

Solvent-free conjugated addition of thiols to citral using KF/alumina: preparation of 3-thioorganylcitronellals, potential antimicrobial agents

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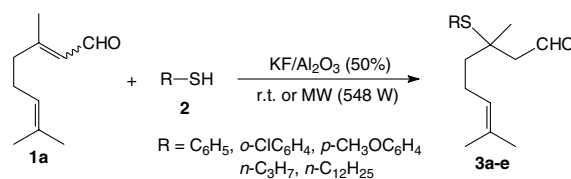
Abstract—A general, clean and easy method for the conjugated addition of thiols to citral promoted by KF/Al₂O₃ under solvent-free conditions at room temperature or under MW irradiation is described. It was found that the same protocol is applicable to the direct reaction of thiophenol with essential oil of lemon grass (*Cymbopogon citratus*) to afford directly 3-thiophenylcitronellal, a potential bactericide agent. The method was extended to others electron-poor alkenes with excellent results. The catalytic system can be reused up to three times without previous treatment with comparable activity.
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Besides important commodities in the flavor and fragrance industry, the natural occurring α,β -unsaturated aldehyde citral, together with its analog citronellal, are key compounds in organic synthesis.¹ The conjugated addition (Michael addition) of thiols to α,β -unsaturated compounds (electron-poor alkenes) is a very useful method for new carbon–sulfur bond-forming in organic synthesis.² This reaction also plays critical roles in the biosynthesis and synthesis of bioactive compounds.³ Besides, the 1,4-addition is a highly atom-efficient, green reaction, in agreement with the principle #2 of the green chemistry.⁴ In view of these aspects, there is a large number of reported methods for both basic and acidic promoted selective 1,4-additions, including heterogeneous⁵ and homogeneous catalyses⁶ and asymmetric versions.⁷ Thus, solid catalysts, such as basic anion-exchange resins,^{5a} natural^{5b} and synthetic phosphates,^{5c} montmorillonite clays,^{5d} solid potassium carbonate,^{5e} base^{5f} and acid supported in alumina^{5g} have been used to perform the 1,4-addition of thiols to a series of electron-poor alkenes. However, the use of solid-supported

catalysts in Michael addition to α,β -unsaturated aldehydes was not explored.⁵

In the last years, our group has studied the use of renewable feed stocks in organic synthesis, following the green and sustainable chemistry principles.^{1,8} As a continuation of our studies, we describe here the solvent-free synthesis of new 3-thioorganylcitronellal derivatives (**3a–e**), starting from citral (**1a**) and thiols (**2a–e**) using KF/Al₂O₃ as catalyst (Scheme 1, Table 1).^{9,10}

Our initial efforts were made towards the determination of the optimum conditions to perform the protocol. Thus, we choose citral (**1a**), easily available from the essential oil of lemon grass (*Cymbopogon citratus*) and thiophenol (**2a**) to establish the best conditions for the Michael addition.

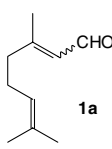
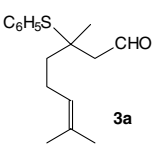
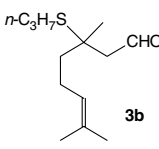
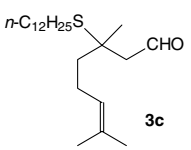
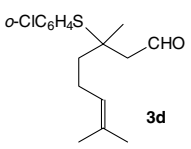
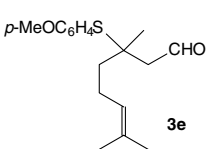
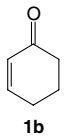
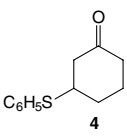
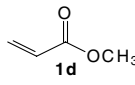
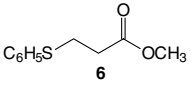
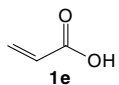
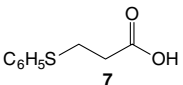


Scheme 1.

Keywords: Solvent-free; 1,4-Addition of thiols; Microwave irradiation; Citronellal; Citral.

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Table 1. Conjugated addition of thiols to citral and electron-poor alkenes under solvent-free conditions

Entry	Alkene 1	Thiol 2	Product	Method ^a	Time	Yield ^b (%)
1		C_6H_5SH 2a		A	4 h	70
2	1a	2a	3a	B	6 min	65
3	1a	$n-C_3H_7SH$ 2b		A	7.5 h	50
4	1a	2b	3b	B	1 min	67
5	1a	$C_{12}H_{25}SH$ 2c		A	7.5 h	60
6	1a	2c	3c	B	2 min	35
7	1a	$o-C_6H_4SH$ 2d		A	9 h	70
8	1a	2d	3d	B	0.5 min	38
9	1a	$p-MeOC_6H_4SH$ 2e		A	8 h	81
10	1a	2e	3e	B	1 min	90
11		C_6H_5SH 2a		A	2 h	95
12	1c	2a	5	A	1 h	96
13		2a		A	0.5 h	94
14		2a		A	3 h	80

^a Method A: The experiments were performed at room temperature. Method B: The experiments were performed under MW at 548 W.

^b Yields in pure products isolated by chromatography (AcOEt/hexanes) and identified by mass spectra, ¹H and ¹³C NMR.

With the aim to promote the selective 1,4-nucleophilic addition, several reaction conditions were tested, and the best results were obtained when KF/Al₂O₃ (50%, 0.07 g) was added to a mixture of citral (**1a**, 1 mmol) and thiophenol (**2a**, 1.2 mmol) at room temperature and stirred for 4 h (Table 1, entry 1).¹⁰

The use of a larger amount of KF/Al₂O₃ (50%), or of a larger concentration of KF (60% m/m) did not increase the yield of **3a**. On the other hand, using 0.050 g of KF/Al₂O₃ (50%) at room temperature makes the reaction proceed slowly, in 40% yield after 12 h. Aiming to reduce the reaction time, the mixture was irradiated with microwaves. The product **3a** was obtained in good yield after 6 min of irradiation at 548 W (Table 1, entry 2). It was observed that the protocol works with aromatic and aliphatic thiols, and it can be extended to a variety of electron-poor alkenes (ester, acid, nitrile and ketone). The experimental procedure is very easy, and the products were obtained after stirring a few hours at room temperature or irradiated for few minutes with microwaves (Table 1). The best conditions were extended to others thiols **2** and a series of 3-thioorganylcitronellals were obtained in moderate to good yields (Table 1, entries 3–10). It was observed that the catalytic system can be re-used for three cycles, just by washing it with ethyl acetate and drying under vacuum. The recycled catalytic system was successfully employed to both the methods, at room temperature and under microwave irradiation.

Due to our interest in the synthetic use of the essential oils of plants cultivated in southern Brazil and their constituents as raw material of renewable source for use in organic synthesis,^{1,8} we tried to use one of our reaction conditions (KF/Al₂O₃ (50%) under MW) in the direct 1,4-addition of thiophenol to the crude lemon grass oil (*C. citratus*). The major component of the essential oil of lemon grass, extracted from the plant that grew in southern Brazil, was found to be citral (80–85%).¹¹ Thus, when a mixture of thiophenol (**2a**) and the essential oil of lemon grass was submitted to MW irradiation (548 W) for 0.5 min in the presence of KF/Al₂O₃ (50%, 0.07 g), 3-thiophenylcitronellal (**3a**) was obtained in 52% yield, together with unreacted mircene, linalool, geraniol and other minor constituents of the starting oil, which were recovered.

The 3-thioorganylcitronellal derivatives **3a–e** were tested for their antimicrobial activity and preliminary studies showed that all of them present bactericide activity against *Staphylococcus* sp. The antimicrobial activity of some 3-thioorganylcitronellals was higher than that observed for the parent citral or even for non-functionalized citronellal.

In conclusion, we have presented here an easy and general method for the preparation of new 3-thioorganylcitronellal derivatives with antimicrobial activity. This eco-friendly protocol can be successfully applied to the synthesis of 3-thiophenylcitronellal (**3a**) from crude lemon grass oil, avoiding the necessity for separation of citral (**1a**). The procedure is very simple, makes use

of renewable and easily available starting materials, no solvent is necessary and the catalytic system can be re-used. The use of microwaves accelerates the reaction with comparable yields in most of the examples. Studies looking for synthetic applications of these new sulfur-containing citronellal derivatives are in course in our laboratory and will be described soon.

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9. *Preparation of alumina supported potassium fluoride*:¹² To a 100 mL beaker were added alumina (4.0 g of Al₂O₃ 90, 0.063–0.200 mm, Merck), KF·2H₂O (6.0 g) and water (10 mL). The suspension was stirred for 1 h at 65 °C, dried at 80 °C for 1 h and for additional 4 h at 300 °C in an oven and then cooled in a desiccator. The content of KF is about 50% (m/m).

10. *General procedure for the 1,4-addition of thiols 2 to electron-poor alkenes 1. Method A:* To a mixture of citral (**1a**, 0.152 g; 1 mmol) and thiophenol (**2a**, 0.13 g; 1.2 mmol), KF/Al₂O₃ (0.07 g, obtained as described above) was added. The mixture was stirred at room temperature. The reaction progress was followed by TLC, and after 4 h the product was filtered off the aluminum oxide by washing with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel (SiO₂) eluting with hexane/ethyl acetate (97:3), yielding product **3a** (0.183 g, 70%) as a colorless oil. ¹H NMR (200 MHz, CDCl₃) δ (ppm) 9.95 (t, *J* = 2.6 Hz, 1H); 7.47–7.53 (m, 2H); 7.34–7.43 (m, 3H); 5.03–5.10 (m, 1H); 2.46 (d, *J* = 2.6, 2H); 2.05–2.28 (m, 2H); 1.69 (s, 3H); 1.64 (s, 3H); 1.56–1.64 (m, 2H); 1.37 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ (ppm) 201.5, 137.4, 131.9, 130.5, 129.0, 128.6, 123.2, 52.1, 49.5, 40.2, 26.0, 25.5, 22.8, 17.5. MS *m/z* (rel. int., %) 243 (M⁺–H₂O, 1.9), 134 (73.8), 81 (90.8), 69 (100.0). *Method B:* The aforementioned whole mixture was previously stirred for 1 min and then irradiated with microwave (a domestic Panasonic model Piccolo NN–S42BK operating at 2.45 MHz) at 548 W¹³ for 0.5–6 min and the product was purified according to on Method A.
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