# Organic & Biomolecular Chemistry

# PAPER

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# A recyclable and base-free method for the synthesis of 3-iodothiophenes by the iodoheterocyclisation of 1-mercapto-3-alkyn-2-ols in ionic liquids<sup>†</sup>

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The first example of an iodocyclisation reaction made recyclable by the use of an ionic liquid as the reaction medium is reported. Readily available 1-mercapto-3-alkyn-2-ols were smoothly converted into the corresponding 3-iodothiophenes (50–81% yields, 10 examples) when allowed to react with iodine (1–2 equiv.) in a proper ionic liquid, such as 1-ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO<sub>4</sub>), as the solvent under mild reaction conditions (25 °C) and in the absence of an external base. The reaction medium can be recycled several times without significantly affecting the reaction outcome. Theoretical calculations have also been performed to investigate the role of the ionic liquid anion in the reaction.

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# Introduction

The iodocyclisation of functionalised alkynes, bearing a nucleophilic group in a suitable position, is a powerful method for the one-step regioselective synthesis of iodine-containing carbo- and heterocyclic derivatives starting from readily available substrates (Scheme 1).<sup>1</sup> The reaction is usually carried out in an aprotic organic solvent, such as MeCN or  $CH_2Cl_2$ , in the presence of an electrophilic iodine species (generally indicated by I<sup>+</sup>) under mild reaction conditions (room temperature). The presence of the iodo substituent in the final product allows for further functionalisation and diversification through metal-catalysed cross-coupling reactions, thus increasing the attractiveness of the iodocyclisation process.

As shown in Scheme 1, the iodocyclisation process takes place through the formation of an iodirenium intermediate from the reaction between the carbon–carbon triple bond and  $I^+$ , followed by intramolecular exo- or endocyclic nucleophilic attack. The reaction is usually carried out in the presence of a base (B), necessary to trap the acid generated during the process. Recently, we reported a novel application of the iodocyclisation approach, which has permitted the direct synthesis of 3-iodothiophene derivatives 2 starting from readily available 1-mercapto-3-alkyn-2-ols 1, according to eqn (1).<sup>2</sup> Reactions were carried out at 25 °C in MeCN as the solvent, with I<sub>2</sub> as the iodine source and in the presence of NaHCO<sub>3</sub> as the base (1:I<sub>2</sub>:NaHCO<sub>3</sub> molar ratio = 1:2:2, 1:2:1, or 1:3:3, depending on the nature of the starting material).

$$R^{2} \xrightarrow{OH} R^{3} + I_{2} + NaHCO_{3} \xrightarrow{MeCN, 25 \circ C} R^{1} \xrightarrow{R^{2}} R^{3}$$
(1)

We have now found that the reaction can also be conveniently carried out in ionic liquids (ILs) as the solvent, still under very mild reaction conditions (25 °C, eqn (2)). The use of such unconventional media allows one to carry out the iodo-heterocyclisation process in the absence of the external base and with the possibility to recycle the reaction medium several times without significantly affecting the reaction outcome. To

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(YH = nucleophilic group; I<sup>+</sup> = electrophilic iodine species; B = base)

Scheme 1 lodocyclisation of acetylenes bearing a suitably placed nucleophilic group leading to iodine-containing carbo- and heterocycles.

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the best of our knowledge, this is the first example of the use of ionic liquids as solvents<sup>3</sup> in an iodocyclisation reaction. The screening, carried out using several ILs characterised by significant hydrogen bond basicity, shows that substrate conversion and product yields strongly depend on the structure of the ILs. Additional information about the role played by the IL anion in the iodocyclisation reaction has been obtained through a theoretical investigation.



# **Results and discussion**

# Iodoheterocyclisation of 1-mercapto-3-alkyn-2-ols in ionic liquids

4-Mercapto-3-methyl-1-phenylpent-1-yn-3-ol (1a) was chosen as the model substrate for testing the reactivity of 1-mercapto-3-alkyn-2-ols in ionic liquids. Initially, the reaction of 1a was carried out in 3-butyl-1-methyl-imidazolium dicyanamide, BmimN(CN)<sub>2</sub>, as the solvent (0.25 mmol of 1a per mL of solvent) at 25 °C for 24 h, affording the desired 3-iodo-4,5dimethyl-2-phenylthiophene (2a) in a 43% isolated yield (entry 1, Table 1). This result was very promising, since it suggested the possibility of carrying out the iodoheterocyclisation process in an ionic liquid under base-free conditions. We then tested several other ILs, all characterised by significant hydrogen bond basicity (the Kamlet–Taft  $\beta$  values ranged from 0.44 to 1),<sup>4</sup> and the results are reported in Table 1, entries 2-13. As can be seen from these data, not all of the ILs tested were equally effective in promoting the process; the best result in terms of product yield (70%) was observed with 1-ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO<sub>4</sub>) (entry 7), which was accordingly chosen as the reference solvent to verify IL recyclability and to generalize the process to other differently substituted 1-mercapto-3-alkyn-2-ols.

Regarding the IL recycling experiments, the reaction crude obtained from **1a** in EmimEtSO<sub>4</sub> (Table 2, entry 1, run 1) was extracted with Et<sub>2</sub>O to separate the 3-iodothiophene **2a**, and then fresh substrates **1a** and I<sub>2</sub> (1 : 1 molar ratio) were added to the IL residue and the mixture was allowed to stir at 25 °C for 24 h. Gratifyingly, **2a** was formed again in a comparable yield (68%) with respect to the parent reaction (Table 2, entry 1, run 2). The recycling procedure was then repeated up to 6 times, without significant variation of the reaction outcome (Table 2, entry 1, runs 3–7). We also carried out the reaction with a slight excess of I<sub>2</sub> (1.5 equiv., Table 2, entry 2), but the result was similar to that obtained using an equimolar amount with respect to **1a** (Table 2, entry 1, run 1).

A variety of 1-mercapto-3-alkyn-2-ols **1** were then allowed to react under the same reaction conditions successfully employed for 4-mercapto-3-methyl-1-phenylpent-1-yn-3-ol (**1a**)

Table 1Iodocyclodehydration of 4-mercapto-3-methyl-1-phenylpent-<br/>1-yn-3-ol(1a)to3-iodo-4,5-dimethyl-2-phenylthiophene(2a)indifferent ionic liquidsa









<sup>*a*</sup> Unless otherwise noted, all iodocyclisation reactions were carried out under nitrogen at 25 °C for 24 h with a substrate concentration of 0.25 mmol of **1a** per mL of ionic liquid. Unless otherwise noted, substrate conversion was quantitative. The formation of a complex mixture of products accounted for the difference between substrate conversion and the yield of **2a**. <sup>*b*</sup> Isolated yield based on the starting thiol **1a**. <sup>*c*</sup> Substrate conversion was 85%. <sup>*d*</sup> Substrate conversion was 80%. <sup>*e*</sup> Substrate conversion was 65%. <sup>*f*</sup> Substrate conversion was 60%. in order to develop a general, base-free and recyclable synthesis of 3-iodothiophenes 2. The results obtained by varying the nature of the substituent  $\alpha$  to the mercapto group,  $\alpha$  to the hydroxyl group, and on the triple bond are reported in Table 2. As can be seen, good to excellent yields of the corresponding 3-iodothiophenes were obtained with all of the substrates tested. In some cases, the reaction worked better with an excess of  $I_2$  (1.5–2 equiv.) with respect to the substrate; this was particularly evident in the case of a substrate bearing a hindered triple bond, such as 2-mercapto-3,6,6-trimethylhept-4-yn-3-ol (2g) (Table 2, entries 13-15). The method also worked nicely with substrates bearing an additional alkynyl substituent at C-2, such as 3-(1-mercaptoethyl)-1,5-diphenylpenta-1,4divn-3-ol (1i), which was smoothly converted into the corresponding 3-iodo-5-methyl-2-phenyl-4-(2-phenylethynyl)thiophene (2i) without affecting the additional triple bond (Table 2, entries 18 and 19). The recycling procedure was tested in several cases, still with satisfactory results (Table 2; entries 3, 11, 14, 15 and 19).

## Theoretical calculations

Data reported in Table 1 show that substrate conversion and product yields strongly depend on the IL structure. As expected for a reaction involving a rate determining cyclisation with proton abstraction, the nature of the IL anion significantly affected both these parameters, although a simple correlation

Table 2 Recyclable and base-free synthesis of 3-iodothiophenes 2 by iodocyclisation of 1-mercapto-3-alkyn-2-ols 1 in EmimEtSO<sub>4</sub> <sup>a</sup>



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## Table 2 (Contd.)

|                             |                            | $R^{2} \xrightarrow{OH} R^{3} \xrightarrow{I_{2} (1-2 \text{ equiv})}_{\text{EmimEtSO}_{4}} R^{1} \xrightarrow{F^{2}} R^{3}$ |                    |                    |                    |                    |                    |                    |                    |  |
|-----------------------------|----------------------------|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--|
|                             |                            |  | Yield of $2^b$ (%) |                    |                    |                    |                    |                    |                    |  |
| Entry                       | 1                          | 2  | Run 1 <sup>c</sup> | Run 2 <sup>c</sup> | Run 3 <sup>c</sup> | Run 4 <sup>c</sup> | Run 5 <sup>c</sup> | Run 6 <sup>c</sup> | Run 7 <sup>c</sup> |  |
| 7                           | Me H<br>Me SH 1d           | Me<br>Me<br>S<br>2d  | 50                 |                    |                    |                    |                    |                    |                    |  |
| 8 <sup><i>d</i></sup>       | 1d                         | 2d   | 62                 |                    |                    |                    |                    |                    |                    |  |
| 9                           | Me H<br>Me H<br>SH 1e      | Me I<br>Me S<br>2e   | 61                 |                    |                    |                    |                    |                    |                    |  |
| $10^d$                      | 1e                         | 2e   | 69                 |                    |                    |                    |                    |                    |                    |  |
| 11                          | Me H<br>Me Bu<br>SH 1f     | Me<br>Me<br>S<br>Bu  | 77                 | 68                 | 67                 | 69                 | 68                 | 70                 | 71                 |  |
| $12^d$                      | 1f                         | 2f   | 95                 |                    |                    |                    |                    |                    |                    |  |
| 13                          | Me H-t-Bu<br>Me SH 1g      | Me<br>Me<br>S<br>2g  | 20                 | 25                 | 23                 |                    |                    |                    |                    |  |
| $14^{d}$<br>15 <sup>e</sup> | 1g<br>1g                   | 2g<br>2g   | 64<br>77           | 60<br>73           | 59<br>70           | 60<br>65           | 65<br>61           | 66<br>60           | 63<br>60           |  |
| 16                          | Me OH Ph<br>Me SH 1h       | Me<br>Me<br>S<br>2h  | 50                 |                    | ,,,                |                    | 01                 |                    |                    |  |
| $17^d$                      | 1h                         | 2h   | 62                 |                    |                    |                    |                    |                    |                    |  |
| 18                          | Ph<br>OH<br>Me<br>SH<br>1i | Ph<br>Me<br>S<br>2i  | 40                 |                    |                    |                    |                    |                    |                    |  |
| $19^d$                      | 1i                         | 2i   | 81                 | 73                 | 76                 | 75                 | 72                 | 73                 | 74                 |  |
| 20                          | HOPh<br>SH 1j              |  | 50                 |                    |                    |                    |                    |                    |                    |  |

<sup>*a*</sup> All reactions were carried out at 25 °C for 24 h in EmimEtSO<sub>4</sub> as the solvent (0.25 mmol of starting **1** per mL of solvent). Conversion of **1** was quantitative in all cases. <sup>*b*</sup> Isolated yield based on starting **1**. <sup>*c*</sup> Run 1 corresponds to the 1<sup>st</sup> experiment, and the next runs to recycles. See text for details. <sup>*d*</sup> The reaction was carried out with a substrate : I<sub>2</sub> molar ratio of 1.5. <sup>*e*</sup> The reaction was carried out with a substrate : I<sub>2</sub> molar ratio of 2.



**Fig. 1** Product yield (%) with respect to IL hydrogen bond acceptor ability ( $\beta$ ). The numbers refer to the entries in Table 1.  $\beta$  values for entries 3, 4, and 6 are not available.

between hydrogen bond acceptor ability ( $\beta$ ) and conversion/ yield cannot be established (Fig. 1).

The ILs characterised by a high  $\beta$  value (*i.e.* chloride 0.94) give relatively low yields and/or conversions. Nevertheless, EmimNO<sub>3</sub> and EmimEtSO<sub>4</sub>, two ILs characterised by similar  $\beta$  values (0.66 and 0.71, respectively), provide the same product with significantly different yields. In the case of halide based ILs, this behaviour can be attributed, at least partially, to the ability of these anions (Cl<sup>-</sup> and Br<sup>-</sup>) to interact with molecular iodine to give trihalide anions (I<sub>2</sub>Cl<sup>-</sup>, ICl<sub>2</sub><sup>-</sup>, I<sub>3</sub><sup>-</sup> or I<sub>2</sub>Br<sup>-</sup>, IBr<sub>2</sub><sup>-</sup>) that, despite being electrophilic species, are significantly less reactive than the free halogen.<sup>5</sup> A similar explanation, however, cannot account for the reactivity of the other anions. Therefore, to better define the role of the ionic solvent anion in the reaction profile for the iodocyclisation of 1-mercapto-3-alkyn-2-ols, a theoretical investigation on three anions (Br<sup>-</sup>, NO<sub>3</sub><sup>-</sup> and EtSO<sub>4</sub><sup>-</sup>) characterised by similar  $\beta$  values (0.74, 0.66 and 0.71, respectively), but giving significantly different yields, has been performed. For this investigation, since the effects of ILs on chemical reactions have not yet been sufficiently rationalised to allow the development of a computational model that takes into account their activity, and with a limited computational effort, it was necessary to plan carefully the model system in order to obtain useful data. In particular, considering that the iodocyclisation reaction is a multistep process, we decided to focus our efforts exclusively on the "critical" step(s). The reaction implies the initial formation of an iodirenium-(iodide)triiodide intermediate by electrophilic attack of I2 on the triple bond, followed by the intramolecular nucleophilic attack of the S atom on the iodirenium carbon to give a heterocyclic system. The subsequent dehydration-aromatisation reaction allows isolation of the aromatic compounds 2. Since the formation of an iodirenium ion is generally a reversible process, we considered as the "key-step" for the development of the model system the cyclisation reaction. At this point, the main questions were: (i) what is the IL component that plays a specific role during the attack of the SH group on the iodirenium carbon; and (ii) how many IL ions are necessary to define the model system? The iodirenium intermediate is a positively charged species; therefore, it is reasonable to



hypothesize that the IL anion can easily replace the  $I_3^-$  species as a counterion for I<sup>+</sup>. Furthermore, another IL anion is probably involved in the proton abstraction process from the SH group determining the ring closure. The reaction model employed is consequently represented in Scheme 2.

Both the molecular clusters 1ec and 1r carry a total single negative charge and, with the exception of the hydroxyl group, all of the functional groups are solvated by the IL anion. However, steric and electrostatic interactions exclude the possibility of placing another ion in the proximity of the hydroxyl group. It is noteworthy that in the calculated reaction paths this group interacts alternatively with both of the anions. In the IL, the interactions between a single charged system of the type reported here and the bulk can be considered to be aspecific and, in our approach, disregarded.<sup>6</sup> The main weakness of this model might be, however, the total absence of cations that hamper the evaluation of the role played by the concurrent interactions between anions-cations and anionssubstrate. However, in a relevant number of computational investigations on chemical reactivity in ILs, one of the two ions is often omitted. There are indeed computational studies on anion related reactions and cation related reactions. In the first category can be included many metal catalysed reactions, in which the metal is coordinated by the IL anion.<sup>7</sup> In the second category are included reactions such as the Diels-Alder cycloaddition,8 in which the specific IL effect is due to the hydrogen bonding between the IL cation and the polar group on a reagent (the dienophile in the case of the Diels-Alder cycloadditions). On the other hand, for reactions such as the Menschutkin substitution,<sup>9</sup> in which two neutral reagents give a charged product (an ion pair), it is necessary to take into account both IL components. The presently investigated process can be classified, with good approximation, as an anion related reaction, although a small cation effect can be evidenced comparing the yield values obtained in four dicyanamide based ILs (Table 1, entries 1 and 11-13). The limited number of data does not allow us to rationalize the cation effect; small differences might be due to transport phenomena related to the different viscosities; however it is possible that also this parameter might be used to fine tune the reaction outcome.

Finally, to optimize the setup of the computational experiment, it was necessary to select the reaction coordinate and the level of the theory to adopt. The reaction coordinate was defined considering as the main target of this reaction the formation of the C–S bond, and the distance  $R_{SC}$  between sulfur

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and carbon was taken into account. Reactions that involve organic molecules, without the presence of critical issues like radical intermediates, carbenes, transition metal catalysts, *etc.*, are well described by standard density functional theory. Therefore, we have chosen the widely used B3LYP functional and, considering the computational resources available nowadays, the use of a triple-zeta basis set has been mandatory. All of the calculations have been performed using the 6-311++G(d,p) basis set for hydrogen, second and third row elements. For heavier elements, like iodine and bromine, we used the triple zeta LANL08<sup>10</sup> basis set with pseudopotentials. LANL08 has been conceived as a heavy element companion to the 6-311G basis set family. All calculations have been performed using the Gaussian package.<sup>11</sup>

As explained above, to evaluate the role of the IL anion (size, hydrogen acceptor ability or basicity), we decided to investigate the effect of EtSO<sub>4</sub><sup>-</sup>, Br<sup>-</sup> and NO<sub>3</sub><sup>-</sup>. Furthermore, we have considered two different side chains on the substrate, investigating the effect of an aliphatic flexible chain (n-butyl moiety, R = Bu) and of a rigid aromatic ring (phenyl, R = Ph). A total of six reaction paths have been investigated. The calculated reaction paths are represented in Fig. 2, whereas some energetic and geometrical quantities related to the reaction paths are reported in Table 3. It is noteworthy that all of the six reaction profiles show minima corresponding to the 1r structure, at a value of  $R_{SC}$  of about 1.8 Å. Furthermore, the stationary point at about 5 Å corresponded to the structure 1ec. Profiles corresponding to reactions performed in ILs having the same anion, but on substrates bearing different substituents, are very similar. It is notable that profiles related to nitrate-based ILs are very irregular and contain several local minima connected by transition states.

Attempts to obtain the transition state structures (**1ts**) were carried out exclusively for the higher energetic structure (**1h**) of each profile, disregarding the other transition states and intermediate minima. Only for the model system based bromide and a phenyl substituted substrate was it possible to achieve the goal; consequently, in all of the other cases, we used the higher energy structure to estimate the activation barrier. It is noteworthy that for the sole case for which both structures are available, the difference in the reaction coordinate is 0.005 Å



Fig. 2 Reaction profiles (distances in Å and energies in kcal mol<sup>-1</sup>).

 Table 3
 Geometric and energetic quantities related to the reaction profiles<sup>a</sup>

| Molecular<br>system  |                  | $R_{\rm CS}/{ m \AA}$   | $R_{ m SH}/{ m \AA}$    | $R_{\rm AH}$            | $\Delta E$             | Barrier | Structure |
|----------------------|------------------|-------------------------|-------------------------|-------------------------|------------------------|---------|-----------|
| Bu–Br                | 1ec<br>1h<br>1r  | 5.131<br>4.6<br>1.819   | 1.379<br>1.388<br>2.159 | 2.394<br>2.371<br>1.498 | 23.63<br>34.30<br>0.00 | 10.67   | Chelate   |
| Ph-Br                | 1ec<br>1ts<br>1r | 5.067<br>4.595<br>1.823 | 1.356<br>1.380<br>2.198 | 3.046<br>2.397<br>1.490 | 23.69<br>28.37<br>0.00 | 4.68    | Cyclic    |
| Bu-NO <sub>3</sub>   | ec<br>1h<br>1r   | 5.300<br>4.2<br>1.816   | 1.349<br>1.879<br>2.171 | 4.421<br>1.084<br>1.006 | 33.35<br>55.37<br>0.00 | 22.02   | Chelate   |
| Ph-NO <sub>3</sub>   | 1ec<br>1h<br>1r  | 5.026<br>4.6<br>1.819   | 1.370<br>1.863<br>2.184 | 1.896<br>1.091<br>1.004 | 39.54<br>53.87<br>0.00 | 14.33   | Chelate   |
| Bu-EtSO <sub>4</sub> | 1ec<br>1h<br>1r  | 5.001<br>3.2<br>1.812   | 1.348<br>1.365<br>2.170 | 3.380<br>1.929<br>1.004 | 37.55<br>49.73<br>0.00 | 12.18   | Cyclic    |
| Ph-EtSO <sub>4</sub> | 1ec<br>1h<br>1r  | 4.937<br>4.2<br>1.82    | 1.354<br>1.356<br>2.177 | 2.221<br>2.094<br>1.003 | 37.28<br>43.77<br>0.00 | 6.49    | Cyclic    |

<sup>*a*</sup> Distances in Å; energies in kcal mol<sup>-1</sup>. The H–A distance is referred to the atom of the anion nearest to the hydrogen. A = Br for Br<sup>-</sup>, A = O for NO<sub>3</sub><sup>-</sup>, A = O for EtSO<sub>4</sub><sup>-</sup>. The structures of **1ec** and **1r** are shown in Scheme 2. **1ts** = transition state. **1h** = higher value of the energy profile when the transition state is not available. Barrier refers to **1ec** $\rightarrow$ **1ts** or **1ec** $\rightarrow$ **1h** ones. **1r** $\rightarrow$ **1h** values correspond to the **1ts** or **1h** energies.

and  $\Delta E = 0.14$  kcal mol<sup>-1</sup>. Undoubtedly, the molecular systems under investigation present several conformational degrees of freedom (rotation of methyl and phenyl groups, conformational motion of aliphatic substituents, and so on) and consequently it can be too complex for the automated procedures used to find stationary points, in particular the transition states. However, useful information can be simply obtained by the reaction profiles, also without an exact knowledge of the transition states.

Some relevant structures are shown in Fig. 3. Structures **1ec** represent a situation of optimal solvation in the absence of any reactive process. In particular, we have found two kinds of structures:

• The chelated structure, in which one anion is chelated to the OH and SH moieties. Both of these groups point outward with respect to the reactive site (the iodirenium complex). A structure of this type is represented in Fig. 3b.

• The cyclic structure, in which the SH group is coordinated to the anion pointing toward the reactive site. Structures of this type are represented in Fig. 3a, c and d.

The chelate structures correspond to higher activation barriers than the cyclic ones. From the geometrical point of view, the cyclic structures are more similar to the final products. In particular, the position of the anion coordinating the SH group is in the cyclic structure nearer to the final location, thus playing a fundamental role in the reaction pathway. Related to these structures, some considerations need to be made for the anion and substrate dependent selectivity



**Fig. 3** Some molecular structures discussed in the paper. (a) **1ec** with R = phenyl and A = bromine. (b) **1ec** with R = phenyl and A =  $NO_3^-$ . (c) **1ec** with R = phenyl and A =  $EtSO_4^-$ . (d) **1ec** with R = phenyl and A =  $EtSO_4^-$ . (e) **1r** with R = phenyl and A =  $EtSO_4^-$ . (f) **1ts** with R = phenyl and A = bromine.

towards the cyclic or chelate (less reactive) molecular structure **1ec**, arising from *ab initio* calculations. In the case of the monoatomic bromide ion, the cyclic structure is probably favoured by the interaction of  $Br^-$  with the phenyl group on the substrate. The nitrate anion appears too small to stabilize the large ring of the cyclic structure and, in contrast, ethyls-ulfate too sterically hindered to form a chelate system. Completely different is the situation for the **1r** structures. As easily deduced from the geometrical parameters reported in Table 3 and from Fig. 3, the **1r** structures are very similar, regardless of the anion structure and the substituent; they can be considered to be equivalent from the point of view of bonding and solvation. Consequently, they have been chosen as zero in the energy profiles.

It is remarkable that phenyl-substituted substrates are always characterised by lower activation barriers with respect to the analogous butyl-substituted structures. As shown in Fig. 3a and 3c, the hydrogen atom in the *ortho* position of the phenyl ring is able to interact with the IL anion due to the partial positive charge on the related carbon, represented by the resonance structures shown in Fig. 4.

The iodirenium asymmetry, clearly visible in Fig. 3a and 3c (where R = phenyl), but not in 3b and 3d (where R = butyl), reinforces this interpretation. The difference between **1ec** with A = Br– and R = phenyl (Fig. 3a) and the corresponding **1ts** structure (Fig. 3f) is essentially a torsion of the  $CH_2CH(CH_3)SH$  group around its first C–C bond.



**Fig. 4** Possible resonance structures for phenyl-substituted substrates, showing the interaction between the hydrogen atom in the *ortho* position of the phenyl ring and the IL anion.

An accurate analysis of the reaction paths shows furthermore that the anions always exert the same function, although the anion structure, and therefore the extent of the interactions, affect significantly the reaction course. In particular, the anion associated with the iodirenium moiety plays a function which is independent of the anion structure and becomes totally marginal in 1r, where the charged iodirenium species is transformed into a neutral iodine substituent. In contrast, the other anion, initially coordinated to the thiol group and subsequently primarily involved in proton abstraction, exerts a function that is profoundly affected by the anion shape, size and nature. These features determine the structure of 1ec and consequently the energetic differences between 1ec and 1r. The reaction paths involving ethylsulfate and bromide are indeed very similar, but the energetic difference between 1ec and 1r, larger for ethylsulfate, ensures in the latter case a

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minor reversibility of the cyclisation step. The lower yields characterizing the reactions performed in bromide-based ILs can therefore be ascribed not only to the ability of bromide to form with  $I_2$  less reactive trihalide species ( $I_2Br^-$ ,  $IBr_2^-$  and  $I_3^-$ ), but also to a higher reversibility of the cyclisation process. The reversibility of the cyclisation step, related to the stability of **1ec**, might be the key factor that determines the IL anion dependence of this reaction. Since the structure of **1ec** is significantly affected by anion shape and dimensions, features not affecting the  $\beta$  parameters, calculations help explain the poor (if any) correlation found between yields and  $\beta$ .

## Experimental

## Materials and methods

General experimental methods. Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded at 25 °C in CDCl<sub>3</sub> solutions using a Bruker DPX Avance 300 spectrometer operating at 300 MHz and 75 MHz, respectively, with Me<sub>4</sub>Si as an internal standard. Chemical shifts ( $\delta$ ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken using a JASCO FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionisation voltage. Microanalyses were carried out using a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analysed by TLC on silica gel 60 F254 (Merck) or on neutral alumina (Merck) and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone + 5% polyphenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70-230 mesh) or neutral alumina 90 (Merck, 70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

**Preparation of substrates.** All starting 1-mercapto-3-alkyn-2-ols **1a–j** were prepared as we had already reported.<sup>2</sup> All other materials were commercially available and were used without further purification.

### Synthetic procedures

General procedure for the iodocyclisation of 1-mercapto-3-alkyn-2-ols 1a–j to 3-iodothiophenes 2a–j. To a solution of 1 (0.5 mmol) (1a, 103 mg; 1b, 110 mg; 1c, 142 mg; 1d, 106 mg; 1e, 105 mg; 1f, 93 mg; 1g, 93 mg; 1h, 118 mg, 1i, 146 mg; 1j, 178 mg) in EmimEtSO<sub>4</sub> (2 mL) was added I<sub>2</sub> (127, 190, or 253 mg; 0.5, 0.75, or 1.0 mmol; see Table 1) under nitrogen. The mixture was allowed to stir at 25 °C for 24 h and then extracted with Et<sub>2</sub>O (7 × 3 mL). After evaporation of the solvent, the products 2a–j were purified by column chromatography on silica gel using 99:1 hexane–AcOEt as the eluent. The IL residue was reused in the recycling procedure as described below. The water content as well as the amount of the residual iodine in the IL residue was not determined, because they did not affect the outcome of the recycling process.

Recycling procedure. To the IL residue obtained as described above was added a solution of 1 (0.5 mmol) and  $I_2$ 

(0.5, 0.75, or 1.0 mmol) in  $Et_2O$  (3 mL). The  $Et_2O$  was removed under vacuum and then the same procedure described above was followed.

**Characterisation of products.** All products **2a-j** were characterised by spectroscopic comparison with the corresponding products obtained in our previous report.<sup>2</sup>

## Conclusions

In conclusion, we have reported the first example of an iodocyclisation reaction in several ionic liquids, showing that 1-ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO<sub>4</sub>) is the best solvent for this reaction. This has allowed the smooth conversion of a variety of 1-mercapto-3-alkyn-2-ols 1 into the corresponding 3-iodothiophenes 2 under base-free conditions and with the possibility to recycle the reaction medium several times without affecting the reaction outcome. The computational results show that the IL anion strongly affects the cyclisation step favouring or disfavouring the right disposition of the atoms (S–C) involved, depending on the shape and size.

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## Notes and references

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