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An improved method for aldol condensation catalyses by Amberlyst A-26 OH: application in the synthesis of pseudoionone derivative, 11,15-dimethylhexadeca-8,10,14-trien-7-one

Abstract: This paper reports the improved procedure for aldol condensation between citral and 2-octanone with Amberlyst A-26 OH to give 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. The improved synthesis utilizing Amberlyst A-26 OH as the solid catalyst produces better yield (93.0%) and enables simple work-up procedure. The experimental conditions are evaluated and optimized at 2-octanone/citral molar ratio of 10, catalyst amount of 5% (mole of citral), and temperature of 60°C in 3.5 h reaction time. 11,15-Dimethyl-hexadeca-8,10,14-trien-7-one is isolated using preparative thin layer chromatography with hexane:ethyl acetate (9.5:0.5) and confirmed by gas chromatography-mass spectrometry (GC-MS), ultraviolet-visible (UV-Vis), Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR).

Keywords: 2-octanone; aldol condensation; Amberlyst A-26 OH; citral; pseudoionone.

1 Introduction

Pseudoionone (PSI) is a terpene ketone derived from essential oils with vast applications in pharmaceutical, fragrance and cosmetic industries [1]. PSI is typically produced from the aldol condensation of citral with ketone catalysed by sodium hydroxide [2] and lithium hydroxide [3] with yields of 60–80%. Various undesired side reactions

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exist with these homogeneous catalysts such as the self-condensation of citral and the secondary reactions involving the PSI produced [1]. These homogeneous catalysts are also highly corrosive in nature and require neutralization steps upon reaction completion. Thus, the re-use of the catalyst is not practical [4].

The substitution of this conventional homogeneous process to a heterogeneous one provides a shortened operation procedure [5]. For example, neutralization and washing steps are replaced by a single filtration process. Furthermore, selection of a selective catalyst can increase the total yield and also reduce the formation of byproducts. Heterogeneous catalysts are easily separated from the reaction mixture and therefore, can be regenerated and reutilized. These advantages give rise to a more environmentally friendly process.

The importance of PSI encourages researchers to constantly improve the synthetic process. Table 1 shows the recent modifications and improvements that have been accomplished in the last decade to increase the efficiency of PSI production.

Recently, a new PSI derivative, 11,15-dimethylhexadeca-8,10,14-trien-7-one, was reportedly synthesized in the aldol condensation of citral and 2-octanone with sodium ethoxide catalyst [10]. Regrettably, the new PSI derivative is not characterized in the paper mentioned. One of the weaknesses of this experiment is the use of sodium ethoxide where it is typically made by treating sodium metal with ethanol [11]. In addition to being a costly material, sodium also reacts violently in the presence of water or oxidizing agent. Sodium ethoxide, which is usually used in the form of liquid with ethanol, is highly corrosive due to its strong base nature. Apart from that, inorganic salts formed in the neutralization steps upon reaction completion are undesirable for industry.

Amberlyst A-26 OH is a strong base, anionic, macroreticular polymeric resin based on the crosslinked styrene divinylbenzene copolymer containing quaternary ammonium groups. It is highly suitable to serve as a green catalyst. In its solid form, it is nonhazardous and

Table 1: Recent development in the synthesis of pseudoionone (PSI) derivatives.

	Starting material		Catalyst	Advantage(s)	Disadvantage(s)
	Aldehyde	Ketone			
1. [6]	Citral	Acetone	Activated hydrotalcites	(a) Low molar ratio of acetone to citral (b) PSI selectivity of 100%	Catalysts used are easily contaminated by CO_2
2. [7]	Citral	Acetone	KF on γ-alumina	High selectivity of PSI between 82% and 97%	
3. [8]	Citral	Acetone	$LiOH.H_2O$	(a) Conversion of 98.9% (b) Selectivity of 97.7%	Careful handling of LiOH is required as short exposure could cause serious residual injury
4. [9]	Citral	(a) Acentone (b) 2-Pentanone	Ca/Na on silica	(a) High yield of PSI derivative at 87.5% (b) Catalyst is reusable up to 10 times	(a) High molar ratio of 2-pentanone to citral is used (b) Average yield of PSI (acetone) of 61.1%
5. [10]	Citral	(a) 2-Octanone	Sodium ethoxide	(a) New PSI derivative discovered (b) High yield of PSI derivative at 87.6%	(a) No structure elucidation was done on the new PSI derivative synthesized (b) Highly corrosive catalyst used (c) Neutralisation step needed (d) Column chromatography elution system found not suitable

PSI, Pseudoionone.

can be used in a heterogeneous catalysis. After a reaction reaches completion, it can be recovered by simple filtration. Furthermore, many researches have shown that this catalyst can be regenerated with ease using a 1 M NaOH solution [12, 13]. Both of these excellent green approaches are highly demanded for its green organic synthesis qualities. This paper describes the aldol condensation of citral and 2-octanone using Amberlyst A-26 OH, with the manipulation of the reactant ratio, catalyst amount and temperature.

2 Materials and methods

2.1 Instrumentation

Ultraviolet-visible (UV-Vis) (Shimadzu UV 2450, Japan) analysis was run in ethanol, Fourier transform infrared (FTIR) (Perkin Elmer Model Spectrum GX, USA) and gas chromatography (GC)/GC-mass spectrometry (MS) analyses were performed on an Agilent 7890A (USA) gas chromatograph coupled with a mass spectrometer system of an Agilent 5975C inert mass selective detector with a triple-axis detector. The gas chromatograph was equipped with a fused silica capillary column DB-5 (5% phenylmethylpolysiloxane, 30 m×0.32 mm, film thickness 1.50 μm). The injector and interface were operated at 250°C and 300°C, respectively. The oven temperature was raised from 50°C to 300°C at a heating rate of 8°C/min and then isothermally held for 5 min. The constant head pressure was 0.6 bars. As a carrier, gas helium was used at 1.0 ml/min. The samples were injected in a pulsed split mode. The mass selective detector was operated at the ionization energy of 70 eV, in the 35–500 amu range with a scanning speed of 0.34 s and nuclear magnetic resonance (NMR)

(600 MHz, Bruker, USA) was used in the characterization process in the experiment. The calculation was done using an external calibration curve prepared from the pure product isolated, using preparative thin layer chromatography (hexane:ethyl acetate=9.5:0.5). All chemicals used were purchased from Aldrich (Reagent grade) and used without further purification.

2.2 Aldol condensation between citral and 2-octanone

The reaction was carried out in a 250 ml three-necked bottom flask equipped with a thermometer and a reflux condenser. Some 0.975 g (0.156 mmol) of Amberlyst A-26 OH was stirred in 30 ml of ethanol for 10 min. Citral (0.5 g, 3.12 mmol) and 2-octanone (4.00 g, 0.0312 mol) were added, and the mixture was heated at 60°C for 3.5 h. The reaction mixture was cooled to room temperature. The catalyst was filtered and washed with ethanol. The combined organic phases were concentrated by vacuum evaporation. The pure product was isolated by preparative thin layer chromatography with hexane:ethyl acetate (9.5:0.5) and characterised using UV-Vis, FTIR, GC-MS and NMR. 2-Octanone/citral molar ratio was tested first. Once the best molar ratio was achieved, the catalyst amount (5%, 10% and 15%) and temperature (25°C, 40°C and 60°C) were optimized.

3 Results and discussion

3.1 2-Octanone/citral molar ratio

Figure 1 shows the influence of the molar ratio of 2-octanone on the yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. The basic sites of Amberlyst A-26 OH are responsible
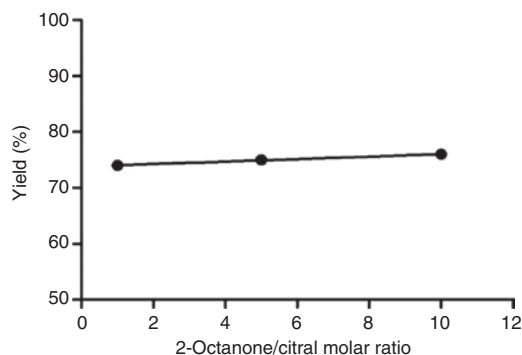
Figure 1: Effect of 2-octanone/citral molar ratio on yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. (Catalyst amount of 5%, 60°C, 3.5 h).

for the proton abstraction of the aldehyde or ketone. Increasing the molar ratio of 2-octanone/citral from 1 to 10 does not improve the yield significantly. The little increase in yield may be contributed to by the increased chances of α-proton abstraction from 2-octanone, therefore reducing the possibility of α-proton abstraction from the citral molecule. Thus, a molar ratio of 10 was chosen to investigate the effect of catalyst amount used.

3.2 Catalyst amount

The study on catalyst amounts of 5%, 10% and 15% (% mole of citral) was done to investigate its effect on the yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. It can be understood that the increase in the amount of catalysts allows higher chances of α-proton abstraction from citral that may lead to more side reaction products. Five percent catalyst usage was found to produce almost no side reaction products with a yield of 93% (Figure 2). Therefore, it
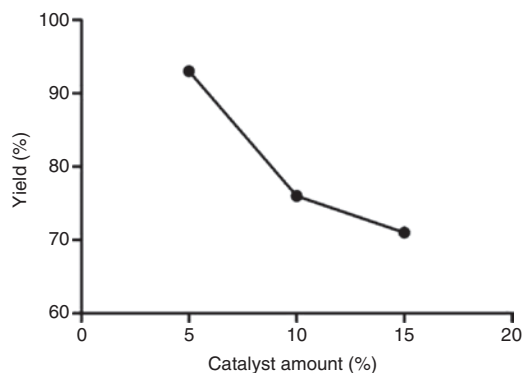

Figure 2: Effect of catalyst amount on yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. (2-Octanone/citral molar ratio of 10, 60°C, 3.5 h).

was selected to study the influence of temperature on the yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one.

3.3 Temperature

The effect of temperature on the yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one was evaluated at 25°C (room temperature), 40°C and 60°C. In Figure 3, it was observed that the yield increased with the increase of temperature. This is because a higher temperature provides more kinetic energy for the reaction that hastens the conversion rate of citral. At 60°C, a maximum yield of 93% was achieved.

3.4 Catalyst reusability

Amberlyst A-26 OH used in the reaction was regenerated from a basic treatment and reused several times without loss of activity. The catalyst was filtered after an experiment and washed several times with ethanol, followed by treatment with aqueous 1.0 M NaOH solution for 2 h. The catalyst was then washed with distilled water until the eluate was neutral. This efficient catalyst is proven to be economical, useful and suitable for this aldol condensation reaction with excellent regeneration and reusability shown. Table 2 shows the number of runs completed on the regenerated and reused Amberlyst A-26 OH on the aldol condensation of citral and 2-octanone.
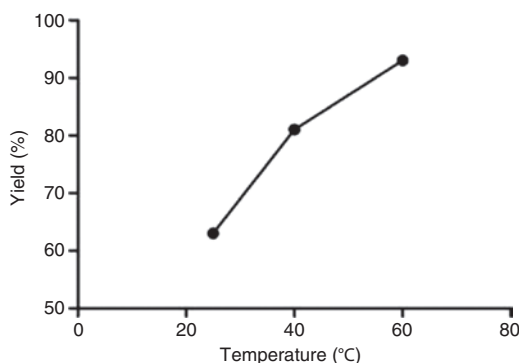

Figure 3: Effect of temperature on yield of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one. (2-Octanone/citral molar ratio of 10, catalyst amount of 5%, 3.5 h).

Table 2: Reusability of Amberlyst A-26 OH on the aldol condensation of citral and 2-octanone.

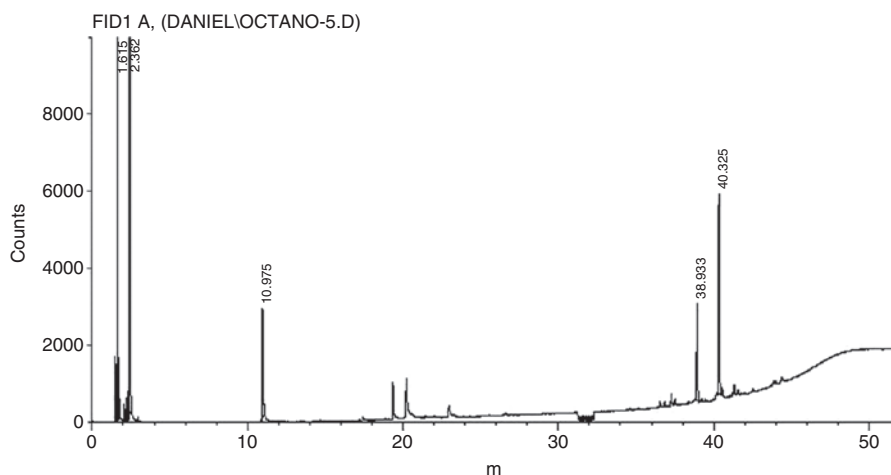| Number of reuse	1	2	3	4
Yield	93	91	89	90

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Figure 4: Gas chromatogram of the optimised parameters for aldol condensation of citral and 2-octanone.

3.5 GC-MS analysis

Figure 4 shows the chromatogram of the optimized reaction parameter carried out in the experiment. The peaks in the chromatogram are analysed using MS and the compounds are listed in Table 3.

The characteristic fragmentations in the mass spectrum of peaks 4 and 5 are m/z 262.3, m/z 179.2, m/z 109.1, m/z 81.1, m/z 69.1, m/z 69.1 and m/z 41.1. The molecular ion shown from the mass spectrum is the same as the molecular weight number of the expected 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers (Figure 6). As an initial assumption, E and Z isomers are expected to form because of the existence of E and Z citral isomers used as starting materials. Therefore, further confirmations were performed to confirm the structure of the 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers.

3.6 UV-Vis spectroscopy

Each compound gives out a characteristic wavelength when put under the UV-Vis test depending on its structure. Woodward's rules can be used to predict the particular wavelength. Figure 5 shows the UV-Vis spectrum of the isolated 11,15-dimethyl-hexadeca-8,10,14-trien-7-one
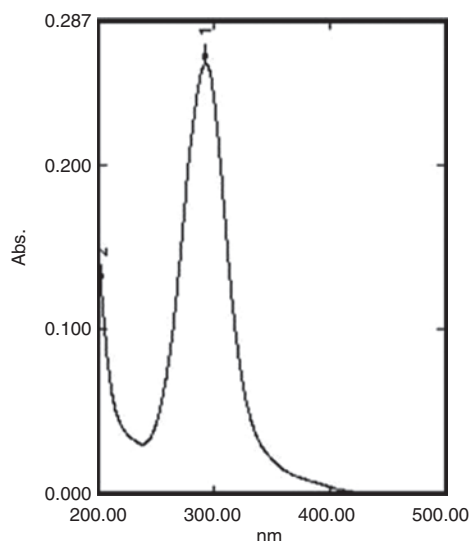

Figure 5: Ultraviolet-visible (UV-Vis) spectrum of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers.

isomers. In Table 4, it can be observed that the predicted UV-Vis wavelength number (293) is similar to the experimental wavelength number (292.6) of the 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers.

Table 4: Ultraviolet-visible (UV-Vis) wavelength prediction by Woodward's rules.

Structure	Woodward's rules
(Use Figure 6)	Acyclic dienone: 245 nm
	Double-bond-extending conjugation: 30 nm
	δ Alkyl group: 18 nm
	Observed: 293 nm
	Experimental value: 292.6 nm

Table 3: Gas chromatography-mass spectrometry (GC-MS) identification of chromatogram peaks.

Peak number	Compound
1	2-Octanone
2 and 3	Citral (neral and geranial)
4 and 5	11,15-Dimethyl-hexadeca-8,10,14-trien-7-one isomers

Table 5: 11,15-Dimethyl-hexadeca-8,10,14-trien-7-one isomers absorption peaks in Fourier transform infrared (FTIR) spectrum.
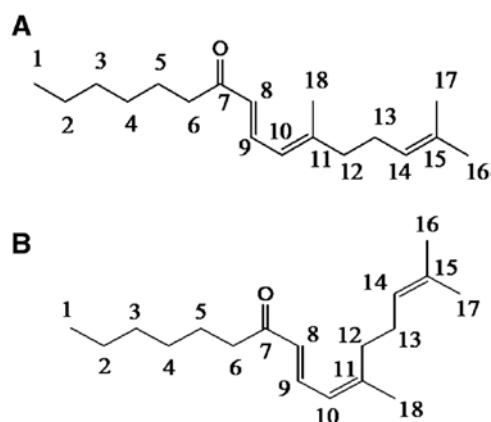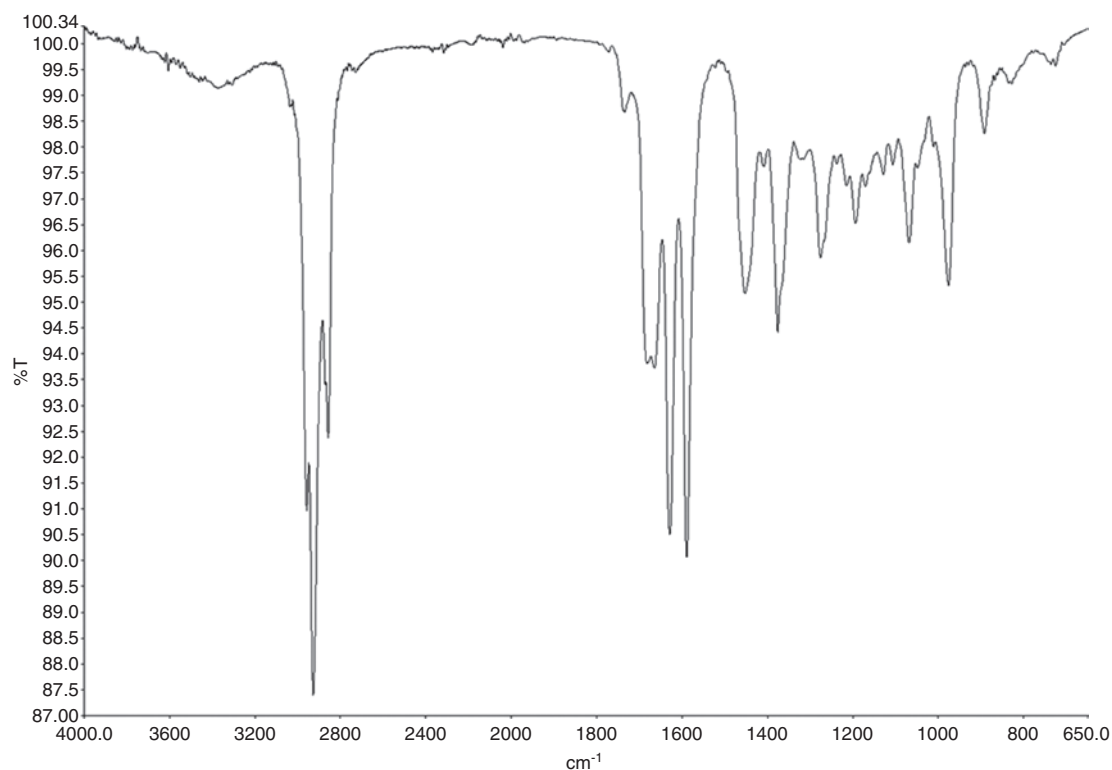
Functional group	Absorption value (cm^{-1})
sp^3 C-H stretch	2956.34, 2927.31, 2857.46
C=O stretch	1680.83
C=C	1628.72, 1588.47
-CH$_3$ bend	1452.02, 1376.06
C⟩=O stretch C	1275.89, 1194.05
sp^2 C-H out of plane bend	976.57, 891.68

3.7 FTIR spectroscopy

FTIR provides powerful information on the functional group present in the compound. Figure 7 shows the FTIR spectrum of the isolated 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers. Table 5 summarises the absorption peak in the FTIR spectrum where one can observe that the C=O stretch at 1680.83 cm^{-1} is the result of the conjugation effect where C=O stretch absorbs at a lower frequency than normal. The C=C absorption at 1628.72 cm^{-1} and 1588.47 cm^{-1} absorptions belong to the C=C bond.

3.8 NMR spectroscopy

The structures of dimethyl-hexadeca-8,10,14-trien-7-one are characterized using ^{1}H (Figure 8A–D) and ^{13}C (Attached Proton Test) NMR spectroscopy. Figure 6 shows the two isomeric structures of dimethyl-hexadeca-8,10,14-trien-7-one synthesized. The double bond at the carbon positions 8 and 9 is the bond formed in the aldol condensation reaction. This double bond raises the possibility of a *cis trans* isomerism in the new structure formed. From the ^{1}H NMR spectrum obtained, the proton positions 8 and 9 of both isomers are assigned to a *trans* configuration because of the *j* value of 15 Hz shown.

Figure 6: Expected structures.

Figure 7: Fourier transform infrared (FTIR) spectrum of isolated 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers.
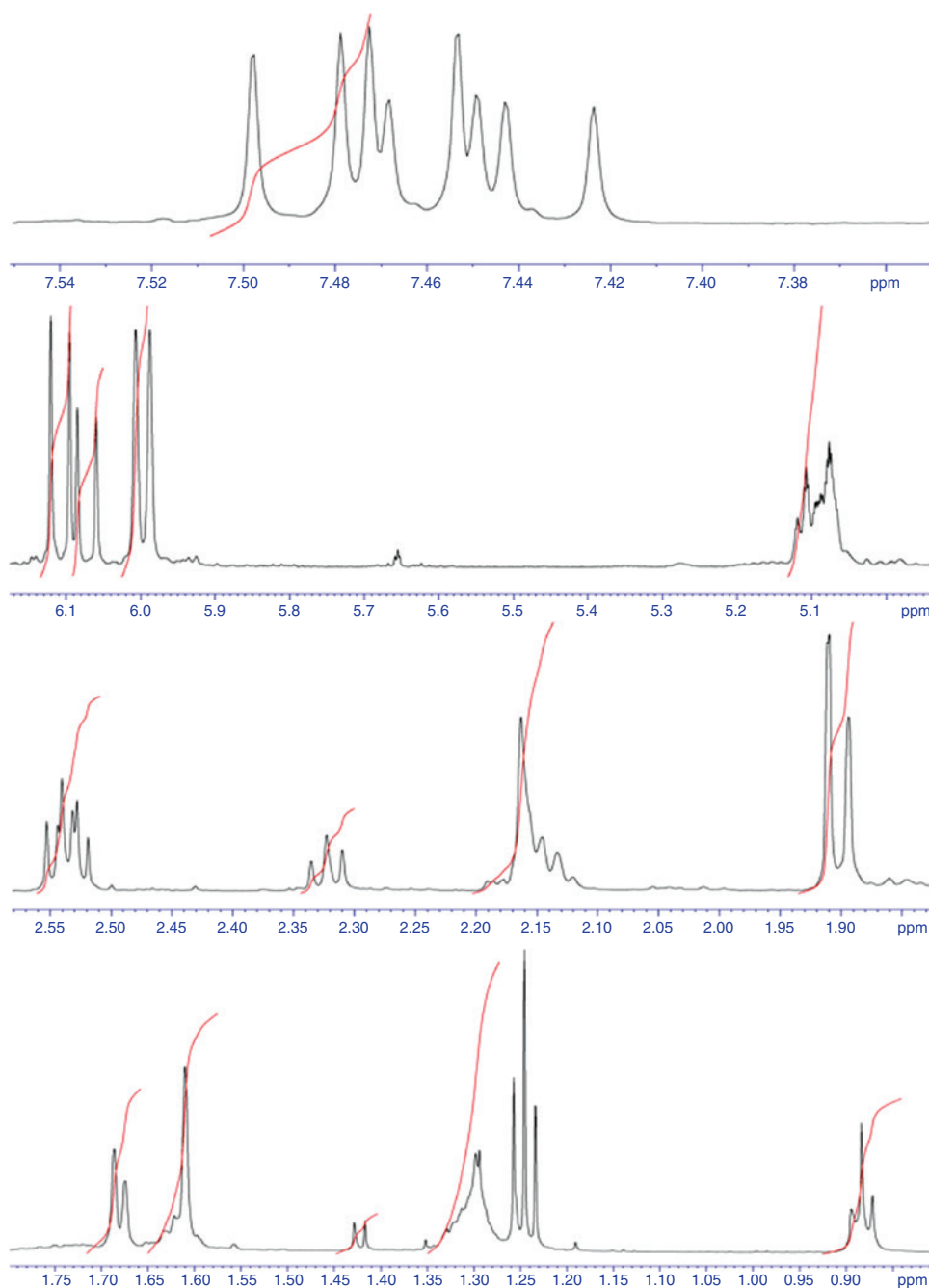
Figure 8: [1]H Nuclear magnetic resonance (NMR) spectrum of 11,15-dimethyl-hexadeca-8,10,14-trien-7-one isomers.

Due to the use of the starting material citral which consisted of geranial and neral as Z and E isomer, respectively, the PSI derivative formed in the aldol condensation process was expected to have a mixture form of Z and E isomers too. This was because the chain at the stereoisomer point of Z and E isomers was not involved in the aldol condensation process.

^{13}C NMR spectroscopy is a valuable tool to identify E and Z isomerism. The gamma effect shown by the E and Z isomers allows us to differentiate them by their chemical shift shown. A gamma effect is defined as the replacement of an H by X on the second atom. An alkyl group which is *cis* to a substituent will have a lower frequency (upfield) of the isomer in which the carbon substituent is *cis* to a hydrogen [14]. Therefore, the gamma effect of carbon at positions 12 and 18 is identified. The chemical shifts at carbon 18 of 25.7 Hz and 24.6 Hz belong to the Z and E isomers, respectively. This is because the CH_3 group of carbon 18 is *cis* to an H rather than a long alkyl chain, as shown in the E isomer. This also applies to the chemical shifts at carbon 12 of 31.6 Hz

and 33.0 Hz where they belong to the Z and E isomers, respectively. By assigning these two important peaks of the spectrum, we can distinguish the two sets of ^{1}H and ^{13}C data of which the major intensity peaks belong to the Z isomer while the minor intensity peaks belong to the E isomer.

Being closely related to the structure of PSI, the ^{1}H and ^{13}C NMR of PSI are referred to as the assignation of the PSI derivative and the signals summarized below.

(11Z)-11,15-dimethyl-hexadeca-8,10,14-trien-7-one ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.48(C$_9$-H, 1H, dd, J=15, 11.4), 6.11(C$_8$-H, 1H, d, J=15), 6.00(C$_{10}$-H, 1H, d, J=12), 5.07(C$_{14}$-H, 1H, t, J=6.6), 2.54(C$_6$-H, 2H, t, J=7.2), 2.32(C$_{12}$-H$_a$, 1H, t, J=7.8), 2.16(C$_5$-H, 2H, overlap), 2.14(C$_{12}$-H, 1H, t, J=overlap), 1.91(C$_{16}$-H, 3H, s), 1.68(C$_{17}$-H, 3H, s), 1.62(C$_{13}$-H$_a$, 1H, t, J=overlap), 1.61(C$_{18}$-H, 3H, s), 1.42(C$_{13}$-H$_b$, 1H, d, J=6.6), 1.35-1.26(m, 6H, bulk-CH$_2$), 0.88(C$_1$-H, 3H, J=6.6).^{13}C NMR (600 MHz, CDCl$_3$): δ 201.4(C$_7$=O), 151.0(C$_{11}$=C), 138.7(C$_9$=C), 132.3(C$_{15}$=C), 127.5(C$_8$), 123.7(C$_{10}$=C), 123.3(C$_{14}$=C), 41.0(C$_6$), 40.4(C$_5$), 31.6(C$_{12}$), 29.0(C$_4$), 26.3(C$_{13}$), 25.7(C$_{18}$), 24.5(C$_3$), 22.5(C$_2$), 17.7(C$_{16}$), 17.5(C$_{17}$), 14.0(C$_1$).

(11E)-11,15-dimethyl-hexadeca-8,10,14-trien-7-one ^{1}H NMR (600 MHz, CDCl$_3$): 7.45(C$_9$-H, 1H, dd, J=15, 11.4), 6.07(C$_8$-H, 1H, d, J=15.6), 6.00(C$_{10}$-H, 1H, d, J=12), 5.10(C$_{14}$-H, 1H, t, J=6.6), 2.52(C$_6$-H, 2H, t, J=7.2), 2.32(C$_{12}$-H$_a$, 1H, t, J=7.8), 2.16(C$_5$-H, 2H, overlap), 2.14(C$_{12}$-H, 1H, t, J=overlap), 1.89(C$_{16}$-H, 3H, s), 1.67(C$_{17}$-H, 3H, s), 1.62(C$_{13}$-H$_a$, 1H, t, J=overlap), 1.61(C$_{18}$-H, 3H, s), 1.42(C$_{13}$-H$_b$, 1H, d, J=6.6), 1.35-1.26(m, 6H, bulk-CH$_2$), 0.88(C$_1$-H, 3H, J=6.6).^{13}C NMR (600 MHz, CDCl$_3$): δ 201.4(C$_7$=O), 151.1(C$_{11}$=C), 138.5(C$_9$=C), 132.6(C$_{15}$=C), 127.4(C$_8$=C), 124.6(C$_{10}$), 123.2(C$_{14}$=C), 40.8(C$_6$), 40.4(C$_5$), 33.0(C$_{12}$), 29.0(C$_4$), 26.9(C$_{13}$), 24.6(C$_{18}$), 24.6(C$_3$), 22.5(C$_2$), 17.7(C$_{16}$), 17.5(C$_{17}$), 14.0(C$_1$).

4 Conclusion

Amberlyst A-26 OH is proven to be a suitable and efficient catalyst for the aldol condensation between citral and 2-octanone. Compared to the previous article that newly discovered 11,15-dimethylhexadeca-8,10,14-trien-7-one, this experimental procedure seems to be more environmentally friendly, where the catalyst is safe, cheap, requires no neutralization step, can be recovered by simple filtration, regenerated and reused. It also gives an excellent yield of 11,15-dimethylhexadeca-8,10,14-trien-7-one of 93.0% (2-octanone/citral molar ratio of 10, catalyst amount of 5% of citral, 60°C, 3.5 h) which is higher than the mentioned finding in the previous article (87.6%). In summary, this paper describes a very simple route to

11,15-dimethylhexadeca-8,10,14-trien-7-one. Our procedure presents advantages including environmentally friendly reaction conditions, needing a shorter reaction time, having a simple work-up procedure and very high yields.

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Bionotes

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Daniel J.W. Chong is a 2015 Chemistry (MSc) graduate from the National University of Malaysia. After graduation, Daniel is currently developing his laboratory synthetic skills in the University of Malaya as a research officer. One of his dreams is to go industrial scale in the field of medicinal chemistry. As a preparation for that, he has been actively practicing his skills set to get into the National University of Singapore for his PhD degree in upcoming years.

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Jalifah Latip

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