Click Chemistry

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# Thiol–Ene "Click" Reaction Triggered by Neutral Ionic Liquid: The "Ambiphilic" Character of [hmim]Br in the Regioselective Nucleophilic Hydrothiolation**

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***Abstract:*** *Thiol–ene "click" chemistry has emerged as a powerful strategy to construct carbon–heteroatom (C–S) bonds, which generally results in the formation of two regioisomers. To this end, the neutral ionic liquid [hmim]Br has been explored as a solvent cum catalyst for the synthesis of linear thioethers from activated and inactivated styrene derivatives or secondary benzyl alcohols and thiols without the requirement of using a metal complex, base, or free radical initiator. Furthermore, detailed mechanistic investigations using $^1$H NMR spectroscopy and quadrupole time-of-flight electrospray ionization mass spectrometry (Q-TOF ESI-MS) revealed that the "ambiphilic" character of the ionic liquid promotes the nucleophilic addition of thiol to styrene through an anti-Markovnikov pathway. The catalyst recyclability and the extension of the methodology for thiol–yne click chemistry are additional benefits. A competitive study among thiophenol, styrene, and phenyl acetylene revealed that the rate of reaction is in the order of thiol–yne > thiol–ene > dimerization of thiol in [hmim]Br.*

The overwhelming success of "click" chemistry[1] coined by Sharpless in 2001 has encouraged researchers to develop a variety of chemical transformations. Among various click procedures,[2] the thiol–ene/yne reactions[3] have also come to the fore as click reaction because of their many inherent benefits like high atom economy, simple synthetic procedures, and minimum waste generation, besides their applications[4] in the fields of nanoengineering, polymer science, and medicine (Figure 1).

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Thiol–ene coupling (TEC) between an olefin and thiol, better known as hydrothiolation may proceed through an electrophilic[5]/free radical[6] or nucleophilic pathway[7] leading to the branched Markovnikov[5] or linear anti-Markovnikov[6,7] product, respectively. Among both products, the less studied anti-Markovnikov addition is generally performed in the presence of transition metal/nonmetal complexes[6a–h] and base.[7] Recently, Tyson and co-workers[6a] reported the use of a ruthenium catalyst $(Ru(bpz)_3)^{2+}$ in a radical thiol–ene reaction for anti-Markovnikov hydrothiolation. Beside this, some metal-free approaches[6i–j] have gained importance in linear hydrothiolation reactions. However, many of the existing strategies are still limited due to the expensive nature and tedious synthesis of the catalysts, cumbersome product isolation procedures, formation of two regioisomers, acidic reaction conditions, usage of unstable styrene, and lack of catalyst recyclability. Hence, the challenge for improving sustainability is to develop more general and viable routes, which would be of great relevance to synthetic chemists.

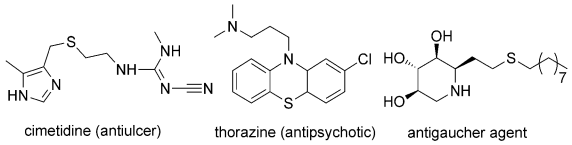
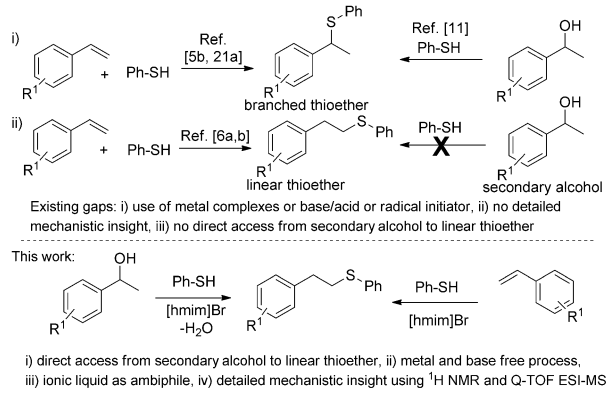



***Figure 1.*** Biologically active scaffolds containing a C–S bond.

In this context, ionic liquids (ILs) constitute an attractive alternative for a number of organic transformations[8] due to catalyst recycling,[8b] improved selectivity, and ease in product isolation. So far acidic ILs[9] in conjunction with a free radical initiator[9a] have been utilized for the synthesis of linear thioethers from thiol and styrene; however, the acidic nature of the IL may lead to the polymerization of styrene.[10] Thus, realization of the hydrothiolation reaction by in situ formation of styrene from innocuous and inexpensive raw materials (i.e., secondary benzyl alcohol)[11] and subsequent addition to thiol would be practically useful. In this context, there are a few reports available utilizing secondary benzyl alcohols for the synthesis of only branched thioethers[11] rather than linear ones.

In continuation of ongoing interest in using neutral [hmim]Br for various chemical transformations,[12] including the dehydrative Heck reaction[12a] and the oxidative coupling of thiophenols to form disulfides,[12b] we herein present a tunable role of [hmim]Br for an exclusive synthesis of linear thioethers from styrenes or secondary benzyl alcohols

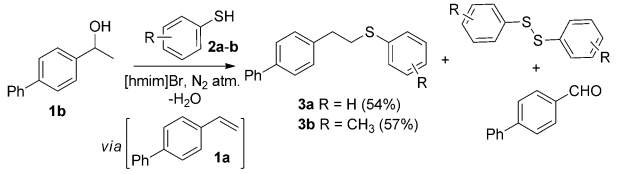
  




***Scheme 1.*** Thiol–ene reaction in neutral [hmim]Br.

(through in situ dehydration) and thiophenols (Scheme 1) by overcoming the dimerization of thiol in ILs (see the Supporting Information, SI). Furthermore, $^1$H NMR and Q-TOF ESI-MS-based mechanistic studies proved that the "ambiphilic" character of the IL promotes the nucleophilic addition of thiol to styrene through an anti-Markovnikov pathway.

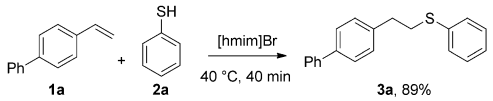
Initially, a mixture of 1-(4-biphenyl)ethanol[12d] (**1b**, 0.28 mmol) and thiophenol (**2a**, 1.0 mmol) in [hmim]Br (0.5 mL; Scheme 2) was irradiated in a tandem manner with




***Scheme 2.*** Dehydrative thiol–ene reaction in [hmim]Br.

microwave (MW) irradiation (120 W, 150 °C) for 15 min under $N_2$ atmosphere (to ward off the formation of disulfide from **2a** in IL/$O_2$).[12b] GC-MS analysis of the crude product revealed the formation of the desired product **3a** only in 10 % yield along with unreacted biarylethene[12d] intermediate, diphenyldisulfide,[12b] and biarylaldehyde (see SI). Thereafter, varying amounts of thiophenol (1.1–1.3 mmol) and IL (0.75–1.5 mL) as well as different reaction times (10–30 min) and temperatures (120–180 °C) were taken into account. However, no significant improvement of the yield of **3a** was observed. Further, the dehydration of **1b** (0.28 mmol) in [hmim]Br (0.5 mL) under MW irradiation (120 W, 150 °C) for 15 min, followed by addition of thiophenol (1.2 mmol) and then stirring at 40 °C[13] under an $N_2$ atmosphere for 40 min favored the formation of **3a** in 54 % yield (62 % measured by GC-MS). However, disulfide and biarylaldehyde (Scheme 2) side products were still detected, possibly due to oxidative scission[14] of the biarylethene by in situ-generated water during the dehydration of **1b** (see SI). Similarly **3b** was obtained in 57 % yield from **2b** and **1b** (Scheme 2).

Based on the above-described encouraging results for the synthesis of thioethers **3a**–**3b** through dehydrative thiol–ene reaction (Scheme 2), we next examined the concept of "click chemistry"[1,3] to get a maximum yield of **3a** from **1a** and **2a** (see SI, Table S1) with ease in recyclability[8c] in [hmim]Br, which is considered as a neutral[12e–g] reaction medium. Interestingly, a reaction between biarylethene (**1a**, 0.28 mmol) and thiophenol (**2a**, 1.2 equiv) at 40 °C in [hmim]Br (0.5 mL) for 40 min resulted in the formation of **3a** in 89 % yield (95 % measured by GC-MS; Scheme 3) under $N_2$ atmosphere or open air condition (see SI).



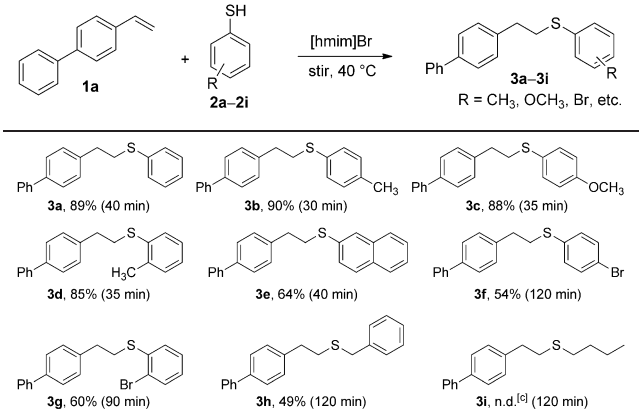

***Scheme 3.*** Click thiol–ene reaction in [hmim]Br for the synthesis of **3a**.

To further increase the yield of **3a**, different ILs including basic and acidic ILs as well as [hmmim]Br (1-hexyl-2,3-dimethylimidazolium bromide),[12b] a C-2 methylated IL were screened but none of them led to an increase in the yield of **3a** (see SI, Table S1). Further, hydrothiolation between **1a** and **2a** in the presence of 10 mol % ascorbic acid (a free radical quencher; Table S1, entry 10) or in the dark under $N_2$ atmosphere (Table S1, entry 11) provided a still high yield of 88–86 % of **3a**, thus ruling out the possibility of a free radical pathway (see SI, Table S1).

Having established optimal reaction conditions, we examined the substrate scope for the thiol–ene coupling reaction between biarylethene **1a** and thiols **2a**–**2i** with varying electronic character, which afforded the corresponding products **3a**–**3h** in moderate to good yields (Table 1). It was noticed that starting materials with electron-withdrawing substituents on the thiol (Table 1, **3f**–**3g**) and benzylthiol (Table 1, **3h**) required longer reaction time due to their weak nucleophilicity. However, an aliphatic thiol **3i** (Table 1) did not undergo hydrothiolation with **1a**.

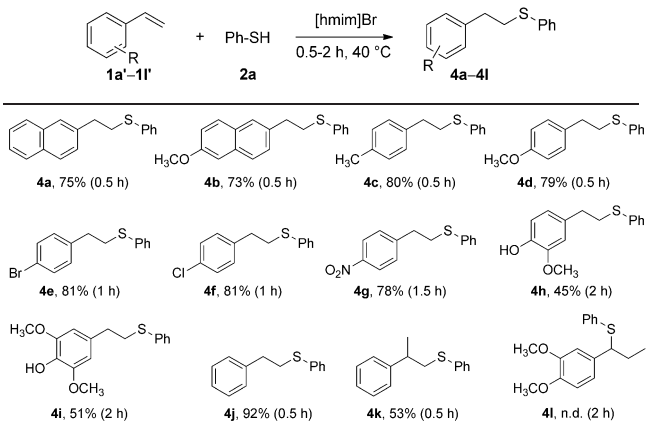
To further demonstrate the versatility of the above-described TEC protocol, a diverse array of styrenes (Table 2, **1a′**–**1l′**) possessing electron-donating as well as electron-withdrawing groups were coupled with thiophenol (**2a**),

***Table 1:*** [hmim]Br-catalyzed anti-Markovnikov hydrothiolation between biarylethene **1a** and different thiols **2a**–**2i**.[a,b]




[a] Reaction conditions: **1a** (0.28 mmol), thiol (1.2 equiv), [hmim]Br (0.5 mL), stir at 40 °C. [b] Yields of isolated products. [c] Not detected.

***Table 2:*** [hmim]Br-catalyzed anti-Markovnikov hydrothiolation between thiophenol **2a** and different styrene derivatives **1a′–1l′**.[a,b]




[a] Reaction conditions: **1a** (0.28 mmol), thiophenol (1.2 equiv), [hmim]Br (0.5 mL), stir at 40 °C for 0.5–2 h. [b] Yields of isolated products. n.d. = not detected (see SI).

which provided the desired products **4a–4k** in good yield. Interestingly, also the coupling of hydroxy-substituted styrenes **1h′–1i′** (Table 2), including commercially unavailable 4-hydroxy-3,5-dimethoxy-styrene (**1i′**),[15] with **2a** provided the desired products **4h–4i** (Table 2) without the need for a protection–deprotection strategy for the hydroxy group, albeit only moderate yields were achieved. Similarly, α-methyl styrene (**1k′**) undergoes hydrothiolation, giving 53 % yield of the corresponding diarylalkane motif **4k** (Table 2), which is an integral part of a number of biologically active compounds.[16]

Mechanistically, there are two plausible pathways for the synthesis of thioether **4c** (Figure 2) either through a free radical[6] or base-mediated nucleophilic hydrothiolation.[7] Our studies preclude the use of free radical initiator or base, therefore, it was presumed that the ambiphilic[12b,17] "electrophilic and nucleophilic" character of [hmim]Br promotes the nucleophilic addition of thiophenol (**2a**) to 4-methyl styrene (**1c′**) through intermediate (B), in which the S atom of thiophenol undergoes hydrogen bond (H–B) formation[17b] (nucleophilic activation) with the Br anion of the IL due to its H–B acceptor ability. Likewise, the C-2 hydrogen of the hmim cation interacts with **1c′** through H–B[17c] (electrophilic activation) formation due to its acidic nature. Subsequently, nucleophilic attack of thiophenol on styrene leads to the formation of the C–S bond (Figure 2).

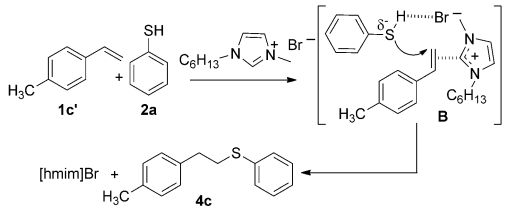



***Figure 2.*** Proposed mechanism of the [hmim]Br-catalyzed thiol–ene addition.

To prove this hypothetical interaction[17a,18] between **1c′**, [hmim]Br, and **2a**, the reaction was examined by $^1$H NMR spectroscopy in $CDCl_3$ (Figure 3). When **1c′** was mixed with [hmim]Br, the proton at the C-2 position (peak c) of the imidazolium moiety and the vinyl protons of **1c′** (peaks b) shifted from $\delta$ 10.24 to 10.29, from $\delta$ 5.72, 5.65 to $\delta$ 5.67, 5.58, and from $\delta$ 5.20, 5.16 to $\delta$ 5.12, 5.08, respectively, after 5 min of stirring at room temperature (see SI). These shifts could be considered as evidence that the cation of the IL activates styrene (**1c′**) through H–B formation and similarly that the Br anion of IL activates thiophenol by accepting the hydrogen bond as evident from the shifting of peak a from $\delta$ 3.36 to 3.82 (Figure 3a and e).

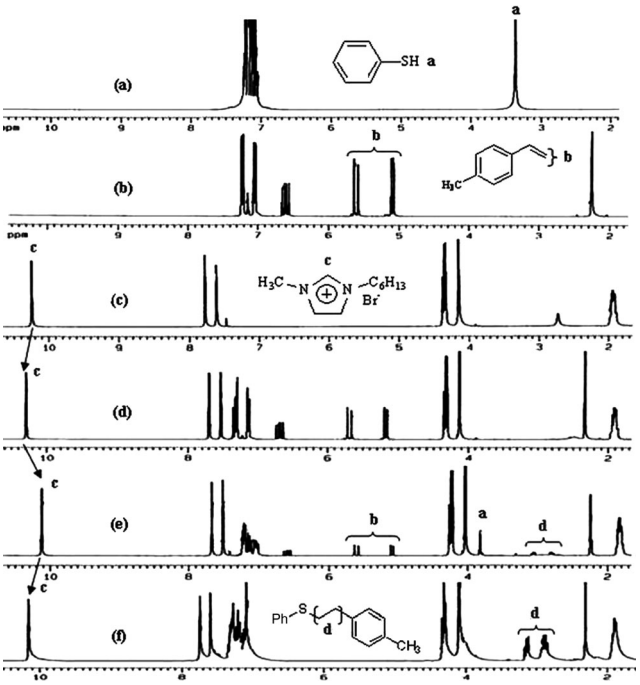



***Figure 3.*** $^1$H NMR spectra of a) thiophenol, b) 4-methyl styrene, c) [hmim]Br, d) the interaction between 4-methyl styrene and [hmim]Br after 5 min. e, f) The interaction between 4-methyl styrene, [hmim]Br, and thiophenol in $CDCl_3$ after 15 min (e) and 30 min (f).

For the direct proof of our perception, we planned to identify and characterize the intermediate **B** (Figure 2) using electrospray ionization mass spectrometry (ESI-MS),[8d,19] which can be used to efficiently generate ions of noncovalent adducts in the gas phase. We performed (+ ve) Q-TOF ESI-MS studies of samples taken after 10 min during the [hmim]Br-catalyzed reaction of **1c′** with **2a** (Figure 4). The total ion chromatogram (TIC) revealed the presence of ions at *m/z* 493.31 ($m_1$), 413.42 ($m_2$) (see SI), 379.31 ($m_3$), 347.21 ($m_4$), 257.10 ($m_5$), 243.07 ($m_6$), 227.09 ($m_7$), 214.26 ($m_8$), and 167.19 ($m_9$) (see SI) corresponding to $[B+H+NH_3]^+$, $[B+H+NH_3-Br]^+$, $[B-H-Br-CH_3]^+$, $[B-H-NH_3-thiol]^+$, $[B+K-thiol-styrene-C_2H_5]^+$, $[B+K-thiol-styrene-C_3H_7]^+$, $[B-IL-H]^+$, $[B+H-IL-CH_3]^+$, and $[B-thiol-Br-styrene]^+$, respectively (Figure 4), which are diagnostic of intermediate **B**. Thus, the mechanistic study

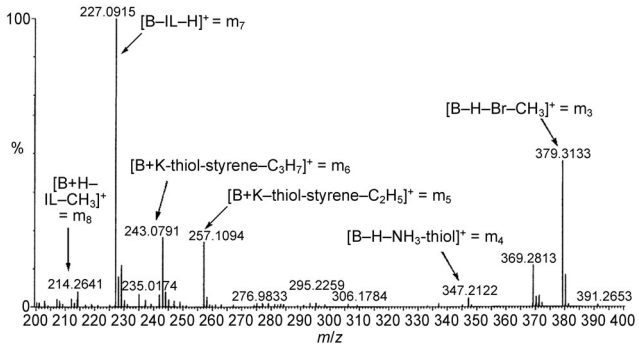
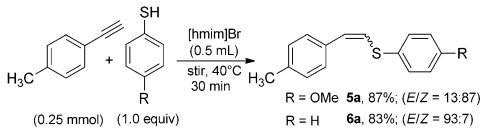



***Figure 4.*** TIC of (+ve) ESI-MS spectra of sample taken after 10 min from the reaction of **1c′** and **2a** catalyzed by [hmim]Br. See SI for the $m_1$, $m_2$, and $m_9$ peaks.

based on $^1$H NMR spectroscopy and Q-TOF ESI-MS proved for the first time that the "ambiphilic" character of [hmim]Br promotes the nucleophilic addition of thiophenol to styrene through intermediate **B** for the construction of a C–S bond through an anti-Markovnikov pathway.

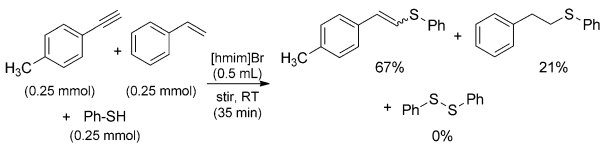
From an economical point of view, the recyclability of [hmim]Br for the formation of **3a** (Scheme 3) was tested. It was found that the IL retained a high reactivity for up to five cycles varying from 95–80 % yield (see SI).

After the establishment of the mechanism, the recyclability, and the substrate scope for the TEC (Tables 1 and 2), we investigated the importance of the terminal hydrogen in thiol–yne click (TYC)[3] chemistry. To further ascertain the role of terminal hydrogen, experiments with 4-ethynyltoluene (0.25 mmol) and thiols (1.0 equiv) were conducted in [hmim]Br (0.5 mL) at 40 °C for 30 min, which furnished the target molecules **5a** and **6a** in high yield (Scheme 4), which are key intermediates for the synthesis of bioactive molecules.[20] Moreover, the *E*/*Z* ratio in thiol–yne coupling reactions is generally substrate-dependent.[21]




***Scheme 4.*** [hmim]Br-catalyzed hydrothiolation of phenyl acetylene.

Under similar reaction condition, an equimolar mixture of 4-ethynyltoluene, styrene, and thiophenol in [hmim]Br (0.5 mL) was stirred at room temperature for 35 min to determine the competing rate of reaction among thiol–yne, thiol–ene, and thiol dimerization reaction (Scheme 5). We




***Scheme 5.*** Competitive reaction of thiophenol, 4-ethynytoluene, and styrene.

obtained a maximum amount of thiol–yne product (67 %), followed by thiol–ene (21 %) and disulfide (0 %) product on the basis of GC-MS analysis. The result revealed that the reaction rates are in the order thiol–yne > thiol–ene > thiol dimerization.

In conclusion, the neutral [hmim]Br-mediated thiol–ene "click" chemistry can be described by a single word: simplicity that leads to ubiquitous implementation. The developed reaction affords the linear thioether from activated and inactivated alkenes with thiophenols in good to excellent yields with high regioselectivity and recyclability of catalyst under metal-, base-, and radical-free conditions. Moreover, a mechanistic study based on $^1$H NMR spectroscopy and Q-TOF ESI-MS proved that the "ambiphilic" character of [hmim]Br promotes the nucleophilic addition of thiols to styrene through an anti-Markovnikov pathway.

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[1] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; *Angew. Chem.* **2001**, *113*, 2056; b) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249; c) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed.* **2009**, *48*, 4900; *Angew. Chem.* **2009**, *121*, 4998.

[2] a) T. Jin, M. Yan, Y. Yamamoto, *ChemCatChem* **2012**, *4*, 1217; b) A. Massi, D. Nanni, *Org. Biomol. Chem.* **2012**, *10*, 3791; c) H. Stöckmann, A. A. Neves, S. Stairs, K. M. Brindle, F. J. Leeper, *Org. Biomol. Chem.* **2011**, *9*, 7303; d) C. Spiteri, J. E. Moses, *Angew. Chem. Int. Ed.* **2010**, *49*, 31; *Angew. Chem.* **2010**, *122*, 33.

[3] a) C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540; *Angew. Chem.* **2010**, *122*, 1584; b) C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355; c) A. Dondoni, *Angew. Chem. Int. Ed.* **2008**, *47*, 8995; *Angew. Chem.* **2008**, *120*, 9133; d) R. L. A. David, J. A. Kornfield, *Macromolecules* **2008**, *41*, 1151; e) K. L. Killops, L. M. Campos, C. J. Hawker, *J. Am. Chem. Soc.* **2008**, *130*, 5062; f) V. X. Truong, A. P. Dove, *Angew. Chem. Int. Ed.* **2013**, *52*, 4132; *Angew. Chem.* **2013**, *125*, 4226.

[4] a) V. T. Huynh, G. Chen, P. Souza, M. H. Stenzel, *Biomacromolecules* **2011**, *12*, 1738; b) B. Helms, E. W. Meijer, *Science* **2006**, *313*, 929.

[5] a) K. Griesbaum, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 273; *Angew. Chem.* **1970**, *82*, 276; b) M. Weïwer, L. Coulombel, E. Dunach, *Chem. Commun.* **2006**, 332; c) M. Takeuchi, H. Shimakoshi, K. Kano, *Organometallics* **1994**, *13*, 1208; d) B. Basu, S. Kundu, D. Sengupta, *RSC Adv.* **2013**, *3*, 22130; e) K. J. Miller, M. M. A. Omar, *Eur. J. Org. Chem.* **2003**, 1294; f) J. R. Cabrero-Antonino, A. Leyva-Perez, A. Corma, *Adv. Synth. Catal.* **2012**, *354*, 678.

[6] a) E. L. Tyson, M. S. Ament, T. P. Yoon, *J. Org. Chem.* **2013**, *78*, 2046; b) C. Munro-Leighton, S. A. Delp, N. M. Alsop, E. D. Blue, T. B. Gunnoe, *Chem. Commun.* **2008**, 111; c) S. Banerjee, J. Das, S. Santra, *Tetrahedron Lett.* **2009**, *50*, 124; d) S. Banerjee, J. Das, R. P. Alvarez, S. Santra, *New J. Chem.* **2010**, *34*, 302; e) C. C. Silveira, S. R. Mendes, F. M. Libero, *Synlett* **2010**, 790; f) P. Kumar, R. K. Pandey, V. R. Hegde, *Synlett* **1999**, 1921; g) B. C. Ranu, T. Mandal, *Tetrahedron Lett.* **2006**, *47*, 6911; h) S. Kanagasabapathy, A. Sudalai, B. C. Benicewicz, *Tetrahedron Lett.* **2001**, *42*, 3791; i) B. C. Ranu, T. Mandal, *Synlett* **2007**, 925;

  

j) B. Movassagh, M. Navidi, *Arkivoc* **2008**, *xv*, 47; k) G. Povie, A.-T. Tran, D. Bonnaff, J. Habegger, Z. Hu, C. L. Narvor, P. Renaud, *Angew. Chem. Int. Ed.* **2014**, *53*, 3894; *Angew. Chem.* **2014**, *126*, 3975.

[7] a) A. B. Lowe, *Polym. Chem.* **2010**, *1*, 17; b) B. D. Mather, K. Viswanathan, K. M. Miller, T. E. Long, *Prog. Polym. Sci.* **2006**, *31*, 487; c) J. W. Chan, C. E. Hoyle, A. B. Lowe, *J. Am. Chem. Soc.* **2009**, *131*, 5751.

[8] a) J. P. Hallett, T. Welton, *Chem. Rev.* **2011**, *111*, 3508; b) P. Hapiot, C. Lagrost, *Chem. Rev.* **2008**, *108*, 2238; c) U. K. Sharma, N. Sharma, R. Kumar, R. Kumar, A. K. Sinha, *Org. Lett.* **2009**, *11*, 4846; d) A. K. Chakraborti, S. R. Roy, D. Kumar, P. Chopra, *Green Chem.* **2008**, *10*, 1111; e) C. Chiappe, S. Rajamani, *Eur. J. Org. Chem.* **2011**, 5517.

[9] a) T. Lanza, M. Minozzi, A. Monesi, D. Nanni, P. Spagnolo, C. Chiappe, *Curr. Org. Chem.* **2009**, *13*, 1726; b) Z. S. Qureshi, K. M. Deshmukh, K. P. Dhake, B. M. Bhanage, *RSC Adv.* **2011**, *1*, 1106.

[10] a) M. J. Rosen, *J. Org. Chem.* **1953**, *18*, 1701; b) V. Strehmel, H. Wetzel, A. Laschewsky, *Macromol. Symp.* **2014**, *342*, 78.

[11] a) B. C. Ranu, R. Jana, *Adv. Synth. Catal.* **2005**, *347*, 1811; b) see Ref. [5f]; c) S. Biswas, J. S. Samec, *Chem. Asian J.* **2013**, *8*, 974.

[12] a) R. Kumar, A. Sharad, R. Bharti, Y. Thopate, A. K. Sinha, *Angew. Chem. Int. Ed.* **2012**, *51*, 2636; *Angew. Chem.* **2012**, *124*, 2690; b) R. Kumar, N. Sharma, U. K. Sharma, A. Sharad, A. K. Sinha, *Adv. Synth. Catal.* **2012**, *354*, 2107; c) N. Sharma, U. K. Sharma, R. Kumar, N. Katoch, R. Kumar, A. K. Sinha, *Adv. Synth. Catal.* **2011**, *353*, 871; d) R. Kumar, A. Sharma, N. Sharma, A. K. Sinha, *Eur. J. Org. Chem.* **2008**, 5577; e) H. Alireza, Z. Abdolkarim, S. Mohsen, A. R. Javad, *J. Comb. Chem.* **2010**, *12*, 844; f) S. Mohsen, H. Alireza, *Ultrason. Sonochem.* **2012**, *19*, 307; g) M. Xia, Y.-D. Lu, *J. Mol. Catal. A* **2007**, *265*, 205.

[13] In most cases, the molecular level of interaction with an ionic liquid is studied at ambient temperature ($\approx$40 °C) or room temperature (see Ref. [8d] and [12b]), because at higher temperature disruption of molecular interaction may occur that could be the reason for better hydrothiolation at 40 °C rather than under MW irradiation at 150 °C.

[14] a) X. Baucherel, J. Uziel, S. Juge, *J. Org. Chem.* **2001**, *66*, 4504; b) B. Feng, Z. Hou, X. Wang, Y. Hu, H. Li, Y. Qiao, *Green Chem.* **2009**, *11*, 1446; c) N. Sharma, U. K. Sharma, R. Salwan, R. Kasana, A. K. Sinha, *Catal. Lett.* **2011**, *141*, 616.

[15] It is imperative to mention that commercially unavailable 4-hydroxy-3,5-dimethoxystyrene (**1i′**) was prepared by dehydrating the corresponding 4-hydroxy-3,5-dimethoxy phenylethanol in [hmim]Br under microwave[12d] irradiation. After workup, the obtained **1i′** was used in the hydrothiolation reaction toward the formation of **4i** (see SI).

[16] a) P. J. Skabara, I. M. Serebryako, I. F. Perepichka, *Synth. Met.* **1999**, *102*, 1336; b) J. Jacob, L. Oldridge, J. Y. Zhang, M. Gaal, E. J. W. List, A. C. Grimsdale, K. Mullen, *Curr. Appl. Phys.* **2004**, *4*, 339.

[17] a) A. K. Chakraborti, S. R. Roy, *J. Am. Chem. Soc.* **2009**, *131*, 6902; b) R. Lungwitz, M. Friedrich, W. Linert, S. Spange, *New J. Chem.* **2008**, *32*, 1493; c) R. Lungwitz, S. Spange, *New J. Chem.* **2008**, *32*, 392; d) A. Sarkar, S. R. Roy, A. K. Chakraborti, *Chem. Commun.* **2011**, *47*, 4538.

[18] a) A. Wulf, K. Fumino, R. Ludwig, *Angew. Chem. Int. Ed.* **2010**, *49*, 449; *Angew. Chem.* **2010**, *122*, 459; b) A. G. Avent, P. A. Chaloner, M. P. Day, K. R. Seddon, T. Welton, *J. Chem. Soc. Dalton Trans.* **1994**, 3405; c) P. S. Schulz, N. Müllar, A. Bosmann, P. Wasserscheid, *Angew. Chem. Int. Ed.* **2007**, *46*, 1293; *Angew. Chem.* **2007**, *119*, 1315; d) M. Zanatta, A.-L. Girard, N. M. Simon, G. Ebeling, H. K. Stassen, P. R. Livotto, F. P. dos Santos, J. Dupont, *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/anie.201408151.

[19] a) T. S. Rodrigues, V. H. C. Silva, P. M. Lalli, H. C. B. de Oliveira, W. A. da Silva, F. Coelho, M. N. Eberlin, B. A. D. Neto, *J. Org. Chem.* **2014**, *79*, 5239; b) P. M. Lalli, T. S. Rodrigues, A. M. Arouca, M. N. Eberlin, B. A. D. Neto, *RSC Adv.* **2012**, *2*, 3201.

[20] a) P. Johannesson, G. Lindeberg, A. Johansson, G. V. Nikiforovich, A. Gogoll, B. Synnergren, M. L. Grèves, F. Nyberg, A. Karlén, A. Hallberg, *J. Med. Chem.* **2002**, *45*, 1767; b) E. Marcantoni, M. Massaccesi, M. Petrini, G. Bartoli, M. C. Bellucci, M. Bosco, L. Sambri, *J. Org. Chem.* **2000**, *65*, 4553.

[21] a) R. Sarma, N. Rajesh, D. Prajapati, *Chem. Commun.* **2012**, *48*, 4014; b) A. Kondoh, K. Takami, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2005**, *70*, 6468; c) A. Shard, R. Kumar, Saima, N. Sharma, A. K. Sinha, *RSC Adv.* **2014**, *4*, 33399.

  

# Communications

**Click Chemistry**

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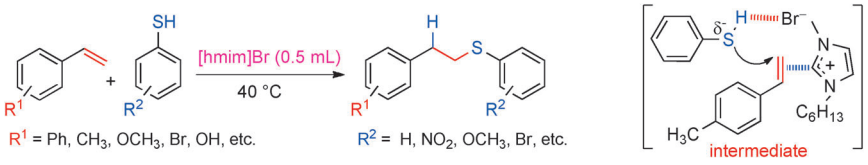


Thiol–Ene "Click" Reaction Triggered by Neutral Ionic Liquid: The "Ambiphilic" Character of [hmim]Br in the Regioselective Nucleophilic Hydrothiolation

**Linear thioethers** are obtained by an atom-efficient thiol–ene "click" reaction in neutral [hmim]Br without the need for base or metal complexes. Detailed mechanistic studies using $^{1}$H NMR spectroscopy and quadrupol time-of-flight electrospray ionization mass spectrometry showed that the "ambiphilic" character of the ionic liquid promotes the regioselective nucleophilic addition of thiol to styrene through an anti-Markovnikov pathway.

  