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Imidazolium ionic liquids containing selenium: synthesis and antimicrobial activity†

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The synthesis and antimicrobial profile of imidazolium ionic liquids containing selenium are described herein. Minimum inhibitory concentration revealed that these compounds are especially active against algae, and their activity is modulated by substituents attached to the selenium moiety as well as by the counterion.

Ionic liquids (ILs) have been attracting considerable attention in the past years. These substances have been extensively used as solvents in many organic transformations with interesting results when compared to conventional organic solvents.[1] Moreover, the investigation of the toxicity[2] and biological activity (*e.g.*, antitumor, anti-cancer, DNA cleavage) of ILs is an emerging area of research.[3] Another important characteristic attributed to ILs concerns their application as antimicrobial agents. Several studies have shown that they display great activity against gram-positive and gram-negative bacteria, fungi and algae.[4] Previous reports have shown that this activity relies mainly on the chain length of the investigated ILs. In general, a higher activity is attributed to ILs assembled with longer carbon chain lengths.[5] Interesting is the enhanced antimicrobial activity of ILs containing alkoxy groups in the side chain, this structural modification allowed the preparation of more potent substances.[6]

On the other hand, selenium is recognized as an essential trace element and is involved in a series of biochemical and biological processes.[7] Very recent reports have described interesting activity of organoselenium compounds such as: anti-HIV,[8] anticancer,[9] as enzyme inhibitors,[10] enzyme mimetics,[11] among others.[12] In addition, organoselenium compounds have been successfully designed and screened as antimicrobial substances.[13] Recently, the preparation of selenonium based ionic liquids has been described,[14] however, to date no biological information is available on these compounds.

According to the above mentioned, and our ongoing research interest in organochalcogen[15] and ILs chemistry,[16] we decided to investigate whether any cooperativity might be gained by combining selenium and ionic liquids, to produce a new class of antimicrobial agents. In this report, we wish to highlight our results on the design, synthesis and antimicrobial screening of novel imidazolium ionic liquids assembled with seleno groups attached to the side chain. In a straightforward route these compounds can be conveniently prepared in good yields and in a modular fashion, which leads to a better understanding of the structure–activity relationship. In this study we used gram-positive and gram-negative bacteria, fungi and algae as representative microorganisms. The minimum inhibitory concentration (MIC) revealed that these substances are particularly active against algae. The activity of selenium ILs is modulated by the substituents attached to the selenium moiety and by the nature of the counterion.

Preparation of the desired compounds is shown in Table 1. We focused our study on the use of diaryl diselenides, due to their stability and ease of handling. Moreover, electronic and steric effects in the selenium atom could be easily introduced by the appropriate choice of substituents in the aryl moiety. Reaction of PhSeSePh **1** (R = H) with $NaBH_4$ in a 1 : 1 mixture of EtOH and THF in an excess of CH_2Cl_2 led to the formation of compound **2**.[17] After work-up **2** was dried over vacuum and used in the next step without purification. Stirring **2** with *N*-methylimidazole under neat conditions (4 h at 100 °C) gave product **3a** with chloride as the counterion in 76% overall yield (Table 1, Entry 1). A lower yield was obtained for the same product by stirring substrate **2** in MeCN for 48 h under reflux (71% overall yield). Preparation of compounds **3b** and **3c** was performed by ion exchange of **3a** using aqueous solutions of $NaBF_4$ and KPF_6 for **3b** and **3c**, respectively. These products were achieved in 61 and 71% yield, respectively, from **1** (Table 1, Entry 1). Once that we found the best reaction conditions to prepare our desired products, we used different diselenides as starting materials. Electron donating and electron withdrawing groups attached at the *para* position were efficiently used to prepare ionic liquids **4–6** in the range of 45–71% yield (Table 1, Entries 2, 3 and 4). Diaryl diselenides carrying electron donating substituents at the *ortho* position were also prepared (Table 1, Entries 5 and 6). However, reaction of 2-$ClC_6H_4Se)_2$ proved to be impractical, giving the desired product in very low yield. We were also able to prepare compounds **9a–c** in good yields from sterically hindered dimesityl diselenide (Table 1, Entry 7).

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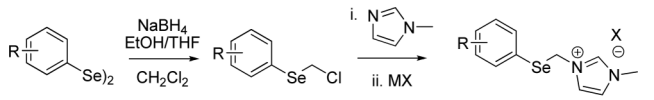
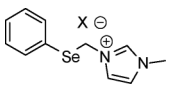
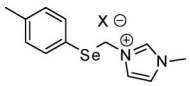
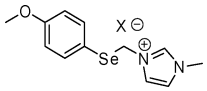
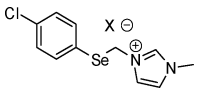
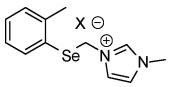
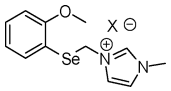
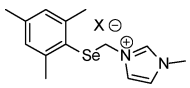
Table 1 Synthesis of selenium based ionic liquids **3–9**



Entry	Product		X	Yield (%)[a]
1		**3a**	Cl	76
		3b	BF_4	61
		3c	PF_6	71
2		**4a**	Cl	71
		4b	BF_4	68
		4c	PF_6	69
3		**5a**	Cl	51
		5b	BF_4	48
		5c	PF_6	45
4		**6a**	Cl	69
		6b	BF_4	66
		6c	PF_6	62
5		**7a**	Cl	66
		7b	BF_4	56
		7c	PF_6	61
6		**8a**	Cl	65
		8b	BF_4	64
		8c	PF_6	57
7		**9a**	Cl	62
		9b	BF_4	54
		9c	PF_6	54

[a] Isolated overall yield from **1**.

Dialkyl diselenides were also used, but many byproducts were obtained, making the preparation of these products difficult. All products described in Table 1 were characterized by ^1H, ^{13}C NMR and HRMS (see ESI†).

Antimicrobial screens were conduced against a panel of microorganisms including bacteria (*Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853), yeast like fungi (*Candida albicans* ATCC 24433), filamentous fungi (*Aspergillus fumigatus* ATCC 204305), and *Prototheca zopfii* (algae). The antimicrobial activity of each compound was measured by determination of the minimal inhibitory concentration (MIC). The assays were performed by broth microdilution techniques according to CLSI (Clinical Laboratory Standards Institute): M07-A8 (2009) for bacteria, M27-A3(2008) for *C. albicans* and *P. zopfii* and M38-A2 (2008) for filamentous fungi. The results are shown in Table 2.

These results clearly indicate that compounds **3a–9a**, all of them with chloride as counterion were especially active against algae (Table 2, Column 3, Entries 1–7). Our results also demonstrated that the activity of these compounds is influenced by their structures, the most effective (lower MIC values) being ILs **4a**, **5a**, **6a**, **7a** and specially **9a** (Table 2, Column 3, Entries 2, 3, 4, 5 and 7 respectively). Selenium ionic liquid **6a** was also efficiently employed against bacteria, showing improved activity with MIC values of 0.10 μM for *S. aureus* (Table 2, Column 4, Entry 4). In another assay, *E. coli* proved to be more susceptible to the action of the tested compounds, IL **5a** and **6a** exhibited MIC values of 0.10 and 0.20 μM respectively (Table 2, Column 5, Entries 3 and 4). On the other hand, the tested selenium ILs had a lower activity against *P. aeruginosa* (bacteria) and *C. albicans* and *A. fumigatus* (fungus). The MIC values for most of the ILs were higher than 0.40 μM for these microorganisms (Table 2, Columns 6–8, Entries 1–7). However, although our results suggest that the performance of the tested ILs is modulated by their structure it does not follow an obvious trend, showing different activities depending on the microorganism and the calalyst tested.

Table 2 Antimicrobial profile of selenium ILs **3–9**[a]

#		*P. zopfii*	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. fumigatus*
1	**3a**	0.22	>0.45	>0.45	>0.45	0.45	>0.45
2	**4a**	0.05	>0.42	>0.42	>0.42	>0.42	>0.42
3	**5a**	0.05	>0.40	0.10	>0.40	>0.40	>0.40
4	**6a**	0.05	0.10	0.20	0.40	>0.40	>0.40
5	**7a**	0.05	0.42	>0.42	>0.42	>0.42	>0.42
6	**8a**	0.20	>0.40	>0.40	>0.40	>0.40	>0.40
7	**9a**	0.01	>0.39	0.39	>0.39	0.39	0.39

[a] MIC (triplicates) expressed in μM.

In order to evaluate the influence of selenium in the biological activity of the ILs screened, we performed a second set of experiments (Fig. 1). Once that algae proved to be particularly susceptible to the action of selenium ILs, compound **10**[18] was employed as a selenium "blank" ionic liquid and its activity was compared to that of IL **3a** in the *P. zopfii* assay. The results clearly indicate that selenium plays an important role in the activity of compound **3a**, with a MIC value which is less than a half of that observed for the selenium "blank" IL **10**. Nonetheless, the performance of selenium IL **3** is also intrinsically associated to the nature of the anionic counterion. Simple replacement of chloride in IL **3a** by BF_4 or PF_6 in ILs **3b** and **3c** respectively,[19] was reflected by a decrease in their activity.

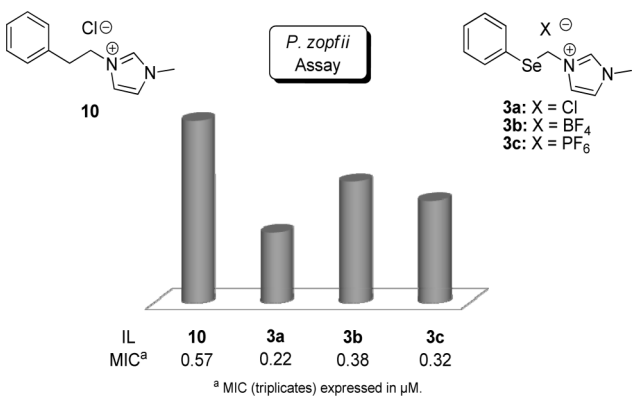


Fig. 1 Effect of selenium and the anionic counterion in the activity of selenium ILs **10** and **3a–c** against *P. zopfii*.

Conclusions

To summarize, in this study we described the preparation of imidazolium based ionic liquids functionalized with selenium in the side chain. These compounds were efficiently prepared through a straightforward sequence, allowing the access to a set of

compounds with modular feature. We also evaluated the antimicrobial profile of these new compounds. Of the microorganisms tested, algae proved to be particularly susceptible to the action of selenium ILs. The minimum inhibitory concentration (MIC) revealed that the activity of these compounds is modulated by structural modifications in the aryl group attached to selenium as well as by the counterion associated with the cationic part. Currently, we are pursuing other synthetic approaches to prepare selenium ILs assembled with longer side chains and evaluate this important feature related to the antimicrobial activity of ionic liquids.

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19 To assure that the purity of ILs **3b–c** was in an acceptable level, they were subjected to ion chromatography analysis to determine the amount of residual chloride. **3b** and **3c** showed an amount of chloride of 2.58% (w/w) and 0.14% (w/w) respectively, see ESI and: C Villagrán, M. Deetlefs, W. R. Pitner and C. Hardacre, *Anal. Chem.*, 2004, **76**, 2118–2123.