Efficient synthesis of selenoesters from acyl chlorides mediated by CuO nanopowder in ionic liquid

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Herein, we report an eco-friendly synthesis of selenoesters from acyl chlorides catalyzed by recyclable CuO nanopowder in ionic liquid as a recyclable solvent in good to excellent yields. This protocol shows high efficiency in catalyzing this transformation in a greener fashion than previous protocols due to the non-residual methodological design.

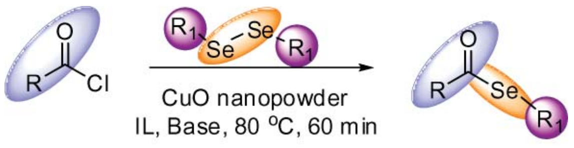
Over the past decades, higher organochalcogenides have been established as functional elements in biochemistry and medicine. In particular, selenium and organoselenium compounds are gaining increasing attention due to their properties as antioxidant and antitumor agents, as apoptosis inducers, and in the effective chemoprevention of cancer in a variety of organs.[1–4]

Selenoesters are important intermediates in several organic transformations. The compounds in this class have been used as precursors of acyl radicals[5] and anions[6] and have attracted attention for the synthesis of new molecular materials, especially superconducting materials and liquid crystals.[7] Applications of selenoesters have been expanded to the synthesis of proteins by chemical ligation of chalcogenol esters,[8] to the synthesis of substrates which undergo facile and efficient radical decarbonylation, as well as to the synthesis of the natural alkaloid (+)-geissoschizine.[9]

There are a number of methods reported in the literature to synthesize selenoesters using different metals, including palladium complexes (such as $Pd(PPh_3)_4$),[10] samarium di-iodide,[11] indium,[12] indium(I) iodide,[13] $Hg(SePh)_2$,[14] $PhSeSnBu_3/Pd$,[15] and Rh/H_2[16] systems. However, these procedures have limitations such as the air reactivity of metals, harsh conditions, and the difficulty involved in handling selenium compounds, besides the use of toxic and carcinogenic solvents.

From a sustainable chemistry point of view, there is a need for new methods that are truly efficient, high yielding, responsive to mild reaction conditions, and byproduct-free. In this regard, ionic liquids have frequently been used in the last few years as alternative reaction media for a broad range of chemical transformations. They present various interesting properties which could alleviate environmental problems, such as no effective vapor pressure, nonvolatility, nonflammability, excellent chemical and thermal stability, and recyclability, which make them attractive media for organic reactions.[17] Additionally, organic reactions catalyzed by metallic nanostructures are currently an area of intensive research, with many reports in the literature.[18] Generally, catalysts in nanoscale afford a more effective process and allow a genuine advance in relation to traditional methodologies. Nanomaterials containing high surface area and reactive morphologies have been studied as effective catalysts for organic synthesis.[19] In this new intensive area, CuO has emerged as a useful catalyst in several transformations.[20]

Considering our ongoing research into organochalcogen chemistry,[21] herein we wish to disclose a new and more eco-friendly approach to the synthesis of selenoesters employing recyclable ionic liquids and CuO nanopowders, as depicted in Scheme 1.



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Scheme 1 General synthesis of selenoesters.

In order to optimize the protocol and to understand the influence of different variables on this reaction, several components were studied. To this end, we carried out the reaction employing 4-methylbenzoyl chloride **1e** as a representative acyl chloride and 0.5 equiv. of diphenyl diselenide affording the corresponding selenoester **2e** (Table 1). In a first set of experiments, we studied the influence of different ionic liquids. It was possible to observe that in all examples the desired product was obtained with yields ranging from 82% to 90%. Nevertheless, BMIM-PF_6 was the most efficient ionic liquid for this reaction affording a better yield for selenoester **2e** (Table 1, entry 3).

The influence of different bases was studied to perform a more efficient cleavage of the diselenides, affording the nucleophilic selenolate species. Cs_2CO_3 and KOH provided the selenoester **2e** in good yields (Table 1, entries 3 and 5), whereas other bases, such as K_2CO_3 and Na_2CO_3, gave only moderate yields (Table 1, entries 6 and 7). The product was not observed in the absence of base (Table 1, entry 10), and the best base for this reaction was Cs_2CO_3 (Table 1, entry 3). The variation in the reaction time from 30 to 60 min was studied. The yield increased from 30 min to a maximum of 60 min (Table 1, entries 3, 8 and 9). Longer

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Table 1 Optimization of the reaction: ionic liquid and base

Entry	Ionic Liquid	Base (2 eq.)	Time/min	Yield[a] (%)
1	BMIM-BF_4	Cs_2CO_3	60	82
2	BMIM-NTf	Cs_2CO_3	60	84
3	BMIM-PF_6	Cs_2CO_3	60	90
4	BMIM-PF_6	Cs_2CO_3	60	Traces[b]
5	BMIM-PF_6	KOH	60	88
6	BMIM-PF_6	K_2CO_3	60	72
7	BMIM-PF_6	Na_2CO_3	60	73
8	BMIM-PF_6	Cs_2CO_3	40	76
9	BMIM-PF_6	Cs_2CO_3	30	60
10	BMIM-PF_6	none	60	—
11	BMIM-PF_6	Cs_2CO_3	240	90
12	BMIM-PF_6	Cs_2CO_3	240	30[c]

[a] Yields determined by GC. [b] Reaction performed at room temperature. [c] Reaction performed without CuO nanopowder.

reaction times did not have an influence on the product yield (Table 1, entry 11).

Finally, to further optimize the protocol, it was necessary to examine the effect of the amount of catalyst in promoting the reaction efficiency. Without catalyst, the reaction worked very slowly and the product was obtained in low yield (Table 1, entry 12). We found that varying the amount of CuO nanopowder had an effective influence on the reaction course. When the amount of CuO nanopowder was increased from 1.0 to 2.0 mol%, the yield of compound **2e** was significantly modified from 48% to 82%. By using 5.0 mol% of CuO nanopowder, the yield was further improved to 90%. Nonetheless, raising the amount of CuO nanopowder up to 10 mol% did not change the yield of the desired product, affording the same level of 90%, as shown Fig. 1.

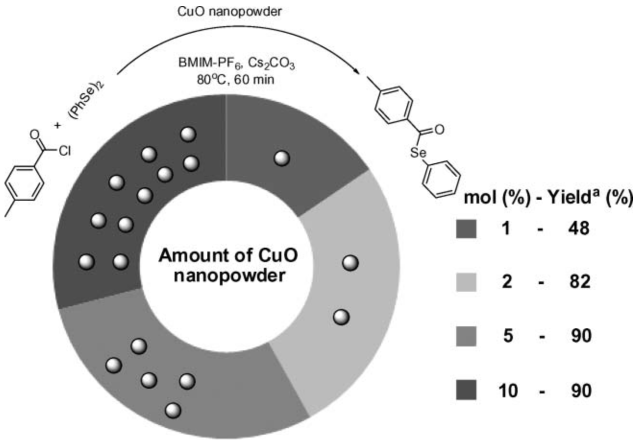
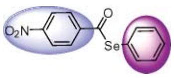
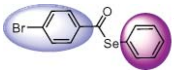
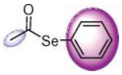
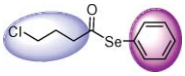
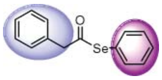
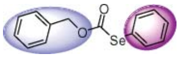
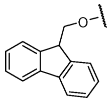
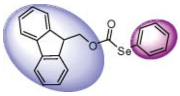


Fig. 1 Optimization of CuO nanopowder. [a]Yields determined by GC.

After the optimizations, under standard conditions we performed a series of reactions using different kinds of acyl chlorides with diaryl diselenides to synthesize the selenoesters **2a–l**. All reactions were clean and efficient and the respective compounds were obtained in good to excellent yields, as depicted in Table 2.[22] In terms of electronic effects, it was possible to verify that the reaction is more sensitive to the acid chloride than the diselenide moiety. For instance, a strong electron withdrawing group, such as the nitro attached to acyl chloride (Table 2, entry 3) affords a moderate yield of 57% of the desired selenolester **2c**. By using **1a** (neutral) and **1e** (electron donating group), the reaction proceeds efficiently and the selenoesters are obtained in excellent yields (Table 2, entries 1 and 5). Aliphatic acyl chlorides were used to afford alkanoate selenoesters. As expected, the corresponding compounds were obtained in good yields (Table 2, entries 6, 7, and 8). In terms of diselenide, this outcome is less effective, but still it was possible to observe that electron withdrawing groups afforded slightly lower yields than the other groups (Table 2, entries 9 and 10). This can be rationalized in terms of the lower nucleophilicity of these selenolate species. As a further extension, we attempted to synthesize a

Table 2 Synthesis of several selenoesters

Entry	*R*	Product		Yield (%)[a,b]
1	Ph, **1a**		**2a**	91
2	*o*-ClPh, **1b**		**2b**	83
3	*p*-NO_2Ph, **1c**		**2c**	57
4	*p*-BrPh, **1d**		**2d**	84
5	*p*-MePh, **1e**		**2e**	90
6	Me, **1f**		**2f**	69
7	ClC_3H_6, **1g**		**2g**	61
8	CH_2Ph, **1h**		**2h**	72
9	Ph, **1a**		**2i**	80
10	Ph, **1a**		**2j**	86
11	$PhCH_2O$, **1i**		**2k**	79
12	 **1j**		**2l**	90

[a] Yields determined by GC. [b] All compounds are reported in our previous work, ref. 12.

Table 3 Synthesis of selenoesters catalyzed by CuO nanopowder

Runs	Catalyst recoverability(%)	Product Yield[a] (%)
1	96	89
2	92	84
3	85	82
4	80	74

[a] Yields determined by GC.

selenocarbonate bearing interesting functionalities and obtained encouraging results. When we used benzyl chloroformate (**1i**) and 9-fluorenylmethyl chloroformate (**1j**), the corresponding selenocarbonates **2k** and **2l** were obtained in yields of 79% and 90%, respectively (Table 2, entries 11 and 12).

In addition, to obtain non-residual version of the protocol, the recyclability of the catalyst and ionic liquid was studied. The CuO nanopowder was recovered from the reaction mixture. It was reused for three further runs and no loss of activity was observed, providing the product in very good yields (Table 3, entries 1–4).

In Fig. 2, the TEM analysis of the CuO nanopowder was performed before and after four reaction runs. The samples showed identical powder morphology and size after reuse of the catalyst in this transformation and, as previously reported,[23] these experimental results suggest that the reaction involves a heterogeneous process *via* surface CuO nanopowder catalysis.

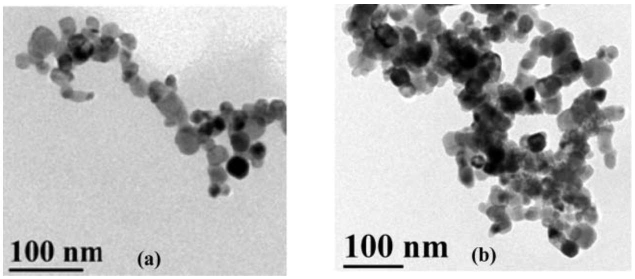


Fig. 2 TEM images of CuO nanopowder. (a) Fresh CuO nanopowder, (b) CuO nanopowder after four reaction runs. CuO nanopowder was purchased from Sigma Aldrich (mean particle size, 33 nm, surface area, 29 m^2 g^{-1} and purity, 99.99%).

Considering the ionic liquid, after the work-up, BMIM-PF$_6$ was separated by filtration and the recovered ionic liquid was used again for the next reactions.[24] This operation was repeated another three times without significant loss of efficiency, as shown in Fig. 3.

A possible mechanism for the CuO nano particle catalyzed C–Se cross-coupling of acyl chlorides and diphenyl diselenide is illustrated in Scheme 2.

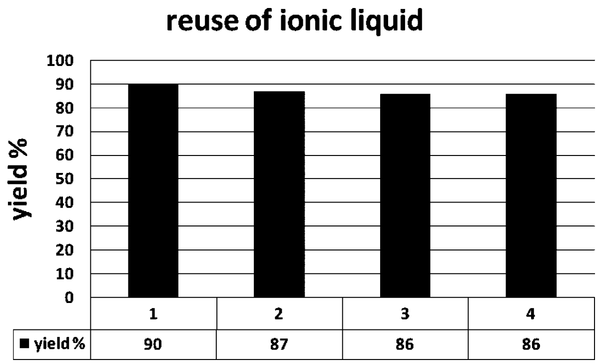
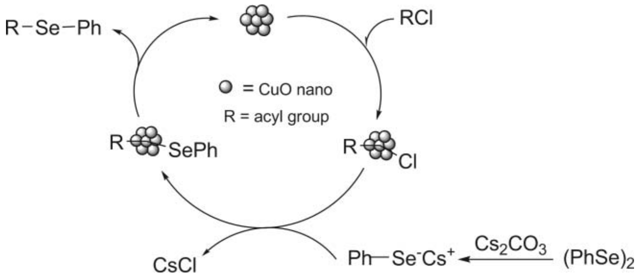


Fig. 3 Recyclability of BMIM-PF$_6$.



Scheme 2 Plausible reaction pathway.

In conclusion, we have developed a nanocrystalline CuO catalyzed coupling of acyl chlorides with diphenyl diselenide to form selenoesters in excellent yields. This new coupling reaction underlines the potential of using nanocrystalline CuO as a very user friendly, inexpensive, and efficient catalyst for this coupling reaction. The catalyst and solvent (BMIM-PF$_6$) can be easily recovered and reused. We are in the process of expanding the substrate scope of the reaction. The important features of this protocol are: (1) recyclable CuO nanopowder; (2) recyclable solvent; (3) mild reaction conditions.

Acknowledgements

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22 General procedure to the synthesis of selenoesters **2a–k**: In a Schlenk tube under nitrogen atmosphere, 4-methylbenzoylchloride **1e** (1.0 mmol) and CuO nanopowders (0.06 mmol, 5.0 mol%) followed by diphenyl diselenide (0.5 mmol) and Cs_2CO_3 (1.0 mmol, 2.0 equiv.) (1.0 mmol) in BMIM-PF_6 (1.0 mL) were stirred at 80 °C for 60 min. The progress of the reaction was monitored by TLC. When, the reaction was complete, the product was extracted by successive washing with n-butanol (5 × 5 mL) and drying over $MgSO_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.

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24 Recyclability experiments: The CuO nanopowders and solvent BMIM-PF_6 can be recycled without loss of activity (Table 3 and Fig. 2). After completion of the reaction workup, the reaction mixture was treated with ethanol, and filtered through a Teflon membrane. The CuO nanopowder was recovered from the membrane by washing with water and collected by further centrifugation and drying under vacuum. It was reused for the reactions in the next three runs, and no loss of activity was observed, providing the product in high yields. The ionic liquid was recovered from the ethanol (10 ml) after filtration, evaporation of the solvent and drying the BMIM-PF_6 (1 ml) under vacuum for reuse in subsequent reactions.