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A new, alternative, halogen-free synthesis for the fragrance compound Melonal using zeolites and mesoporous materials as oxidation catalysts

Avelino Corma *, Sara Iborra, María Mifsud, Michael Renz

Instituto de Tecnología Química, UPV-CSIC, Avda. los Naranjos s/n, 46022 Valencia, Spain

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Abstract

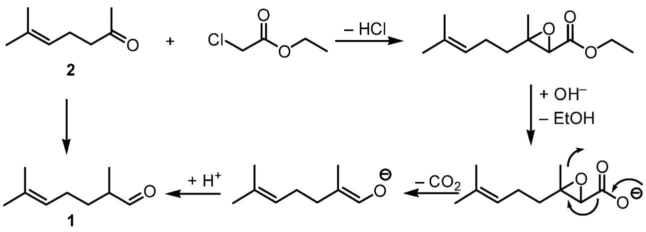
At present Melonal (2,6-dimethyl-5-hepten-1-al) fragrance is industrially produced by a Darzens reaction from 6-methyl-5-hepten-2-one, with ethylchloroacetate as reagent. We present here a novel halogen-free synthesis strategy that involves the chemoselective oxidation of Citral (3,7-dimethyl-6-octen-1-al), a common compound in the fragrance industry, with H_2O_2 and Sn-Beta or Sn-MCM-41 as catalysts. The performance of tin Lewis acid sites is compared with other potential catalytic sites, and it is found that aluminium Brønsted acid sites and zirconium or titanium Lewis acid sites are less efficient and selective than Sn. In the case of Ti, epoxidation by-products could be found. The re-usability of Sn-Beta zeolite is discussed, as is the heterogeneity of the reaction.

Keywords: Baeyer–Villiger oxidation; Citral; Melonal; Solid Lewis acid; Tin centre

1. Introduction

Melonal (2,6-dimethyl-5-hepten-1-al; **1**) is used to introduce melon and cucumber notes into fragrances because of its powerful green melon- and cucumber-like odour [1]. Industrially Melonal is synthesised by a Darzens condensation of 6-methyl-5-hepten-2-one with ethylchloroacetate to yield an α,β-epoxy ester (Scheme 1). This ester is then saponified and decarboxylated to produce the desired aldehyde **1**. In general, the homologation of ketones or aldehydes to yield an aldehyde with one additional carbon atom is a challenging process that cannot be carried out in one step. For this reason, a Darzens reaction using halogenated esters, followed by saponification and decarboxylation, is used for this purpose [2].

We thought of a catalytic and halogen-free alternative synthesis strategy (Scheme 2), where the one carbon homologation can be achieved by transformation of 6-methyl-5-heptene-2-one (**2**) into 3,7-dimethyl-6-octen-1-al (**3**, Citral) by aldol condensation of ketone **2** with acetaldehyde. Subsequent Baeyer–Villiger oxidation of aldehyde **3** affords Melonal (Scheme 2). This new route is quite attractive from a synthetic and industrial point of view, not only because it does not involve any halogenated product, but also because Citral (**3**) is inexpensive and readily available by synthe-



Scheme 1. Synthesis of Melonal (**1**) from 6-methyl-5-hepten-2-one (**2**) by Darzens reaction with subsequent decarboxylation.

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[*] Corresponding author. Fax: +34-96-3877809.
E-mail address: acorma@itq.upv.es (A. Corma).

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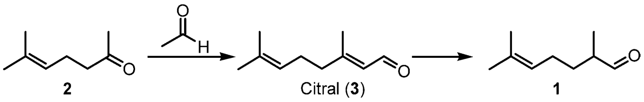


Scheme 2. Synthesis of Melonal (**1**) from 6-methyl-5-hepten-2-one (**2**) by Baeyer–Villiger oxidation of the aldol condensation product with acetaldehyde.

sis [3] and by distillation from essential oils (lemongrass oil or Litsea cubeba oil) [4]. However, it has to be pointed out that this route presents a complication derived from the fact that a tri-substituted double bond is present in the aldehyde chain, and industrial processes for carrying out the Baeyer–Villiger oxidations use peracids that are also good epoxidation agents and do not allow Melonal to be obtained selectively [5,6]. Indeed, when we reacted Citral with *meta*-chloroperbenzoic acid (*m*-CPBA), the selectivity for Melonal or for its precursor **4** is only 33%.

Recently we presented Sn-Beta [7,8] and Sn-MCM-41 [9] materials for the chemoselective Baeyer–Villiger oxidation of cyclic ketones and aromatic aldehydes, with hydrogen peroxide as oxidant. The feasibility of industrial processes with Sn-Beta has been demonstrated successfully in the synthesis of delta-decalactone, which is also a fragrance compound. The zeolite catalyst was used in solvent-free conditions with high substrate/catalyst ratios (up to 200 wt/wt), and high turnover numbers (TONs) were achieved [10]. Here we show that these materials can afford the syntheses of Melonal by this new route, with high selectivities and with hydrogen peroxide as oxidant. It is further demonstrated that the tin Lewis acid sites are better catalytic sites than other Lewis or Brønsted acid sites.

2. Experimental

Hydrogen peroxide (50%), Melonal (**1**), 6-methyl-5-hepten-2-one (**2**), and 3,7-dimethyl-2,6-octadienal (**3**) were purchased from Aldrich. GC analyses were carried out with a HP 5890 gas chromatograph equipped with a 25-m HP-5 column. GC-MS analyses for the identification of products were carried out with an Agilent Technologies 6890N apparatus coupled with a Mass Selective Detector Network. ^{1}H NMR spectra were recorded with a Bruker spectrometer at a frequency of 300 MHz and ^{13}C spectra at a frequency of 75 MHz.

2.1. Synthesis of the molecular sieves

Sn-Beta was synthesised with a procedure described in the literature [8,11]. The Sn content (2.0 wt% as SnO_2) was determined by atomic absorption. The Sn-Beta zeolite was calcined at 853 K for 3 h. The zeolite was highly crystalline, and no peaks of SnO_2 were found by XRD. Nitrogen adsorption experiments on the calcined Beta samples gave an isotherm very similar to that of pure silica Beta with a micropore volume of 0.21 $cm^3\,g^{-1}$ and BET surface areas of 450–475 $m^2\,g^{-1}$.

The two Sn-MCM-41 sample were synthesised according to the following procedure [9]. An aqueous solution of hexadecyltrimethylammonium hydroxide/bromide (C_{16}TABr/OH) was mixed with a tetramethylammonium hydroxide solution (25%, Aldrich) and an aqueous solution of $SnCl_4 \cdot 5H_2O$ (98%, Aldrich). After homogenisation, the silica (Aerosil, Degussa) was added with continuous stirring. The final composition was the following: 1 SiO_2:$(0.16 - 4x)$ C_{16}TABr:$4x$ C_{16}TAOH:0.26 TMAOH:x $SnCl_4$:24.3 H_2O, where x is either 0.040 or 0.008. C_{16}TABr was partially exchanged in order to compensate for the OH^- depletion produced by the incorporation of $SnCl_4$ into the synthesis gel. The homogeneous gel was sealed in Teflon-lined stainless-steel autoclaves and heated at 135 °C under static conditions for 24 h. The resulting solid product was recovered by filtration, washed, and dried at 60 °C for 24 h. We removed the occluded organic by heating the solid at 813 K for 1 h in a flow of N_2, followed by 6 h in air. The solid obtained presents an XRD pattern typical for MCM-41 structure.

2.2. General procedure for the Baeyer–Villiger oxidation

Citral (0.5 g), aqueous hydrogen peroxide (50%, 1.5 equiv.), 3.0 g of solvent, and Sn-Beta catalyst (normally 50 mg) were stirred magnetically and heated to the desired reaction temperature. The reaction was followed by gas chromatography, and the products were identified by comparison with reference samples, by GC-MS spectroscopy, or after purification by ^{1}H NMR spectroscopy. For the isolation of the saponified product, the unreacted hydrogen peroxide was first decomposed with manganese(IV) oxide, followed by treatment with catalytic amounts of sodium hydroxide.

3. Results and discussion

Citral (**3**) was oxidised with hydrogen peroxide with a series of solvents, such as acetonitrile, *iso*-propanol, *tert*-butanol, *tert*-amylalcohol, and cyclohexanol (3.00 g). In all cases the formate ester **4**, which is the Baeyer–Villiger oxidation product of Citral, and Melonal (**1**) are the main products obtained, with added selectivities of $\geqslant$95% when alcohols are used as solvent (Table 1). Since product **4** is easily and quantitatively transformed into Melonal in the presence of catalytic amounts of NaOH, we can say that it is possible to produce with high selectivity ($\geqslant$95%) the homologation of aldehydes through this new halogen-free chemical route. When the yield of the different products is plotted versus total conversion (Fig. 1), it can be seen that the enol ester **4** is a primary unstable product, whereas Melonal (**1**) is a secondary stable product. This behaviour is consistent with the formation of the formate enol ester of Melonal (**4**) by the Baeyer–Villiger oxidation of Citral, whereas Melonal will be the secondary product generated through its hydrolysis. The

Table 1
Baeyer–Villiger oxidation of aldehyde **3** in different solvents. Reaction conditions: 0.5 g of aldehyde **3** (mixture of isomers, 3.7 mmol), 1.5 equiv. of aqueous hydrogen peroxide (50%), 50 mg of Sn-Beta, 3.0 g of solvent, 80 °C reaction temperature, and 1 h reaction time

Entry	Solvent	Conversion (%)	Product distribution			
			1	**4**	**2**	Other
1	Acetonitrile	40	13	78	0	9
2	*iso*-Propanol	33	17	79	0	4
3	*tert*-Butanol	40	10	85	2	3
4	*tert*-Amylalcohol	29	1	95	0	4
5	Cyclohexanol	49	20	75	5	0

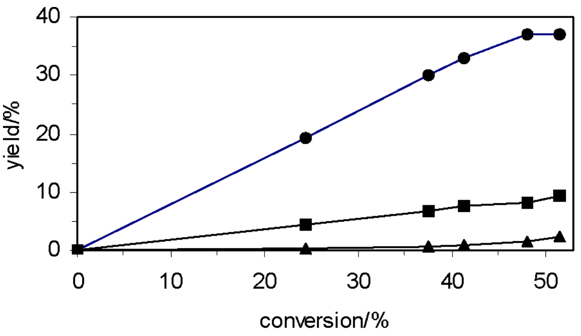
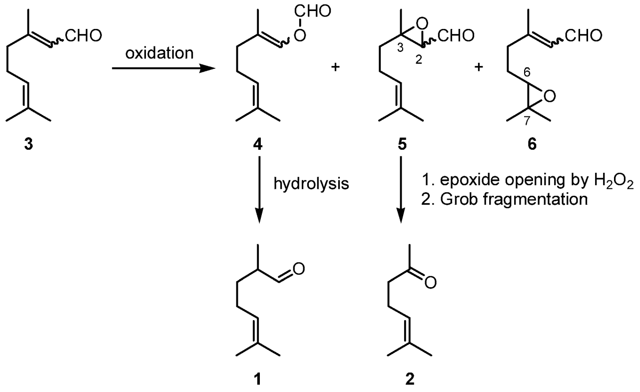


Fig. 1. Yields of Melonal (**1**) (■), ester **4** (●) and ketone **2** (▲) for the Baeyer–Villiger oxidation over the conversion of Citral (**3**) in cyclohexanol.



Scheme 3. Product formation in the Baeyer–Villiger oxidation of aldehyde **3**.

main by-product, ketone **2**, is formed only in small amounts and appears as a secondary product. This could be formed (see Scheme 3) from the 2,3-epoxide **5** after opening with hydrogen peroxide and the Grob fragmentation to give the ketone **2**.

We are saying here that the formation of the ketone **2** requires the formation of an epoxide **5**. However, it has been proposed before that Sn-Beta does not catalyse the epoxidation of olefins by hydrogen peroxide [7,8], and this is indeed confirmed by the fact that we have not detected epoxidation of the 6,7 double bond in the Citral molecule. However, for the double bond in α,β position to the carbonyl group, as it occurs in the case of Citral (**3**), the epoxide can be formed (though in small amounts) by a Weitz–Scheffer-type epoxidation catalysed by the Sn-Beta catalyst. It has been established by in situ IR spectroscopy that the carbonyl oxygen coordinates with the Lewis-acid tin centre, causing a positive partial charge at the carbon atom of the carbonyl group. Then, in the case of the α,β-unsaturated aldehydes, this partial charge can be delocalised to the double bond (β position), and consequently the initial step of the Weitz–Scheffer epoxidation, a nucleophilic attack of the double bond, should be facilitated. Nevertheless, the rate of this reaction is much lower than the corresponding nucleophilic attack by hydrogen peroxide of the carbon atom in the carbonyl group, and the selectivity for the epoxide is rather low ($\leqslant$5%).

Table 2
Baeyer–Villiger oxidation of aldehyde **3** at different temperatures. Reaction conditions: 0.5 g of aldehyde **3** (mixture of isomers, 3.7 mmol), 1.5 equiv. of aqueous hydrogen peroxide (50%), 50 mg of Sn-Beta, 3.0 g of solvent, and 1 h reaction time

Entry	T (°C)	Solvent	Conversion (%)	Product distribution			
				1	**4**	**2**	Other
1	80	*tert*-Amylalcohol	29	1	95	0	4
2	90	*tert*-Amylalcohol	36	11	85	0	4
3	100	*tert*-Amylalcohol	53	10	85	0	5
4	80	Cyclohexanol	49	20	75	5	0
5	100	Cyclohexanol	52	18	72	5	5
6	100	1-Methylcyclohexanol	52	8	83	2	7
7	120[a]	1-Methylcyclohexanol	52	5	89	0	6
8	120	1-Methylcyclohexanol	53	12	71	3	14

[a] 5 min reaction time.

In the different alcohol solvents, conversions in the range of 30 to 50% have been observed. Regardless of the solvent used, conversion was slightly increased, whereas selectivity remained at ~95%, when we increased the temperature to 100 °C. At 120 °C, 52% conversion was already achieved after 5 min of reaction time (Table 2, entry 7), what corresponds to a turnover number (moles converted per mole Sn) of 257 and a turnover frequency (moles converted per mole Sn per hour) of 3060. When the reaction time was prolonged to 1 h at this temperature, no further conversion could be detected, but a small decrease in selectivity could.

Selectivity for hydrogen peroxide was always above 98%, and therefore the controlling reactant was always the Citral (**3**). Thus, the fact that total conversion of Citral was not obtained could be ascribed to catalyst deactivation or to catalyst inhibition due to the adsorption of products at the catalytic sites in the Langmuir–Hinshelwood sense of competing adsorption. This type of product inhibition has been observed in other homogeneously [12] and heterogeneously [8] Lewis-acid-catalysed reactions.

As we have observed in the oxidation of cyclohexanone with hydrogen peroxide in the presence of Sn-Beta, there is a negative effect of water on the reaction rate by competitive adsorption on Sn sites. In any case, a competitive adsorption effect is more important in the case of the lactone product [13]. When this competitive adsorption occurs, the catalyst should not suffer a permanent deactivation, and its activity should be restored simply by desorption of the

Table 3
Re-use of the catalyst for the Baeyer–Villiger oxidation of aldehyde **3**. Reaction conditions: 0.5 g of aldehyde **3** (mixture of isomers, 3.7 mmol), 1.5 equiv. of aqueous hydrogen peroxide (50%), 50 mg of Sn-Beta, 3.0 g of *tert*-amylalcohol as solvent, 100 °C reaction temperature, and 1 h reaction time in the first cycle. For the subsequent runs the amount of substrates and solvent were scaled down with respect to the available amount of catalyst

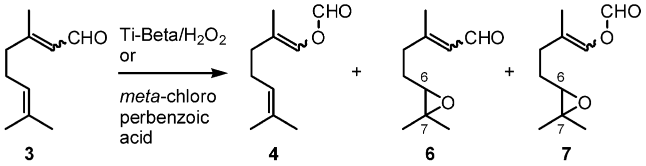
Entry	Cycle	Conversion (%)	Product distribution **1**	**4**	**2**	Other
1	1	53	10	85	0	5
2	2	58	9	87	0	4
3	3	56	11	85	0	4
4	4	56	11	84	0	5
5	5	48	9	85	0	6
6	6[a]	62	12	77	0	11

[a] After activation by calcination.

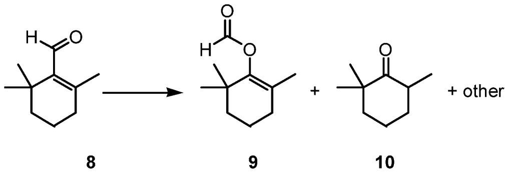
Table 4
Baeyer–Villiger oxidation of aldehyde **3** by different oxidation systems or oxidants. Reaction conditions: 0.5 g of aldehyde **3** (mixture of isomers, 3.7 mmol), 1.5 equiv. of aqueous hydrogen peroxide (50%), 50 mg of Beta zeolite or Sn-MCM-41, 3.0 g of *tert*-amylalcohol, 100 °C reaction temperature, and 1 h reaction time. The reactions with *meta*-chloroperbenzoic acid (*m*-CPBA) were carried out at 100 °C and conversion and selectivity is given for 30 min reaction time

Entry	Oxidant	Conversion (%)	Product distribution **1** + **4**	**2**	**6**	**7**	Other
1	Sn-Beta/H_2O_2	53	95	0	0	0	5
2	Al-Beta[a]/H_2O_2	17	66	34	0	0	0
3	Zr-Beta/H_2O_2	28	59	28	0	0	13
4	Ti-Beta/H_2O_2	16	48	0	39	13	0
5	Si-Beta/H_2O_2	0					
6	$SnCl_4/H_2O_2$	4	100	0	0	0	0
7	Sn-MCM-41[b]/H_2O_2	46	90	7	0	0	3
8	Sn-MCM-41[c]/H_2O_2	40	96	4	0	0	0
9	*m*-CPBA (0.3 equiv.)	19	48	0	39	13	0
10	*m*-CPBA (1.0 equiv.)	49	33	0	33	34	0

[a] Si/Al ratio = 15.
[b] 9 wt% of SnO_2.
[c] 2 wt% of SnO_2.



Scheme 4. Products formed with Ti-Beta/hydrogen peroxide and *m*-CPBA in the oxidation of Citral (**3**).



	Conv./%						
Sn-Beta	43	33	:	3	:	64
Sn-MCM-41	90	100	:	0	:	0

Scheme 5. Baeyer–Villiger oxidation of aldehyde **8**. Reaction conditions: 0.5 g of Cyclocitral (**8**; 3.7 mmol), 1.5 equiv. of aqueous hydrogen peroxide (50%), 50 mg of Sn-Beta or Sn-MCM-41 (each 2 wt% in SnO_2), 3.0 g of *tert*-amylalcohol, 100 °C reaction temperature, and a reaction time of 1 h.

product. Indeed, in the case of Melonal, the catalyst can be re-used after each run with the usual simple activation at 200 °C and 2 Torr for 2 h (Table 3). A final re-calcination provides a more active catalyst at the cost of some selectivity. The fact that the conversion per pass is 50% requires the introduction of a separation and recycling step in the overall industrial process.

We have compared the oxidation activity and selectivity of Sn-Beta with other potential catalysts [14,15]. For instance, after 1 h of reaction time at 100 °C (Table 4), an Al-Beta catalyst gives only 30% of the conversion that was obtained with Sn-Beta, namely 17% versus 53% (cf. Table 4, entries 1 and 2), whereas the undesired ketone **2** was observed in significant yield.

In the Baeyer–Villiger oxidation of aromatic aldehydes with Al-Beta, an activity similar to that observed for Sn-Beta has been found [14], except for substrates with isolated double bonds. It has been proved there that when olefinic groups are present in the reactant molecule, Al-Beta catalyst deactivates readily either by formation of fairly stable unreactive carbocations and/or by blocking of the pores by bulky oligomers. This is indeed what can also occur in the case of Citral/Melonal.

The performance of Zr-Beta is similar to or even better than that of Sn-Beta in the Meerwein–Ponndorf–Verley reaction [15,16]. However, in the Baeyer–Villiger oxidation of Citral (**3**), Zr-Beta was less active and less selective than Sn-Beta. It gives 28% conversion with a selectivity for the desired **1** + **4** products of only 59% (Table 4, entry 3).

Titanium incorporated into the Beta structure resulted in low conversion and low selectivity (Table 4, entry 4). Apart from the Baeyer–Villiger oxidation, epoxidation is observed, yielding products **6** and **7** (Scheme 4). The Si-Beta parent system without metal incorporation showed no catalytic activity (entry 5), and $SnCl_4$ gave a very low conversion (entry 6).

3.1. *Sn-mesoporous material as catalyst*

Interesting results were obtained with Sn-MCM-41, with Citral conversions of 46 and 40% for tin contents of 9 and 2 wt%, respectively (Table 4, entries 7 and 8), with high selectivities for the desired products. As already observed for the Baeyer–Villiger oxidation of cyclic ketones [10], Sn-Beta is intrinsically more active than Sn-MCM-41 (entries 1 and 8), provided that the substrate can diffuse through the Beta channels without any steric restriction. On the other hand, when the pore dimensions of the zeolite present diffusional restrictions for the reactant, then Sn-substituted mesoporous molecular sieves can be an alternative to zeolites [17]. We can see that when Cyclocitral (**8**; 2,6,6-

trimethyl-1-cyclohexene-1-carboxaldehyde) is reacted with Sn-Beta, the conversion decreases to 43%; however, the selectivity for the desired products is only 36% (the missing 64% is the unusual regioisomer of the Baeyer–Villiger oxidation). In contrast, Sn-MCM-41 (2 wt% in SnO_2) converts 90% of the α,β-unsaturated aldehyde **8** into the corresponding formate ester without any saponification to the ketone **10** (Scheme 5).

4. Conclusions

Here we have demonstrated a new strategy for the synthesis of the fragrance compound Melonal. In our alternative route from a different substrate, namely Citral, we avoid halogenated elaborated reagents and use a green oxidant in combination with a heterogeneous catalyst. The most appropriate catalytic sites are Sn Lewis incorporated into a siliceous material. They perform better than Brønsted or other Lewis acid sites like titanium or zirconium. From an industrial point of view, this new synthesis route is interesting, since it has been demonstrated that the catalyst can easily be separated and re-used in several reaction cycles.

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