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Microwave-Assisted Synthesis and Odour Characteristics of Some New Isoxazolidines

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Abstract

We describe herein design and synthesis of new isoxazolidin-5-carboxylates by microwave-assisted 1,3-dipolar cycloadditions of aldonitrones, derived from five fragrant aldehydes, with methacrylate esters. The reaction proceeded regioselectively providing mostly *endo*- diastereomers and in some cases inseperable mixture of *endo*-*exo* products. The structures of target compounds were identified on the basis of IR, NMR and TOF-MS measurements. Besides, both aldonitrone and isoxazolidine derivatives was subjected to olfactory evaluation by an expert nose. Diverse fragrance notes were observed in each series of isoxazolidines bearing different groups from aldonitrons. However, their odour ranges were found as animalic, medical, waxy and ozonic undertones in common.

Keywords

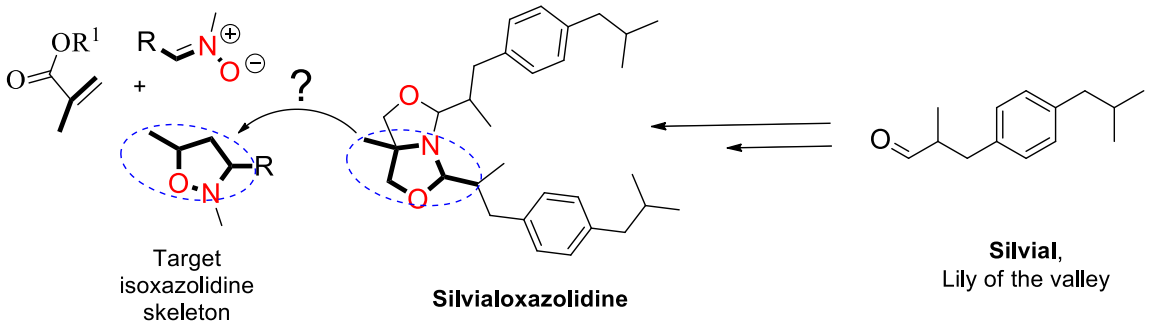
Odour; isoxazolidine; methacrylate ester, microwave heating, aldonitrone

Introduction

Isoxazolidines have been known as privilige core incorparated in numerous natural products and drug candidates with considerable biological and medicinal activities such as antifungal [1] antiviral [2], anti-inflammatory [3], antimicrobial [4] and cytotoxic activities [5]. Besides, due to the reactivity of N-O bond in isoxazolidine ring, they can be regarded as valuable intermediates which may lead to a vast variety of functional groups, complex molecules or open chain products.

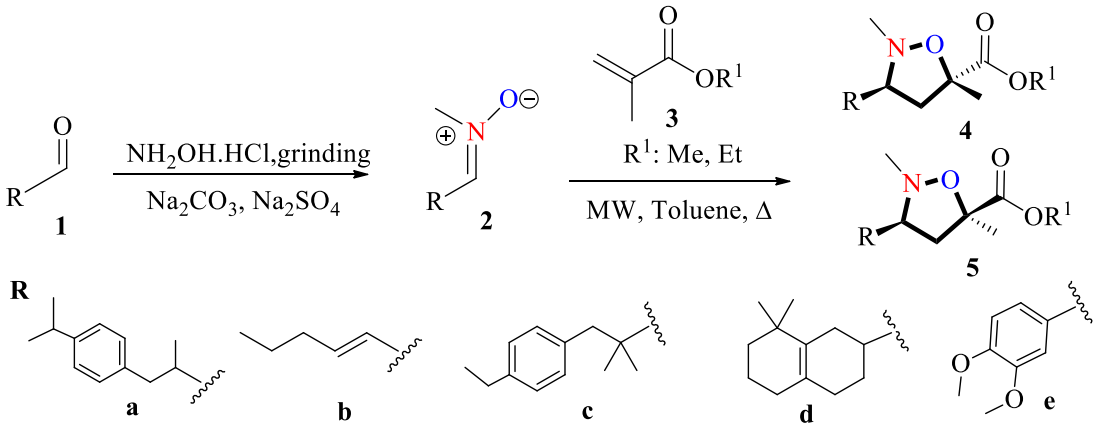
There have been a growing interest for preparation of isoxazolidine containing heterocyclic compounds in past decades [6]. Although, many approaches involving cyclization of unsaturated hydroxylamines [7], asymmetric reduction of isoxazolines or isoxazolidinones [8] have been utilized for achievement of isoxazolidines, 1,3-dipolar cycloaddition is well known route providing to access a wide range of compounds [9-11].

Taking into account of above considerations, plus our ongoing interest for the synthesis of new heterocycles bearing isoxazolidine nuclei, we wondered whether isoxazolidines could be fragrant compounds. From a structure point of view, silvialoxazolidine, a structurally related N-O containing heterocycle, patented by Henkel [12] was considered as an inspiring molecule for our design in terms of its fragrant property that has lily of the walley odor note like its precursor silvial, however, showing more persistent character. Commercially, it has been used in textile laundering instead of silvial due to its particularly long lasting scent result. Thus, the olfactory property of this promising molecule prompted us to design and synthesize some new isoxazolidines that may have potential to be odorant compounds as their isomers, silvialoxazolidine.



Scheme 1: Silvialoxazolidine synthesis and designed isoxazolidine skeleton

In order to reach this ultimate goal, some aldonitrones **2 a-e**, derived from commercially available fragrant aldehydes **1 a-e**, were treated with methacrylate esters **3** under microwave irradiation to give target isoxazolidines **4,5 a-e** or **4,5 a'-e'** in one pot.



Scheme 2: Synthetic route for the synthesis of isoxazolidine-5-carboxylate **4,5**

On the other hand, environmentally benign synthetic approach is described for each part of the study involving aldonitrone formation by solvent-free grinding process and synthesis of isoxazolidine-5-carboxylate derivatives via the use of microwave energy. Also, it should be noted that each synthetic protocol is fast, efficient and eco-friendly when compared to conventional heating.

Results and Discussion

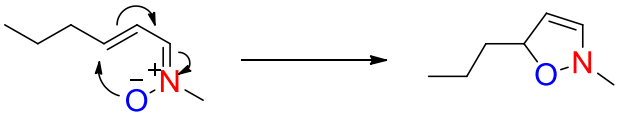
Our initial efforts were to synthesize five nitrones from randomly selected aldehydes presenting different odor characteristic. For this purpose, floralzone **1c** was choosen as a pilot precursor compound for optimization reaction of nitrones. Accordingly, when the reaction was carried out with NEt_3 in DCM at room temperature or reflux, compound **2c** was obtained in 45 and 52% yields, respectively (Table 1, Entry 1 and 2). In another trial, when used NaOH instead of NEt_3 in aqueous medium, the reaction yield for **2c** decreased even if the reaction was heated at 80^oC for prolonged time (Table 1, Entry 3 and 4). Finally, grinding of **1c**, $NH_2OH.HCl$, Na_2SO_4 and Na_2CO_3 in a mortar and pestle gave **2c** with a yield of 62%. This method was comparatively fast and efficient with respect to other ones for preparation of **2c** (Table 1, Entry 5). Therefore, solvent-free grinding method was utilized for the synthesis of **2 a-e** derivatives and gave the desired aldonitrons in moderate to good yields.

Table 1. Reaction optimizations and conditions for **2a-e**

Entry	Compound	Reaction Conditions[1]	Yield (%)[2]
1	**2c**	DCM, NEt_3 25^oC, 24 h	45
2	**2c**	DCM, NEt_3 ,40^oC, 10 h	52
3	**2c**	H_2O, NaOH, 25^oC, 24 h	30
4	**2c**	H_2O, NaOH, 80^oC,12 h	38
5	**2c**	Na_2CO_3, Na_2SO_4, grinding, 10 min	62
6	**2a**	Na_2CO_3, Na_2SO_4, grinding, 10 min	65
7	**2b**	Na_2CO_3, Na_2SO_4, grinding,, 5 min	44
8	**2d**	Na_2CO_3, Na_2SO_4, grinding, 15 min	70
9	**2e**	Na_2CO_3, Na_2SO_4, grinding, 10 min	68

[1]Time determined by TLC control ; [2]isolated yield

The structural characterization of aldonitrones **2a-e** were done by the means of IR, NMR and mass measurements. The diastreomeric ratio (*E* or *Z*) of aldonitrones depicted in Table 2 were determined by comparing integral value of indicative proton signals in ^{1}H-NMR data. Although the indicative proton and carbon signals that are iminic and NMe groups were given for **2 a-e** in Table 2, we were not able to get proper NMR data for compound **2b**. It is assumed that the reason underlying this failure may be resulted from the intermolecular rearrangement of **2b**, however, no structural evidence was found for this transformation (Scheme 3).



Scheme 3. Plausible intramolecular cyclization product of **2b**

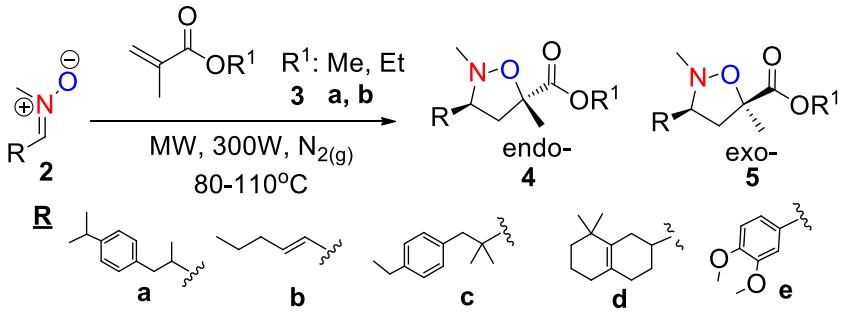
Table 2. Indicative structural data for aldonitrone derivatives **2a-e**

Entry	Compound	IR (C=N) cm^{-1}	^{1}H-NMR δ (ppm) *J*(Hz) NCH$_3$	^{1}H-NMR δ (ppm) *J*(Hz) C=NH	^{13}C-NMR δ (ppm) NCH$_3$	^{13}C-NMR δ (ppm) C=NH	*ZIE* isomer ratio
1	**2a**	1600	3.53 (*Z*)	6.46, dd, 7.2, 0.7 (*Z*)	52.72 (*Z*)	144.30 (*Z*)	100:0
2	**2b**	1575	-	-	-	-	-
3	**2c**	1593	3.63 (*Z*) 3.66 (*E*)	6.33, d, 0.7 (*Z*) 6.39, d, 0.7 (*E*)	53.55 (*Z*) 53.39 (*E*)	142.05 (*Z*) 143.25 (*E*)	70:30
4	**2d**	1600	3.64 (*Z*) 3.65 (*E*)	6.53, d, 0.4 (*Z*) 6.55, d, 0.4 (*E*)	52.72 (*Z*) 52.53 (*E*)	144.30 (*Z*) 144.44 (*E*)	51:49
5	**2e**	1592	3.84 (*Z*)	6.89, d, 8.5 (*Z*)	54.23 (*Z*)	135.37 (*Z*)	100:0

After obtaining new aldonitrones **2 a-e**, we focused on the synthesis of first series of isoxazolidine-5-carboxylates by the treatment of **2 a-e** with methacrylate derivatives **3** via microwave heating in one-pot manner. It was reported that the 1,3-DC reaction of methyl methacrylate with some aryl aldonitrones gave isoxazolidines as diastreomeric mixtures with endo isomer being the major product. These results were in accordance with our nitrone-methacrylate cycloadditions in terms of stereoselectivity providing *endo* isomer as well [13]. However, since use of five

different nitrones would likely result in different manner in the cycloaddition reactions, the reaction conditions will be optimized with each aldonitrone derivatives. First, **2a** and **3a** were irradiated at 110°C for 5h to afford product **4a-5a** with a yield of 45% (Table 1, Entry 1). Fortunately, use of inert atmosphere (N_2 gas) in reaction slightly increased the reaction yield up to 52% (Table 1, Entry 2). Hereby, aldonitrone-methacrylate reactions were carried out in either toluene or neat conditions under inert atmosphere with microwave irradiation (Table 3, Entry 2-15). Then, treatment of 2b and 3a at 110°C in toluene with MW irradiation furnished **4b** with a yield of 45% (Table 1, Entry 4). Since no product formation could be observed in toluene at lower temperatures, **2b** and **3a** were heated under solvent-free conditions at 60 °C for 2 hour, this surprisingly increased reaction yield up to 60% (Table 1, Entry 5). However, it should be noted that no increase in reaction yield was observed under neat condition for compound **4,5 a-e** and **4,5 a'-e'** except **4b** even many trials have been performed. Finally, the best protocol for the preparation of **4,5 a-e** and **4,5 a'-e'** was heating of aldonitrones with methacrylate esters in toluene under reflux conditions for specified time depicted in Table 3.

Table 3. Optimized reaction conditions for preparation of isoxazolidine-5-carboxylate derivatives (4, 5)



Entry	Aldonitrone	Methacrylate Ester	Compound	Reaction Condition	Total Yield (%)[1]
1	2a	3a	4a-5a	110°C, 5h, Toluene, 300W	45
2	2a	3a	4a-5a	110°C, 5h, Toluene, 300W, N_2(g)	52
3	2a	3b	4a'	110°C, 2h, Toluene, 300W, N_2(g)	64

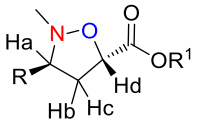
4	2b	3a	4b	110ºC, 2h, Toluene, 300W, N_2(g)	48
5	2b	3a	4b	60ºC, 2h, Neat, 50W, N_2(g)	60
6	2b	3b	4b’	80ºC, 2h, Neat, 50W, N_2(g)	46
7	2c	3a	4c-5c	110ºC, 2h, Neat, 300W, N_2(g)	55
8	2c	3a	4c-5c	110ºC, 2h, Toluene, 300W, N_2(g)	68
9	2c	3b	4c’-5c’	110ºC, 8h, Toluene, 300W, N_2(g)	60
10	2d	3a	4d	110ºC, 3h, Neat, 300W, N_2(g)	55
11	2d	3a	4d	110ºC, 3h, Toluene, 300W, N_2(g)	72
12	2d	3b	4d’	110ºC, 3h, Toluene, 300W, N_2(g)	70
13	2e	3a	4e-5e	110ºC, 5h, Neat, 300W, N_2(g)	48
14	2e	3a	4e	110ºC, 5h, Toluene, 300W, N_2(g)	62
15	2e	3b	4e’	110ºC, 8h, Toluene, 300W, N_2(g)	60

[1] The quantity of major diastereomers after purified by column chromatography

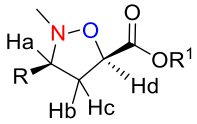
The structures of target isoxazolidines were identified by the means of IR, NMR and mass measurements. In IR spectra, most indicative vibration band was the ester carbonyl streching of target isoxazolidines at around 1726-1736 cm^{-1}. ^{1}H NMR measurements showed that most confirmative proton signal for the formation of isoxazolidine ring were of two diastereotopic methylene hydrogen, hydrogen adjacent to the nitrogen of the ring and methyl proton attached to the quarternary carbon of the ring. Based on the chemical shifts and coupling constants of these protons, especially, aliphatic protons of the ring, it was well understood that only **4a’**, **4b**, **4b’**, **4d**, **4d’** and **4e’** were obtained as *endo* isomers, the rest of cycloadducts yielded in the form of inseparable diastereomeric mixtures (*endo*/*exo*) and their ratios have been determined by comparing integral values of methylene protons (Table 4). As a representative example, expanded ^{1}H-NMR spectrum of **4e’** indicating the assignable three aliphatic and methyl protons was given in Figure 1. Among the aliphatic protons, Ha is the most deshielded one due to the its proximity to nitrogen and it resonated at 3.44 ppm as triplet. The methylene protons of the isoxazolidine ring (Hc and Hd) exhibited typical ABX spin system with Hc and Hd as doublet of doublet with 12.0 and 9.0 Hz. These findings of coupling constants and chemical shifts were also in accordance with the previous reports involving cycloaddition of *N*-methyl nitrone

and methylmethacrylate giving endo isomer as the major product [13]. In addition, ^{13}C-NMR spectra of cycloadducts showed the major signals as methacrylate ester carbonyl carbon in the range of 173-175 ppm along with quarternary carbon of isoxazolidine ring (79-81 ppm). Furthermore, the TOF-MS measurements provided the corresponding molecular ions as expected.

Table 4. Indicative ^{1}H and ^{13}C NMR data of isoxazolidin-5-carboxylate derivatives (**4**,**5**)



endo-



exo-

Entry	Comp.	N(CH_3) δ(ppm)J(Hz)	Ha δ(ppm) J(H_z)	Hb-Hc δ(ppm) J(H_z)	Hd(CH_3) δ(ppm)J(H_z)	Ca δ(ppm)	Cd δ(ppm)	C=O(ester) δ(ppm)	Endo/Exo Ratio
1	4a-5a	2.54, s, (n) 2.61, s, (x)	2.80, dd, 13.7, 7.0, (n)	2.30, dd, 13,4, 8.4, (n) - 1.91, dd, 12.5, 8.4, (n)	1.39, s, (n) 1.45, s, (x)	72.30, (n) 73.32, (x)	81.77, (n) 81.00, (x)	175.85, (n) 175.00, (x)	65:35
2	4a’	2.63, s, (n)	2.89, dd, 13.8, 6.9, (n)	2.39, dd, 13,5, 8.5, (n) - 1.99, dd, 12.6, 8.5, (n)	1.48, s, (n)	71.81, (n)	80.70, (n)	174.97, (n)	100:0
3	4b	2.63, s, (n)	2.97, dd, 16.4, 8.7, (n)	2.68, dd, 12.9, 9.3, (n) - 2.25, dd, 12.8, 7.8, (n)	1.49, s, (n)	72.10, (n)	80.76, (n)	175.33, (n)	100:0
4	4b’	2.56, s, (n)	2.91, t, 7.8, (n)	2.61, dd, 13.3, 9.8, (n) - 2.16, dd, 12.7, 7.8, (n)	1.41, s, (n)	71.04, (n)	79.58, (n)	173.91, (n)	100:0
5	4c-5c	2.83, s, (n) 2.88, s, (k)	2.94, dd, 13.1, 6.6, (n)	2.60 (dd, J = 9.7, 7.5, (n) - 2.27, dd, 13.1, 9.8, (n)	1.53, s, (n) 1.54, s, (k)	77.57, (n)	81.07, (n)	175.36, (n)	100:0
6	4c’-5c’	2.83, s, (n) 2.87, s, (k)	2.94, dd, 13.1, 6.6, (n	2.60 (dd, J = 9.7, 7.6, (n) - 2.27, dd, 13.1, 9.7, (n)	1.52, s, (n) 1.53, s, (x)	77.56, (n) 77.60, (x)	81.03, (n) 81.19, (x)	174.69, (n) 174.78, (x)	73:27
7	4d	2.73, s, (n)	-	-	1.50, s, (n)	73.06, (n)	80.96, (n)	175.78, (n)	100:0
8	4d’	2.69, s, (n)	-	-	1.48, s, (n)	73.02, (n)	80.87, (n)	174.74, (n)	100:0
9	4e-5e	2.53, s, (n) 2.62, s, (x)	3.44, t, 7.3, (n)	2.95, dd, 12.9, 9.1, (n) - 2.41,	1.51, s, (n) 1.61, s, (x)	72.38, (n)	81.17, (n) 81.85, (x)	175.45, (n) 173.91, (x)	88:22

				dd, 12.9, 8.2, (n)		73.46, (x)			
10	4e'	2.54, s, (n)	3.44, t, 7.6, (n)	2.96, dd, 12.9, 9.0, (n) - 2.41, dd, 12.9, 8.2, (n)	1.51, s, (n)	73.42, (n)	81.10, (n)	174.87, (n)	100:0

(n)=endo, (x)=exo

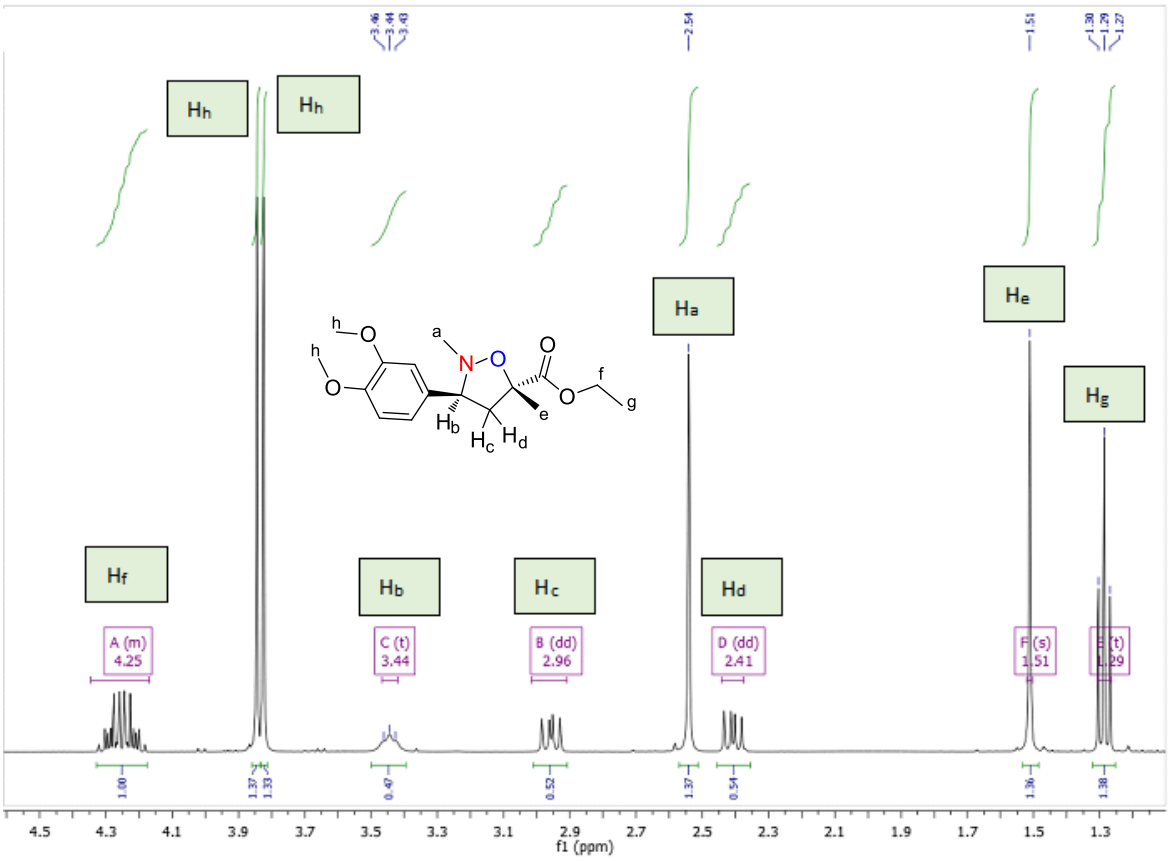


Figure 1. Expanded aliphatic region in ^{1}H-NMR spectrum of **4e'**

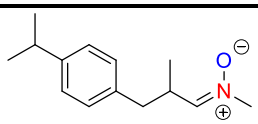
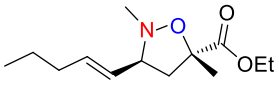
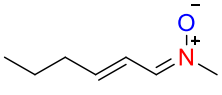
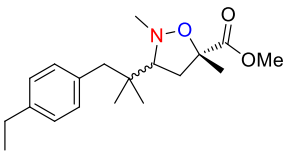
After the synthesis of aldonitrones **2 a-e** and target isoxazolidines **4,5 a-e** and **4,5 a'-e'**, our next goal was to evaluate olfactory properties of column-pure products by an expert nose (Parkim Corp.). For the test, 10% dipropylene glycol (DPG) solutions of each compound (**2**, **4** or **5**) were prepared and applied to the perfume test strips. Olfactory properties of the corresponding compounds were determined by making odor identifications in fresh, 4- and 24-h periods. The main odor notes for each molecule were presented in Table 5.

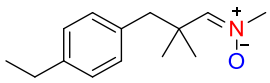
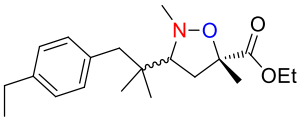
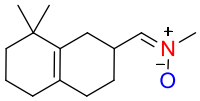
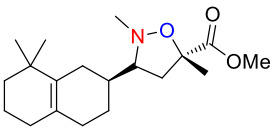
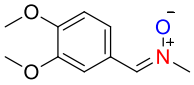
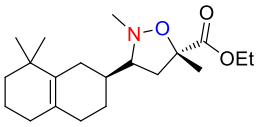
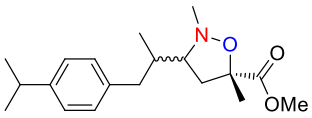
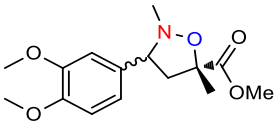
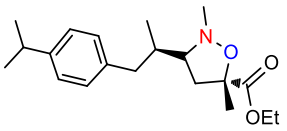
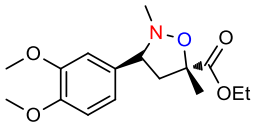
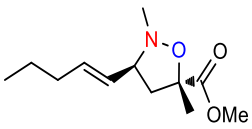
As a result of olfactory evaluation, the odor notes of aldehydes used in this study were completely changed when transformed into aldonitrones (Table 5). For

example, muguet carboxyaldehyde **1d** has known to have floral, clean, muguet, ozone, marine, sandy and balsamic notes. However, **2b** presented strong aquatic, muguet, lily and dusty notes at the beginning and still presented persistent aquatic note after 24 h within the tested concentrations. Hoıwever, there is no specific olfactory link between aldonitrones **2 a-e** and their corresponding isoxazolidines. Their odor profiles were nearly different; aldonitrones **2b** exhibited ozonic, medical and fatty character, whereas isoxazolidines **4a-5a**, **4a'** derived from **2a** are mostly animalic, thinneric and waxy. Also, similar observations were obtained for other aldonitrones and their isoxazolidines in terms of odor characteristics.

On the other hand, although target isoxazolidine-5-carboxylates bear different groups originated from aldonitrones and esters of methacrylate, animalic, medical, waxy and ozonic notes were observed in common. However, interestingly, interchanging of ester group (Me or Et) on the same molecule resulted the totally different odor tonalities for some derivatives (Table 5). For example, compound **4b** and **4b'**are the methyl and ethyl esters of pentenyl substituted isoxazolidine, respectively, presenting paint and weak fatty at the top notes for **4b** whereas **4b'** are clearly garlic, more cut grass with heavy green undertones.

Table 5. Main olfactory notes of aldonitrones **2 a-e** and isoxazolidine-5-carboxylate derivatives **4,5** .

Compound	Olfactory description	Compound	Olfactory description
 **2a**	Top: *Ozonic and Medical* DD: *Fatty*	 **4b'**	Top: *Garlic and Cut grass* DD: *Weak*
 **2b**	Top: Strong *napthyl and floral* DD: *Weak*	 **4c-5c**	Top: *Strong thinneric, animalic* DD: *Strong animalic*

 **2c**	Top: *Napthyl and Floral* DD: Weak *fatty and ozonic*	 **4c'-5c'**	Top: *Animalic and barnyard* DD: *Animalic*
 **2d**	Top: *Muguet, Aquatic, Lily and Dusty* DD: *Strong Aquatic*	 **4d**	Top: *Strong Medical* DD: *Medical*
 **2e**	Top: *Ozonic* DD: *Ozonic and Aquatic*	 **4d'**	Top: *Thinneric, paint, cresolic and animalic* DD: *Weak animalic*
 **4a-5a**	Top: *Thinneric, Animalic and Napthyl* DD: *Animalic*	 **4e-5e**	Top: *Ozonic, aquatic and fatty* DD: *Weak fatty and waxy*
 **4a'**	Top: *Thinneric* DD: Waxy and *Fatty*	 **4e'**	Top: *Ozonic and napthyl* DD: *Weak ozonic*
 **4b**	Top: *Paint* DD: *Weak*		

The top notes corresponds to the evaluations 0-10 min, while the dry down (DD) notes corresponds to the evaluations after 24 h.

Conclusion

Starting from five commercially available fragrant aldehydes, corresponding aldonitrones have been prepared under solvent-free condition and introduced with methacrylate esters by using microwave irradiation to furnish new isoxazolidines with high regio- and diastereoselectivity. Besides, the olfactory evaluation of aldonitrons and target isoxazolidines revealed that there is a significant fragrance diversity between them.

Supporting Information

Supporting Information File 1:

Experimental details, characterization data and copies of NMR spectra

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