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

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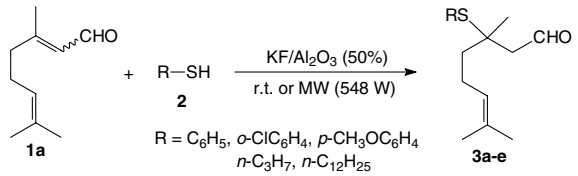
Abstract—A general, clean and easy method for the conjugated addition of thiols to citral promoted by KF/Al_2O_3 under solvent-free conditions at room temperature or under MW irradiation is described. It was found that the same protocol is applicable to the direct reaction of thiophenol with essential 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.

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 heterogeneous[5] and homogeneous catalyses[6] and asymmetric versions.[7] Thus, solid catalysts, such as basic anion-exchange resins,[5a] natural[5b] and synthetic phosphates,[5c] montimorillonite 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/Al_2O_3 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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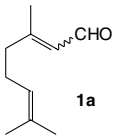
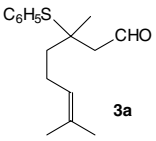
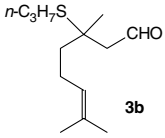
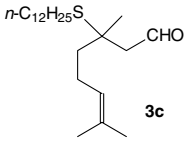
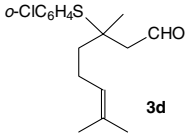
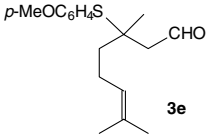
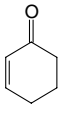
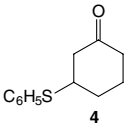
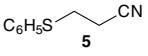
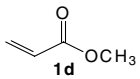
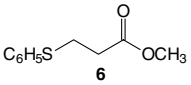
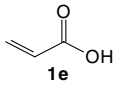
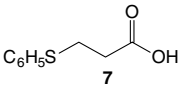
Table 1. Conjugated addition of thiols to citral and electron-poor alkenes under solvent-free conditions

Entry	Alkene **1**	Thiol **2**	Product	Method[a]	Time	Yield[b] (%)
1	 **1a**	C_6H_5SH **2a**	 **3a**	A	4 h	70
2	**1a**	**2a**	**3a**	B	6 min	65
3	**1a**	*n*-C_3H_7SH **2b**	 **3b**	A	7.5 h	50
4	**1a**	**2b**	**3b**	B	1 min	67
5	**1a**	$C_{12}H_{25}SH$ **2c**	 **3c**	A	7.5 h	60
6	**1a**	**2c**	**3c**	B	2 min	35
7	**1a**	*o*-ClC_6H_4SH **2d**	 **3d**	A	9 h	70
8	**1a**	**2d**	**3d**	B	0.5 min	38
9	**1a**	*p*-$MeOC_6H_4SH$ **2e**	 **3e**	A	8 h	81
10	**1a**	**2e**	**3e**	B	1 min	90
11	 **1b**	C_6H_5SH **2a**	 **4**	A	2 h	95
12	 **1c**	**2a**	 **5**	A	1 h	96
13	 **1d**	**2a**	 **6**	A	0.5 h	94
14	 **1e**	**2a**	 **7**	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 ^{13}C NMR.