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KF/Al_2O_3 and PEG-400 as a recyclable medium for the selective α-selenation of aldehydes and ketones. Preparation of potential antimicrobial agents

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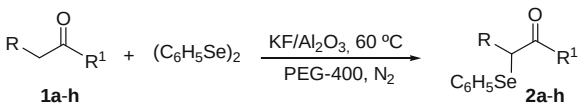
ABSTRACT

2-Phenylseleno aldehydes and ketones were selectively obtained using solid-supported catalyst (KF/Al_2O_3) and PEG-400 as clean, recyclable medium in good to excellent yields. The method was applied in the preparation of highly functionalized 2-phenylseleno citronellal and citronellol, potential bactericide agents. The catalytic system KF/Al_2O_3 and PEG-400 can be re-used for four times without previous treatment.

The synthesis of α-phenylseleno aldehydes and ketones has attracted the attention of synthetic organic chemists because they can be converted to very useful compounds, such as α,β-unsaturated carbonyl,[1] α-amino acids,[2] α-hydroxy esters[3] and allylic amines,[4] aziridines,[5] and alcohols.[6] In a general way, the methods to access α-phenylseleno carbonyl compounds consist in the reaction of an enolate with an electrophilic organoselenium species or by substitution reactions involving nucleophilic organoselenium.[1] Most of the employed methods use strong bases, such as LDA at 78 °C,[1a,b] moisture-sensitive zirconium, aluminum,[7] and selenium-containing tributylstannyl reagents.[8] More recently, the use of secondary amines as organocatalysts for the α-selenylation was described.[9] In recent years, the use of green recyclable systems in organic syntheses, such as solid-supported catalysts and non-volatile solvents, has been growing.[10] In this line, the use of potassium fluoride supported on alumina (KF/Al_2O_3) as a green catalytic system for a number of transformations has been increased.[11] By using KF/Al_2O_3, the products can be easily isolated by filtration and the generation of large amounts of salts at the end of the synthesis, as well as the use of stoichiometric strong bases, can be avoided. On the other hand, polyethylene glycol (PEG-400) is a non-toxic, non-volatile, and recyclable solvent whose use in organic synthesis has been raised in recent years.[10b] Our major research goal is the development of new and cleaner protocols for the preparation and synthetic applications of organochalcogenium compounds.[12,13] More recently, we have described several efficient approaches using KF/Al_2O_3 and recyclable solvents.[13]

In continuation to these studies, here we describe the results on the synthesis of 2-phenylseleno aldehydes and ketones, using KF/Al_2O_3 and PEG-400 (Scheme 1, Table 1).[14,15]

Initially, we chose pentanal (**1a**) and diphenyl diselenide as standard starting materials to perform the optimization studies (Table 1). We examined the temperature, amounts of KF/Al_2O_3 (40%) and solvent, and the use of N_2 atmosphere. When a mixture of **1a** (1.0 mmol) and $(C_6H_5Se)_2$ (1.0 mmol) was stirred in the presence of 0.32 g of KF/Al_2O_3 (40%) and PEG-400 (1.0 g) at room temperature under N_2 atmosphere, no product of α-selenylation was observed after 24 h (Table 1, entry 1). However, when the same mixture was heated at 60 °C, 2-phenylseleno pentanal **2a** was obtained in 97% yield after stirring for 3 h (Table 1, entry 2). The atomic efficiency of the reaction was improved using 0.5 mmol of $(C_6H_5Se)_2$, giving similar yield of **2a** (Table 1, entry 3). Smaller amounts of the solid-supported catalyst give poor yields of **2a** even after longer reaction times (Table 1, entry 4).



1a-h **2a-h**

Scheme 1.

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Table 1
Optimization of the synthesis of 2-phenylseleno pentanal **2a** according to Scheme 1[a]

Entry	$(C_6H_5Se)_2$ (equiv)	KF/Al_2O_3 40% (g)	Temp. (°C)	Time (h)	Yield[b] (%)
1	1.0	0.32	rt	24	NR[c]
2	1.0	0.32	60	3	97
3	0.5	0.32	60	3	95
4	0.5	0.10	60	3	60
5	0.5	0.32	rt	24	NR[c,d]
6	0.5	0.32	60	48	10[d]

[a] Reaction conditions: pentanal (**1a**, 1.0 mmol); PEG-400 (1.0 g); N_2 atmosphere.
[b] The reaction was followed by TLC and GC until complete consumption of **1a**.
[c] No product was detected by GC.
[d] Glycerin (1.0 mL) was used as solvent instead of PEG-400.

Recently, we described the use of glycerin as an efficient recyclable solvent in KF/Al_2O_3-promoted reactions.[12b] Thus, we decide to evaluate this renewable feed-stock as a possible solvent in the α-selenylation of pentanal. Unfortunately, no reaction took place at room temperature and low yield of **2a** was obtained after long reaction time at 60 °C (Table 1, entries 5 and 6).

It was also observed that the catalytic system can be re-used for additional four cycles, just by washing it with hexanes and drying under vacuum. The product **2a** was obtained in 95, 86, 66, 62, and 59% yields after successive cycles.

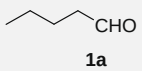
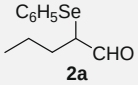
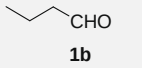
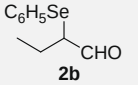
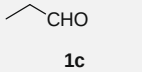
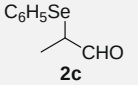
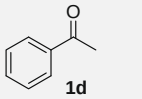
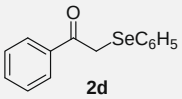
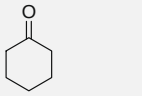
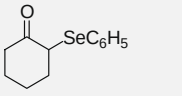
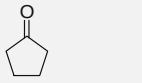
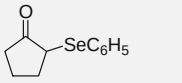
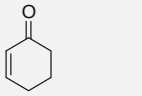
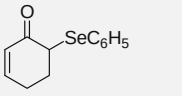
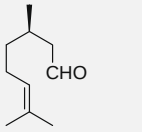
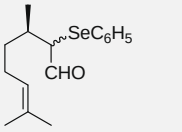
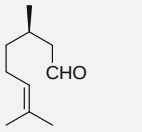
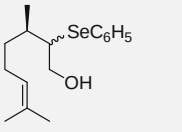
Using the optimized conditions, the protocol was extended with good results to other aldehydes and ketones (Table 2, entries 2–8). It was observed that the reaction yields were slightly lower when aliphatic butanal **1b** and propanal **1c** were used as aldehydes, probably due to their fast auto-condensation under the reaction conditions (Table 2, entries 2 and 3). We also noted that ketones **1d–g** require a longer reaction time to afford the respective 2-phenylseleno derivatives **2d–g** (Table 2, entries 4–7). Because of our interest in the development of new, cleaner synthetic methods using renewable, easily available polyfunctionalized starting materials, we use this new protocol in the α-selenylation of (*R*)-citronellal **1h**, a chiral natural terpene isolated from citronella oil.[16] In this case, a 1:1 mixture of *syn* and *anti* 2-phenylseleno citronellal **2h** was obtained in 80% yield (Table 2, entry 8).

The method described in Scheme 1 was successfully used in the direct preparation of **2h** starting from the essential oil of citronella (*Cymbopogon nardus* (L) Rendle). The major component of the essential oil of citronella, extracted from the plant grown in southern Brazil (Três Passos-RS), was found to be (+)-*R*-citronellal **1h** (40–51%).[17] 2-Phenylseleno citronellal **2h** was obtained in 71% yield and unreacted geraniol, citronellol, geranyl acetate, and other minor constituents of the starting oil were recovered. The protocol was applied in the one-pot preparation of 2-phenylseleno citronellol **3** (Scheme 2). Thus, after the formation of **2h** was added 2 equiv of $NaBH_4$ and the mixture was stirred at room temperature for additional 2.5 h affording the alcohol **3** in 73% overall yield (Table 2, entry 9).

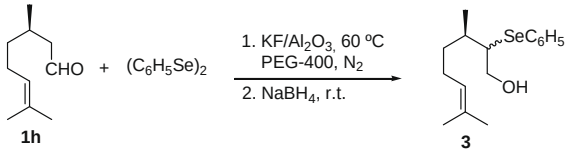
2-Phenylseleno citronellal **2h** and 2-phenylseleno citronellol **3** were screened for their antibacterial activity and preliminary studies showed activity against *Listeria monocytogenes*, *Staphylococcus aureus,* and *Salmonella enteridis*. 2-Phenylseleno citronellal **2h** was the more active against the three tested microorganisms, even compared with the parent citronellal **1h**. The antimicrobial activity presented by **2h** was *L. monocytogenes* > *S. enteridis* > *S. aureus* and for **3** it was *S. aureus* > *S. enteridis* > *L. monocytogenes*.

In conclusion, several 2-phenylseleno aldehydes and ketones could be prepared using the reusable catalytic system KF/Al_2O_3 and PEG-400. This eco-friendly protocol can be successfully applied to the direct synthesis of bactericide agent 2-phenylseleno citronellal **2h** from crude citronella oil.

Table 2
Synthesis of 2-phenylseleno aldehydes and ketones **2a–h**

Entry	Aldehydes or ketones **1**	Product **2**	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	3	95
2	 **1b**	 **2b**	3	67
3	 **1c**	 **2c**	3	70
4	 **1d**	 **2d**	21	96
5	 **1e**	 **2e**	21	70
6	 **1f**	 **2f**	6	69
7	 **1g**	 **2g**	14.5	81
8	 **1h**	 **2h**	3	80
9	 **1h**	 **3**	5.5	73

[a] Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by mass spectrometry, ^1H, and ^{13}C NMR.[1,8,9,11b]



Scheme 2.

Acknowledgments

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14. *Preparation of alumina-supported potassium fluoride*:[18] Alumina (6.0 g of Al_2O_3 90, 0.063–0.200 mm, Merck), $KF{\cdot}2H_2O$ (5.2 g), and water (10 mL) were mixed in a 50 mL beaker and the suspension was stirred at 65 °C for 1 h. The resulting solid was dried at 80 °C for 1 h and subsequently 4 h at 300 °C in an oven and finally cooled to room temperature in a desiccator. The content of KF is about 40% (m/m).
15. *General procedure for the synthesis of 2-phenyseleno aldehydes and ketones*: To a mixture of (*R*)-citronellal (**1h**; 0.154 g; 1.0 mmol), diphenyl diselenide (0.156 g; 0.5 mmol) and PEG-400 (1.0 g) under N_2 atmosphere, Al_2O_3/KF (0.32 g, obtained as described above) was added at room temperature. Then, the temperature was slowly raised to 60 °C. The reaction progress was followed by TLC, and after 3 h (see Table 2) the product was extracted with hexanes (3 × 5 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel eluting with hexanes yielding a 1:1 mixture of *syn* and *anti* 2-phenylseleno citronellal **2h** (0.248 g, 80%) as a light yellow oil. MS *m*/*z* (rel. int.) 310 (M^+), 156, 135, 83, 69. IR (KBr) ν(C=O) 1708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 9.38 and 9.36 (d, J = 2.4 Hz, 1H); 7.48–7.55 (m, 2H); 7.20–7.32 (m, 3H); 5.00–5.15 (m, 1H); 3.43–3.53 (m, 1H); 1.23–2.47 (m, 5H); 1.70, 1.67, 1.62 and 1.58 (4s, 6H); 1.17 and, 1.07 (2d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.8, 192.5, 135.3, 135.2, 132.1, 132.0, 129.3, 129.2, 128.6, 128.5, 127.1, 126.8, 123.7, 123.6, 61.3, 60.5, 35.4, 34.7, 31.6, 31.5, 25.7, 25.6, 25.3, 24.9, 17.9, 17.8, 17.7, 17.6.
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