have described a general, environment-friendly, solvent-free, and reagentless protocol for the preparation of a series of arylalkylidene rhodanine derivatives using 2-hydroxyethylammonium formate as a task-specific ionic liquid. The ease of preparation of the IL from commercially available low cost starting materials, its high conductivity, powerful solvating ability, and low melting point make it an appropriate solvent for room temperature reactions. Furthermore, this method is applicable to both electron-rich as well as electron-deficient aldehydes. In all cases, the reaction proceeds smoothly under very mild con-

Scheme 2. Comparison of the reactions of rhodanine with benzaldehyde and acetophenone in the presence of TSIL.



Scheme 3. Representative mechanism of TSIL-promoted Knoevenagel condensation reaction of aldehydes and ketones with rhodanine.

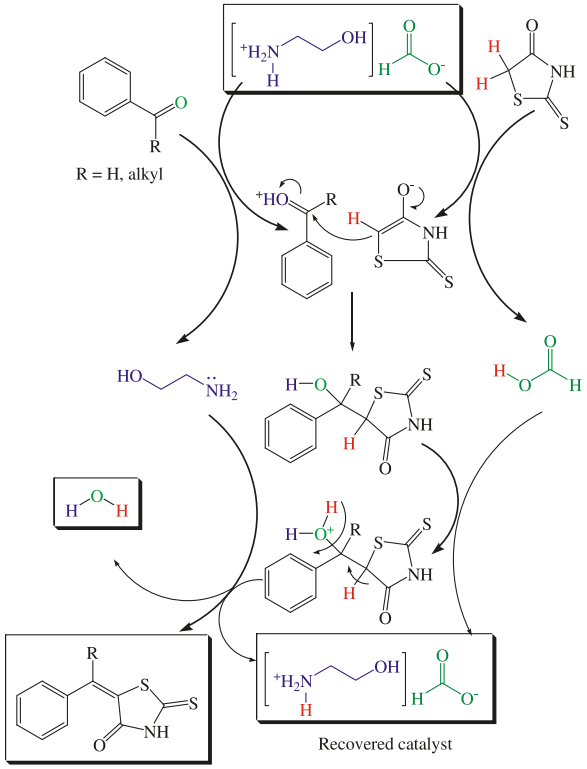
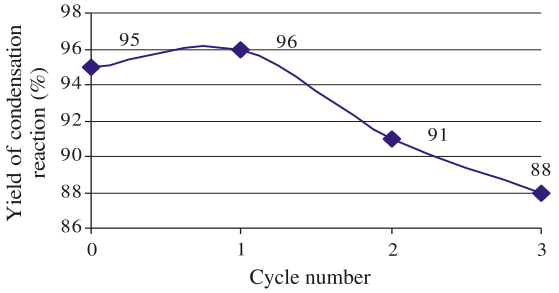


Fig. 2. Successive trials by using the recoverable TSIL.



ditions without introducing any acid, base, or metal catalyst, and water is the only byproduct of the reaction. Compared with those obtained using traditional organic solvents, the yields obtained in the presence of this TSIL are significantly increased. We believe that the low cost and the experimental simplicity of the method gives this green ionic-liquid-catalyzed procedure great potential, and it may find potential applications in synthetic organic chemistry, and more importantly, it can compliment the existing chemical strategies.

Experimental

All chemicals (ethanolamine, formic acid, rhodanine, aldehydes, and ketones) were reagent-grade materials, and they were used without further purification. Throughout all experiments, distilled water was used, and all the experiments were done at room temperature. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 200 and 50 MHz, respectively. Melting points were measured on a BI Branstead Electrothermal 9200 instrument and are uncorrected. FTIR spectra were recorded on a Rayleigh Wqf-510 spectrometer using a drop casting technique on KBr plates and are reported in wavenumbers (cm^{-1}).

Synthesis of arylalkylidene rhodanines: general procedure

Rhodanine (1 mmol) and 2-hydroxyethylammonium formate (1 mL) were mixed together and stirred at room temperature for 2 min after which 1 mmol of aromatic aldehyde or ketone was added to the reaction mixture. After completion of the reaction (monitored by TLC), a mixture of water and ethanol (50:50 *v*/*v*) was added to the reaction flask, and the obtained precipitates were easily filtered leading to the final pure products while no extra purification was needed. Evaporating the water of the filtrate gave the pure IL, which could be reused for further reactions. Selected characterization data for some of the arylalkylidene rhodanines prepared are given below.

5-Phenyl-2-thioxothiazolidin-4-one

Yellow powder, mp 205 °C (lit.[16] mp 204 °C). ^{1}H NMR (DMSO-d_6, 200 MHz) δ (ppm): 7.51–7.85 (m, 5H, H_{ar}), 7.68 (s, 1H, vinyl), 13.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm): 125.9, 127.4, 129.8, 130.8, 131.1, 131.9, 169.8, 196.1.

5-(4-Methylbenzyliden)-2-thioxothiazolidin-4-one

Yellow powder, mp 221 °C (lit.[16] mp 220 °C). ^{1}H NMR (DMSO-d_6, 200 MHz) δ (ppm): 2.40 (s, 3H, CH_3), 7.40 (d, 2H, H_{ar}), 7.53 (d, 2H, H_{ar}), 7.65 (s, 1H, vinyl), 13.88 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm): 21.5, 124.7, 130.4, 130.6, 130.9, 132.1, 141.5, 169.9, 196.1.

5-(2,4-Dimethoxybenzyliden)-2-thioxothiazolidin-4-one

Orange powder, mp 275 °C. IR (KBr) ν (cm^{-1}): 3452, 1707, 1621, 1564, 1445, 1117. ^{1}H NMR (DMSO-d_6, 200 MHz) δ (ppm): 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.70–6.75 (m, 2H, H_{ar}), 7.33 (d, 1H, H_{ar}), 7.74 (s, 1H, vinyl), 13.72 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm): 55.7, 55.9, 98.7, 106.5, 115.5, 123.0, 126.7, 130.6, 159.7, 162.7, 163.2, 199.1. Anal. calcd. for $C_{12}H_{11}NO_3S_2$: C, 51.23%; H, 3.94%; N, 4.98%; S, 22.79%. Found: C, 48.2%; H, 5.0%; N, 6.6%; S, 19.1%.

5-[(E)-3-Phenylallylidene]-2-thioxothiazolidin-4-one

Orange powder, mp 227 °C. IR (KBr) ν (cm^{-1}): 3458, 1691, 1624, 1573, 1448, 1150. ^1H NMR (DMSO-d_6, 200 MHz) δ (ppm): 7.01 (m, 1H, vinyl), 7.31 (d, 1H, vinyl), 7.40–7.47 (m, 5H, H_{ar}), 7.67 (d, 1H, vinyl), 13.64 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm): 124.6, 128.0, 128.9, 129.8, 130.8, 132.9, 136.4, 145.5, 169.6, 196.2. Anal. calcd. for $C_{12}H_9NOS_2$: C, 58.27%; H, 3.67%; N, 5.66%; S, 25.93%. Found: C, 58.2%; H, 4.1%; N, 6.1%; S, 24.1%.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca).

Acknowledgment

Financial support for this work by Razi University is hereby appreciated.

References

(1) (a) Ohishi, Y.; Mukai, T.; Nagahara, M.; Yajima, M.; Kajikawa, N.; Miyahara, K.; Takano, T. *Chem. Pharm. Bull. (Tokyo)* **1990**, *38* (7), 1911. PMID:2125247.; (b) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull. (Tokyo)* **1991**, *39* (6), 1440. PMID: 1934164.

(2) Sudo, K.; Matsumoto, Y.; Matsushima, M.; Fujiwara, M.; Konno, K.; Shimotohno, K.; Shigeta, S.; Yokota, T. *Biochem. Biophys. Res. Commun.* **1997**, *238* (2), 643. doi:10.1006/bbrc.1997.7358. PMID:9299567.

(3) Sim, M. M.; Ng, S. B.; Buss, A. D.; Crasta, S. C.; Goh, K. L.; Lee, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12* (4), 697. doi:10.1016/S0960-894X(01)00832-0. PMID:11844704.

(4) (a) Brown, F. C. *Chem. Rev.* **1961**, *61* (5), 463. doi:10.1021/cr60213a002.; (b) Singh, S. P.; Parmar, S. S.; Raman, K. V.; Stenberg, I. *Chem. Rev.* **1981**, *81* (2), 175. doi:10.1021/cr00042a003.

(5) (a) Cutshall, N. S.; O'Day, C.; Prezhdo, M. *Bioorg. Med. Chem. Lett.* **2005**, *15* (14), 3374. doi:10.1016/j.bmcl.2005.05.034. PMID:15961311.; (b) 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. doi:10.1016/S0960-894X(97)00118-2.

(6) Lee, C. L.; Sim, M. M. *Tetrahedron Lett.* **2000**, *41* (30), 5729. doi:10.1016/S0040-4039(00)00866-2.

(7) Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11* (2), 91. doi:10.1016/S0960-894X(00)00610-7. PMID:11206478.

(8) (a) Zhang, L. *Chem. J. Chin. Univ.* **1994**, *15*, 1647; (b) Bougrin, K.; Soufiaoui, M. N. *J. Chem.* **1998**, *22*, 809.

(9) Bourahla, K.; Derdour, A.; Rahmouni, M.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2007**, *48* (33), 5785. doi:10.1016/j.tetlet.2007.06.078.

(10) Zhou, J. F.; Zhu, F. X.; Song, Y. Z.; Zhu, Y. L. *Arkivoc* **2006**, *iv*, 175.

(11) Brown, F. C.; Bradsher, C. K.; McCallum, S. G.; Potter, M. *J. Org. Chem.* **1950**, *15* (1), 174. doi:10.1021/jo01147a028.

(12) Wasserscheid, P.; Welton, T., Eds. *Ionic Liquids in Synthesis;* Wiley-VCH Verlag GmbH & Co. KGaA, 2003. doi:10.1002/3527600701.fmatter_indsub.

(13) Gong, K.; He, Z. W.; Xu, Y.; Fang, D.; Liu, Z. L. *Monatsh. Chem.* **2008**, *139* (8), 913. doi:10.1007/s00706-008-0871-y.

(14) Bicak, N. *J. Mol. Liq.* **2005**, *116* (1), 15. doi:10.1016/j.molliq.2004.03.006.

(15) Sharma, Y. O.; Degani, M. S. *J. Mol. Catal. Chem.* **2007**, *277* (1-2), 215. doi:10.1016/j.molcata.2007.07.053.

(16) Luo, J.; Li, Y.; Zhou, M. *J. Chem. Int.* **2006**, *8*, 17.

(17) Sortino, M.; Delgado, P.; Juárez, S.; Quiroga, J.; Abonía, R.; Insuasty, B.; Nogueras, M.; Rodero, L.; Garibotto, F. M.; Enriz, R. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007**, *15* (1), 484. doi:10.1016/j.bmc.2006.09.038. PMID:17049255.

(18) Zhou, J. F.; Zhu, F. X.; Song, Y. Z.; Zhu, Y. *Arkivoc* **2006**, *xiv*, 175.