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Metal and base-free synthesis of arylselanyl anilines using glycerol as a solvent†

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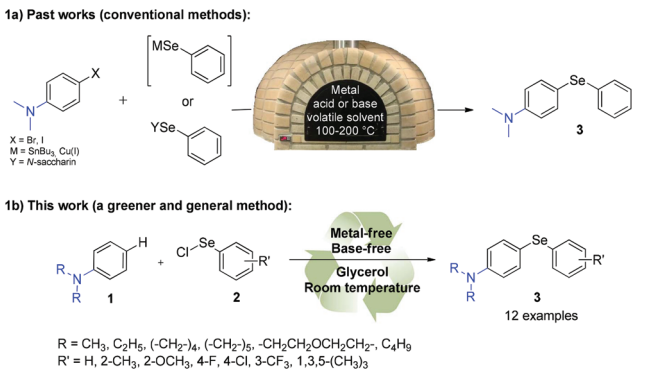
We describe here a metal and base-free straightforward method to access arylselanyl anilines using glycerol as a solvent. Starting from *N*,*N*-disubstituted anilines and arylselanyl chloride, the protocol is general and was successfully applied to a sort of anilines with different substitution patterns in both the aromatic ring and the nitrogen atom. As desirable for a green synthetic procedure, the non-toxic, low volatile, renewable glycerol was used as a solvent at room temperature.

Introduction

The synthetic versatility of organochalcogen compounds is confirmed by the great amount of papers,[1] books[2] and reviews.[3] Among them, organoselenium compounds are an attractive group in organic chemistry and have been receiving attention due to their biological and pharmacological activities (*e.g.* antidepressant, antinociceptive and antioxidant),[4] use in selective reactions,[5] as catalysts,[6] as ionic liquids[7] and synthetic intermediates in total synthesis.[2,3,8] Diaryl selenides are an important class of molecules in organoselenium chemistry, having a fundamental role in organic chemistry[1–3] and pharmacological studies on GPx-like activities.[9] As a consequence, the number of methods for the selective formation of C–Se bonds has been increased throughout the years.[10] In the meantime, the use of electrophilic selenium species to prepare diaryl selenides remains underexplored, although it could be a good strategy to access these compounds.[11] The use of a transition-metal, in the presence of bases such as KOH,[10a,e,g] Cs_2CO_3,[10c] K_2CO_3,[10b] bipyridyl[10f] and organic solvents such as DMSO,[10a,b,e,g] MeCN,[10c] DMF[10f] and high temperature, among the impossibility of recovering the solvent, or reusing the catalyst system are the drawbacks which may increase the cost and limit the scope of the currently described methods. The use of alternative, greener solvents such as ionic liquids[10i,j] and glycerol[10k] has partially circumvented some of these problems.

On the other hand, *N*-substituted aryl compounds and their derivatives are a significant class of compounds, which are widely used in the dyes and paints industry, polymers and applied as intermediates for agrochemicals and pharmaceuticals.[12] Their interesting biological activities include antimicrobial,[13a] antituberculosis,[13a] antioxidant,[13a] antitumor[13b] and antibacterial activities.[13c] *N*,*N*-Dimethylaniline and its analogues are used as photoinitiators in photopolymerization reactions in polymer manufacturing,[14] as a substrate for selective halogenation reactions,[15] oxidation reactions,[16] demethylation[17] and cross-coupling reactions.[18]

Despite the high versatility and the large number of biological activities of organoselenium compounds and *N*,*N*-disubstituted anilines, there are only a few papers describing the synthesis of *N*,*N*-disubstituted anilines functionalized with organochalcogen groups and they are limited to a few, specific examples.[19–22] As a consequence, virtually nothing is known about their chemical and biological properties. The methods to access selenium-containing *N*,*N*-disubstituted anilines involve the use of transition metal-catalysts, specific ligands and volatile solvents. Besides having a low *E* factor,[23] these are not so green protocols, once high temperature, non-reusable catalytic systems and harmful aryl halides are used in the



Scheme 1 General reaction summary of literature precedent (**1a**) and current work (**1b**).

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reaction (Scheme 1a).[19–22] To the best of our knowledge, there is no general method to prepare selectively 4-arylselanyl anilines starting directly from *N*,*N*-disubstituted anilines.

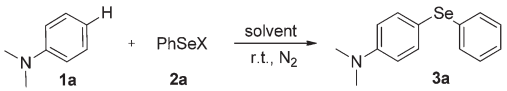
Due to our interest in the synthesis and the biochemistry of organochalcogen compounds exploring green methodologies,[10i,k,24] we describe herein our results on the first direct and regioselective synthesis of *N*,*N*-diorganyl-4-(arylselanyl)-anilines **3**, using glycerol as a green solvent,[25] in reactions at room temperature and without any additives or catalysts (Scheme 1b).

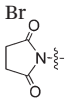
Results and discussion

At first, we chose *N*,*N*-dimethylaniline (**1a**, R = CH_3) and phenylselanyl chloride (**2a**, R′ = H) to determine the best conditions for the reaction. Our initial efforts were addressed to verify whether low volatile, recyclable, green solvents could be used in this reaction. Thus, when **1a** (0.3 mmol) reacted with **2a** (0.5 mmol) at room temperature in the presence of 0.5 mL of [bmim][BF_4], glycerol or PEG-400, the desired 4-(phenylselanyl)aniline **3a** was obtained in almost quantitative yields after 1 h of reaction (Table 1, entries 1–3). Though these three solvents are considered environmentally friendly,[26] the synthesis tree of [bmim][BF_4] has more than 30 steps[27] and PEG-400 is prepared from non-renewable feedstock,[28] placing them in a position not so green if we consider the sustainability in their manufacturing process. Taking these aspects into consideration, glycerol was chosen for further studies on optimizing the reaction conditions since, in addition to being inexpensive and biodegradable, obtaining it from biomass involves very little handling and low consumption of materials and energy.[29]

Subsequently, we examined the effect of the electrophilic selenium species in the reaction and observed that PhSeBr afforded product **3a** in a similar yield compared to PhSeCl, but more time was needed when using PhSeBr (Table 1, entries 2 and 4). We observed that *N*-(phenylselanyl)succinimide was less reactive under the conditions tested (Table 1, entry 5). Aiming to reduce the reaction time, the reaction was carried out at 60 °C. However, the yield decreased to 75% after 1.5 h, with the formation of diphenyl diselenide due the decomposition of phenylselanyl chloride (Table 1, entry 6). This is an interesting finding, once reactions using glycerol as a solvent are almost exclusively carried out at temperatures equal to or above 60 °C.[24a,25] The need to use an excess of PhSeCl **2a** to achieve **3a** in satisfactory yield was observed; when equimolar amounts of **1a** and **2a** were used, **3a** was obtained only in 65% yield (Table 1, entry 7). The excess of PhSeCl is converted *in situ* to diphenyl diselenide, which is easily recovered by filtration over silica gel and reused to make more **2a**.[30] We also found that **3a** was obtained only in 77% yield in open atmosphere, showing that the use of nitrogen atmosphere is essential for the total conversion of aniline **1a** (Table 1, entry 8).

Table 1 Optimization of reaction conditions[a]



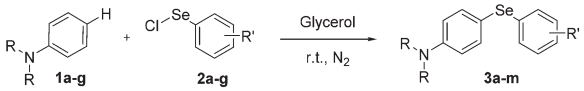
Entry	X	Solvent	Time (h)	Yield[b] (%)
1	Cl	[bmim][BF_4]	1	98
2	Cl	Glycerol	1	99
3	Cl	PEG-400	1	98
4	Br	Glycerol	2	95
5		Glycerol	1	80
6	Cl	Glycerol	1.5	75[c]
7	Cl	Glycerol	2	65[d]
8	Cl	Glycerol	1	77[e]

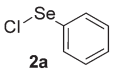
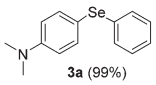
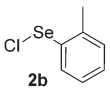
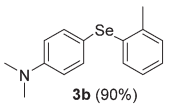
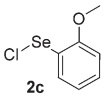
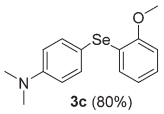
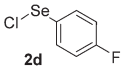
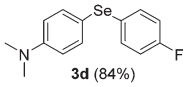
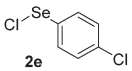
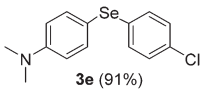
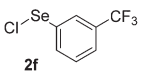
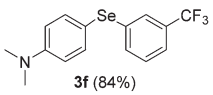
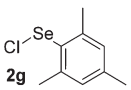
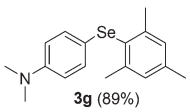
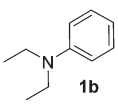
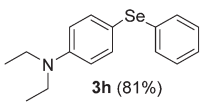
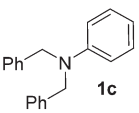
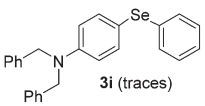
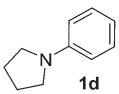
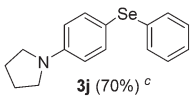
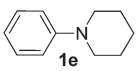
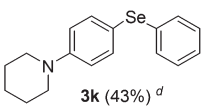
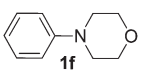
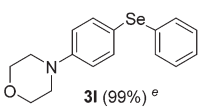
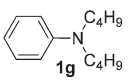
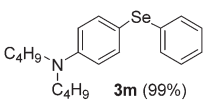
[a] Reaction conditions: a mixture of **1a** (0.3 mmol) and **2a** (0.5 mmol) in 0.5 mL of solvent was stirred at r.t. [b] Isolated yields. [c] Reaction performed at 60 °C. [d] Equivalent amounts of **1a** and **2a** were used. [e] Reaction performed in open atmosphere.

With the best reaction conditions established, we explored the efficiency and generality of our methodology to other substituted arylselanyl chlorides (Table 2, entries 1–7). The reaction works well with a range of arylselanyl chlorides containing both electron-donating (–CH_3 and –OCH_3) and electron-withdrawing groups (CF_3, F and Cl), showing up the sensitivity to electronic effects. It was observed that the reaction is faster when electron-withdrawing groups are present in the aromatic ring of the arylselanyl chloride. Thus, for example, good yields were obtained with **2d** (R′ = 4-F), **2e** (R′ = 4-Cl) and **2f** (R′ = 3-CF_3) after 1–1.5 h, with the respective selanylanilines **3d–f** being obtained in 84, 91 and 84% yield respectively (Table 2, entries 4–6). Conversely, 4 h was necessary to convert **2c** (R′ = 2-OCH_3) to **3c**, indicating the adverse effect of the electron-donating methoxyl group. Satisfactorily, good yield was obtained even for the sterically hindered mesitylselanyl chloride **2g**, which afforded **3g** in 89% yield after 3 h (Table 2, entry 7). We also extend our approach to other *N*,*N*-disubstituted anilines and to our gratification, good results were obtained for a variety of anilines used, including alicyclic ones (Table 2, entries 8–13). As can be seen in Table 2, good yields were obtained when **1b** (R = C_2H_5) and **1g** (R = C_4H_9) were used, affording **3h** and **3m** in 81 and 99% yield after 2 h and 1.5 h respectively (Table 2, entries 8 and 13).

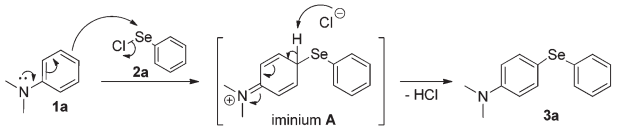
The alicyclic arylamines such as 1-phenylpyrrolidine (**1d**), 1-phenylpiperidine (**1e**) and 4-phenylmorpholine (**1f**) were also successfully reacted with PhSeCl **2a**, with the respective selanylanilines **3j**, **3k** and **3l** being isolated in 70, 43 and 99% yields after 2.5, 3 and 4 h of reaction respectively (Table 2, entries 10–12). In these cases, the respective *ortho*-selanylanilines were also formed and although the mixture could not be separated by column chromatography, the two isomers were observed in the ^{1}H NMR spectra and the *para* : *ortho* ratio was easily determined from them (see Table 2, footnote). The formation of *ortho* and *para* isomers is probable due the activation of the benzene ring by the nitrogen unshared electron-pair. The lower steric hindrance in **1d–f** compared to acyclic

Table 2 Generality of the reaction[a]

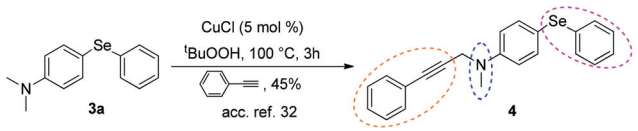


Entry	Aniline	ArSeCl	Time (h)	Product[b] (Yield)
1	 **1a**	 **2a**	1	 **3a** (99%)
2	**1a**	 **2b**	1.5	 **3b** (90%)
3	**1a**	 **2c**	4	 **3c** (80%)
4	**1a**	 **2d**	1.5	 **3d** (84%)
5	**1a**	 **2e**	1	 **3e** (91%)
6	**1a**	 **2f**	1	 **3f** (84%)
7	**1a**	 **2g**	2	 **3g** (89%)
8	 **1b**	**2a**	2	 **3h** (81%)
9	 **1c**	**2a**	24	 **3i** (traces)
10	 **1d**	**2a**	2.5	 **3j** (70%) [c]
11	 **1e**	**2a**	3	 **3k** (43%) [d]
12	 **1f**	**2a**	4.5	 **3l** (99%) [e]
13	 **1g**	**2a**	1.5	 **3m** (99%)

[a] Reaction conditions: a mixture of aniline **1** (0.3 mmol) and arylselanyl chloride **2** (0.5 mmol) in 0.5 mL of glycerol was stirred at r.t. under a nitrogen atmosphere. [b] Isolated yields. [c] Obtained as a mixture of *para* and *ortho* isomers in a *para* : *ortho* ratio = 89 : 11. [d] *para* : *ortho* ratio = 78 : 22. [e] *para* : *ortho* ratio = 81 : 19.



Scheme 2 A plausible mechanism of the reaction.



Scheme 3 Alkynylation of 4-(phenylselanyl)aniline **3a**: preparation of the densely functionalized propargyl amine **4**.

arylamines allows the formation of *ortho* isomers in measurable amounts. Only traces of the product **3i** were observed starting from *N*,*N*-dibenzylaniline **1c**, even after 24 h of stirring at r.t. (Table 2, entry 9).

On the basis of recent publications on Mannich-type reactions involving aniline as a nucleophile,[31] a plausible mechanism to the formation of 4-(phenylselanyl)aniline **3a** from *N*,*N*-dimethylaniline **1a** is depicted in Scheme 2. We believe that, at first, *N*,*N*-dimethylaniline **1a** would attack the phenylselanyl chloride **2a** by the *para*-position, to form the intermediary iminium **A**, which suffers a proton elimination giving the expected product **3a**. We believe that the formation of intermolecular H-bonds between glycerol and the iminium intermediate **A** could favor its stabilization. A similar feature was observed in other reactions performed in the presence of glycerol.[25d–f]

In order to evaluate the synthetic applicability of *N*,*N*-dimethyl-4-(phenylselanyl)anilines **3**, we decided to explore the alkynylation of the sp^3–C–H bond adjacent to the nitrogen atom, firstly described by Li and Li[32] to afford propargyl amines (Scheme 3). Propargyl amines have a great pharmaceutical interest[33] besides being useful intermediates in organic synthesis.[34] By using the Li's conditions, the highly functionalized *N*-methyl-*N*-(3-phenylprop-2-yn-1-yl)-4-(phenylselanyl)aniline **4** could be prepared in 45% yield after 3 h. New studies are necessary to optimize this reaction; however, we envisioned **4** as a promising building block for the synthesis of new drug candidates or more complex nitrogen and selenium-containing molecules.

Conclusions

In conclusion, we have developed a green, additive free methodology to synthesize 4-(arylselanyl)anilines using glycerol as an environmentally friendly solvent. The reaction occurs at room temperature and is suitable for a range of *N*,*N*-disubstituted anilines and arylselanyl chlorides. The products were obtained in good to excellent yields, with alicyclic anilines also affording a small amount of the *ortho* isomer. The 4-(arylselanyl)anilines obtained using this protocol appear highly promising as intermediates for the preparation of more complex molecules, such as *N*-propargyl amines containing arylselanyl moieties. This new protocol to prepare arylselanyl anilines comprises several principles of green chemistry, once the renewable solvent glycerol successfully promotes the reaction at room temperature and in the complete absence of a metal or a base.

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Notes and references

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