

CrossMark
click for updatesCite this: *RSC Adv.*, 2017, 7, 3214

Solvent-free Knoevenagel reaction catalysed by reusable pyrrolidinium base protic ionic liquids (PyrriLs): synthesis of long-chain alkylidenes†

R. C. M. Alves Sobrinho,^a P. M. de Oliveira,^a C. R. Montes D'Oca,^a D. Russowsky^b and M. G. Montes D'Oca^{*a}

In this work, an efficient and reusable pyrrolidinium ionic liquid (PyrriL) catalysis system was developed and used in a Knoevenagel condensation reaction of long-chain aldehydes with several 1,3-dicarbonyl compounds. The Knoevenagel condensation promoted by the PyrriLs proceeded smoothly and cleanly in solvent-free conditions, yielding good quantities of the condensation products, long-chain alkylidenes. Moreover, this catalysis system was recyclable at least four times, and no significant loss of activity was observed. This protocol has notable advantages, such as ease of workup and convenient reuse of the ionic liquid, which could help reduce disposal costs and contribute to the development of new catalysts in chemical processes.

Received 21st October 2016
Accepted 15th December 2016

DOI: 10.1039/c6ra25595g

www.rsc.org/advances

Introduction

The Knoevenagel condensation is a powerful, general, versatile and significant reaction for the formation of carbon–carbon bonds.^{1,2} The classic Knoevenagel transformation³ occurs between aldehydes and active methylene hydrogen compounds, with ammonia or another amines as catalysts in organic solvents. The reaction is considered to be a modification of the aldol condensation.⁴

The synthesis of benzylidenes or alkylidenes, important intermediate products, *via* the Knoevenagel reaction is largely related to structural variations in different nucleophiles, such as 1,3-ketoesters,^{2,5} diketones,² ketothioesters,² malonates, malononitriles,⁶ keto amides, and cyclic esters, and with different aromatic⁷ or aliphatic aldehydes.⁸ Recently, long-chain alkylidene malonates (LoCAMs) have been identified with a novel class of KATs (protein acetyltransferase) modulators, and pentadecylidene malonate, a simplified analogue of anacardic acid, exhibits a good modulation of the activity of histone acetyltransferases (Fig. 1).⁸

Another example comes from the total synthesis of the anticoagulant flocoumafen. The key synthetic step involves Knoevenagel condensation with ethyl cyanoacetate and *p*-methoxybenzaldehyde in the presence of acetic acid and

pyrrolidine; this process generates an excellent yield of the desired product.⁹

In addition, different catalytic systems (such as amines⁵, Lewis acids, and solvents (such as benzene,⁵ toluene, dichloromethane¹⁰ and tetrahydrofuran) have been used, and Knoevenagel condensation in ionic liquids was recently demonstrated as a strongly solvent-dependent process.¹¹

The use of a triethylamine–toluene system in place of pyridine was shown to provide ease of handling, separation, and recycling of the solvent and the catalyst. In that case, the synthesis of cinnamic acids was successfully performed using a pyridine-free Knoevenagel condensation, either in the presence of triethylamine as a solvent or in combination with toluene with catalytic amounts of piperidine.¹²

Knoevenagel condensation of β -ketothioesters with various aldehydes proceeds efficiently in the presence of molecular sieves (MS 5A), and molecular sieves in CH_2Cl_2 was the most effective. The reaction was examined using several β -keto-thioesters and β -ketoesters with various aromatic and aliphatic aldehydes, and the Knoevenagel adducts were obtained in

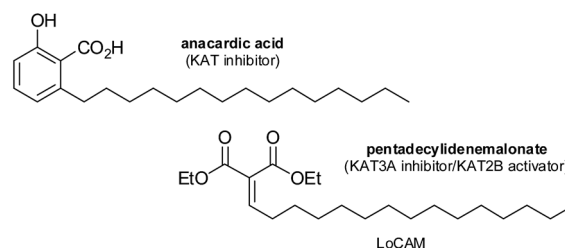


Fig. 1 KAT inhibitors and activator: anacardic acid and pentadecylidene malonate, respectively.

^aLaboratório Kolbe de Síntese Orgânica, Escola de Química e Alimentos, Universidade Federal do Rio Grande, Av. Itália Km 08 s/n, Rio Grande-RS, Brazil. E-mail: dqmdoca@furg.br; Tel: +55 5332336964

^bLaboratório de Síntese Orgânica, Instituto de Química, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves 9500, Porto Alegre-RS, Brazil

† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR analysis for all compounds. See DOI: 10.1039/c6ra25595g

yields of 20% to 95%.¹³ In this work the reaction conditions were mild, and no self-condensation products of the aldehydes were observed. The amount of aldehydes can be reduced to 1.5 equiv. without affecting the yield, although a longer reaction time is necessary. The use of excessive amounts (4–6 equiv.) of aliphatic aldehydes in some cases is necessary to obtain a sufficient yield of the products in a reduced reaction time when the reaction is slow.

According to the literature,¹⁴ a large number of β - and β,β -substituted Morita–Baylis–Hillman (MBH) adducts can be synthesised using Knoevenagel condensation in piperidine and acetic acid or Lewis acid. For the synthesis of β -ketoesters, it was demonstrated that the stereoselectivity of the reaction is improved by alteration of various substituents on the ketone and ester group and various aldehydes. In addition, a Z-selective Knoevenagel condensation can be achieved by the use of *tert*-butyl acetoacetate with either aromatic or aliphatic aldehydes, although this results in low chemical yield.

In recent years, ionic liquids (ILs) have emerged as a greener alternative to commonly used organic solvents and catalysts. Their characteristics, combined with their low volatility, non-flammable nature, thermal stability, and capacity for reuse as catalysts, have made ILs an environmentally friendly option for organic synthesis.¹⁵ However, they are expensive (about 30 000 times greater than common organic solvents); therefore, the use of inexpensive cations and anions is essential to expand their use.²

However, few studies have reported on the use of ILs for both their solvent and catalytic functions; ILs have been used most commonly as solvents in the presence of another catalyst/promoter system¹⁶ or as catalysts in the presence of a solvent.^{6,17,18}

Under ultrasonic irradiation, hexamethylenetetramine (HMTA)–AcOH–H₂O, a protic ionic liquid (PIL) solvent–catalyst, has been used in the Knoevenagel reaction of aromatic aldehydes with ethyl 2-cyanoacetate. However, in solvent-free conditions, the mixture solidifies as soon as the catalyst is added, making the reaction yield low.¹⁹

Anouti *et al.* detailed the synthesis and characterisation of ILs using pyrrolidine as the cation source and different organic and inorganic anions in an easily reproducible experimental procedure.²⁰ They found that pyrrolidinium-based protic ILs (PyrrILs, Fig. 2) have a relatively low cost and low toxicity and exhibit a large electrochemical window compared to other protic ILs. In addition, PyrrILs are superionic liquids with wide application for fuel cell devices, thermal transfer fluids, and acid-catalysed reaction media as an alternative to conventional inorganic acids.

As part of our ongoing efforts to synthesise new fatty derivatives,^{21–25} in this study, we describe the use of PyrrILs 1–3 derived from formate, acetate, and trifluoroacetate (Fig. 2) as a catalyst to the synthesis of long-chain alkylidenes. The Knoevenagel reaction was investigated using several classic 1,3-dicarbonyl compounds (β -ketoesters, 1,3-diketones, Meldrum's acid, and malonates) with long aldehydes in a solvent-free media.

Results and discussion

Initially, Knoevenagel condensation was investigated using the classic experimental protocol, and the catalysts pyrrolidine (Pyrr) or piperidine (Pip) and acetic acid were added directly to a reactional flask containing both 1,3-dicarbonyl compound

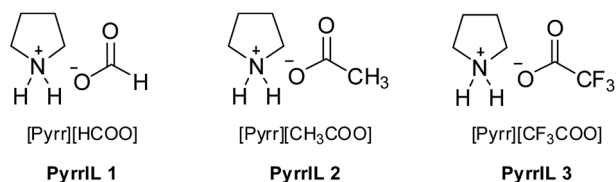


Fig. 2 Pyrrolidinium ionic liquids (PyrrILs) 1–3.

Table 1 Synthesis of long-chain alkylidene **6g** from Knoevenagel condensation

Ent.	Catalyst	Loading (mol%)	<i>T</i> (°C)	Time (h)	Yield (%)
1	Pyrr + CH ₃ COOH ^a	10	0	3	60
2	Pip + CH ₃ COOH ^a	10	0	3	63
3	[Pyrr][HCOO], 1	10	0	1.5	69
4	[Pyrr][CH ₃ COO], 2	10	0	1.5	80
5	[Pyrr][CF ₃ COO], 3	10	0	1.5	68
6	[Pyrr][CH ₃ COO], 2	5	0	1.5	65
7	[Pyrr][CH ₃ COO], 2	20	0	1.5	60
8	[Pyrr][CH ₃ COO], 2	10	–20	1.5	56
9	[Pyrr][CH ₃ COO], 2	10	20	1.5	65
10	[Pip][CH ₃ COO] (solid catalyst)	10	0	1.5	70

^a Reaction performed with CH₂Cl₂ (2 mL), with addition of pyrrolidine or piperidine and acetic acid directly to the reactional flask.



Table 2 Synthesis of long-chain alkylidenes **6a–l** under catalysis with pyrrolidinium acetate (**2**, [Pyrr][CH₃COO])

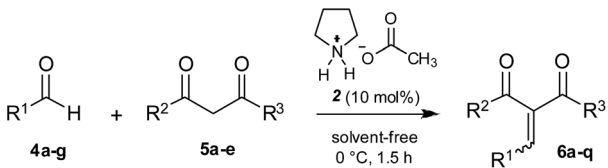

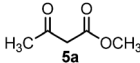
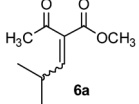

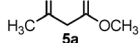
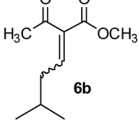

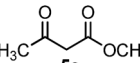
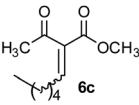

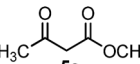
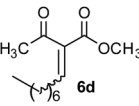

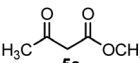
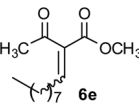

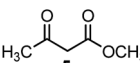
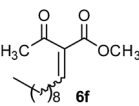

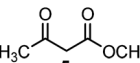
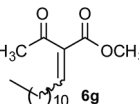

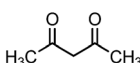
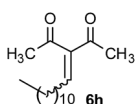

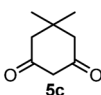
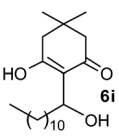

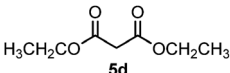
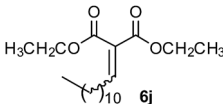

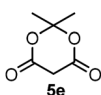
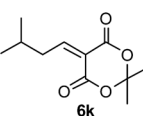

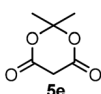
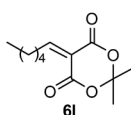
				
Entry	Aldehydes (4a–g)	5a–e	Alkylidenes (6a–q)	Yield (%), (<i>E</i> : <i>Z</i> ratio) ^a
1				83 (1 : 2)
2				77 (1 : 1.8)
3				80 (1 : 1.5)
4				89 (1 : 2.1)
5				72 (1 : 2)
6				90 (1 : 2.1)
7				80 (1 : 2.5)
8				70
9				73
10				70
11				90
12				95



Table 2 (Contd.)

Entry	Aldehydes (4a–g)	5a–e	Alkylidenes (6a–q)	Yield (%), (<i>E</i> : <i>Z</i> ratio) ^a
13				92
14				85
15				85
16				80
17				83

^a Ratio determined by gas chromatography/mass spectrometry.

and aldehyde.⁹ The Knoevenagel reaction between long-chain dodecanaldehyde (4g) and methyl acetoacetate (5a) was tested with loading of 10 mol% of catalyst at 0 °C and in the presence of anhydrous methylene chloride. The reactions were monitored by thin-layer chromatography (TLC), and the consumption of aldehyde was measured. However, pyrrolidine and piperidine in the presence of acetic acid each demonstrated low yields of the product 6g after 3 h. The results are shown in Table 1, entries 1 and 2, respectively.

Based on these results, we decided to investigate the Knoevenagel reaction employing PyrriILs 1–3 (Fig. 2).

The PyrriILs 1–3 were obtained using the same experimental protocol described by Anouti *et al.*²⁰ The nuclear magnetic resonance spectroscopic data of PyrriILs were in agreement with the literature.²⁰ Next, the behaviour and catalytic activity of the heterogeneous PyrriILs 1–3 were initially investigated in the Knoevenagel condensation between dodecanaldehyde (4g) and methyl acetoacetate (5a) using 10 mol% of catalyst at 0 °C in a solvent-free condition.

The reaction using PyrriIL 1 was monitored by TLC and the total consumption of aldehyde 4g was observed after 1.5 h at 0 °C. At this point, the reaction was considered complete, and a 69% yield of product 6g was recorded (Table 1, entry 3). Then

PyrriILs 2 and 3 were tested with loading of 10 mol% under the same experimental conditions (Table 1, entries 4 and 5). Better catalytic behaviour was observed with pyrrolidinium acetate (2) (80%, Table 1, entry 4) than with the catalysts pyrrolidinium trifluoroacetate (3) and pyrrolidinium formate (1) (Table 1, entries 5 and 3, respectively).

The loading of catalyst 2 was then investigated, with the reactions performed with 5 mol% and 20 mol% (Table 1, entries 6 and 7, respectively). The use of 5 mol% provided a 65% yield of the product (Table 1, entry 6), while the use of 20 mol% resulted in a lower yield (Table 1, entry 7). Thus, 10 mol% was chosen for the Knoevenagel reactions catalysed by PyrriIL (Table 1, entry 4).

Next, we studied the influence of temperature on the reactions. In addition to performing the reactions at 0 °C, the reactions were performed at –20 °C and 20 °C (Table 1, entries 8 and 9). Both temperatures resulted in lower yields than the reactions at 0 °C (Table 1, entries 3–7).

In addition, the Knoevenagel reaction employing 10 mol% of piperidinium acetate ([Pip][CH₃COO]) was investigated. The catalyst [Pip][CH₃COO] was obtained from stoichiometric amount of piperidine and acetic acid using the same experimental protocol used for PyrriIL synthesis. The [Pip][CH₃COO] was isolated by crystallization in dry toluene. The reaction using



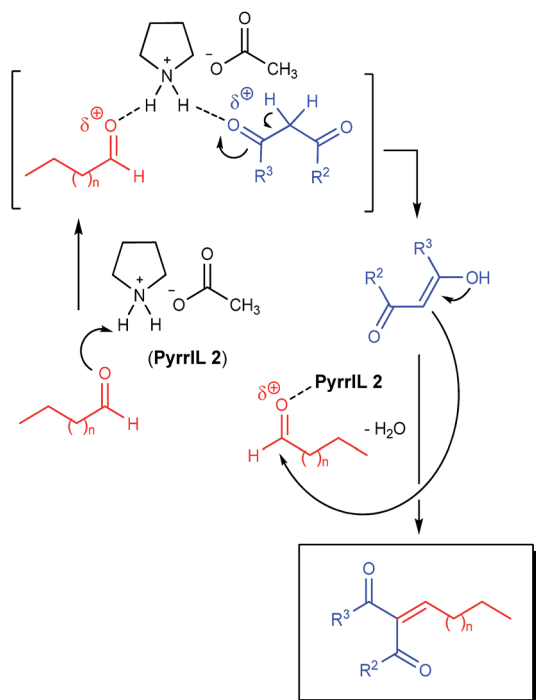
this solid catalyst $[\text{Pip}][\text{CH}_3\text{COO}]$ was monitored by TLC and resulted in a 70% yield of the product **6g** (Table 1, entry 10).

From these results, it was concluded that the best conditions for the Knoevenagel reaction to synthesis of long-chain alkylidene **6g** would employ PyrriL **2**, synthesised singly, at a load of 10 mol% at 0 °C (Table 1, entry 4).

Thus, the Knoevenagel reaction employing PyrriL **2** was investigated using classic 1,3-dicarbonyl compounds (β -ketoesters, 1,3-diketones, Meldrum's acid, and malonates) with long-chain aldehydes. This same experimental protocol was used for the synthesis of long-chain alkylidenes **6a–q** from alkyl aldehydes **4a–g** and 1,3-dicarbonyl compounds **5a–e** (Table 2).

All tested examples resulted in good to reasonable alkylidene yields (70–95%), demonstrating the catalytic effectiveness of PyrriL **2** in the several alkylidene syntheses. These results indicate that Knoevenagel condensation possesses catalytic versatility and efficiency, even in the presence of 1,3-dicarbonyl compounds with different pK_a values, resulting in good yields of the products (Table 2, entries 7–17). As expected, good yields were observed in reactions performed with methyl acetoacetate (Table 2, entries 1–7) and lower yields were observed with ethyl malonate (70%, Table 2, entry 10). Moreover, only the enol **6i** from aldol product was observed in reaction performed with dimedone (**5c**) (73%, Table 2, entry 9). The best results were obtained when Meldrum's acid was used as the 1,3-dicarbonyl compound (80–95%, Table 2, entries 11–17).

Based on the literature,¹⁹ a tentative mechanistic pathway of the Knoevenagel reaction to synthesis of long-chain alkylidenes catalysed by PyrriL is proposed. We believe that the reaction may proceed through the formation of a partial oxonium ion formed from long-chain aldehyde and PyrriL **2** (Scheme 1). The reaction



Scheme 1 The suggested pathway to the synthesis of long-chain alkylidenes via the Knoevenagel condensation catalysed by PyrriL.

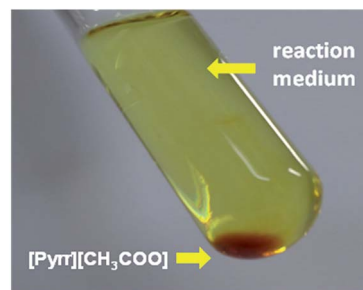


Fig. 3 Solvent-free Knoevenagel condensation catalysed by $[\text{PyrriL}][\text{CH}_3\text{COO}]$ (**2**).

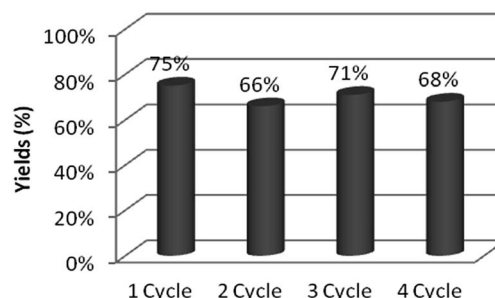


Fig. 4 Results of the recycling of catalyst PyrriL **2** in the Knoevenagel reaction under solvent-free conditions.

of the oxonium ion, which is sufficiently electrophilic, with the enol form of 1,3-dicarbonyl compounds, together with the loss of H_2O , could lead to formation of the long-chain alkylidenes.

In addition, all PyrriLs tested (**1–3**) were insoluble in the reaction medium (Fig. 3); therefore, repeated reuse tests were performed. For this purpose, the reactions were scaled up, with the same optimised experimental conditions maintained. Repeated experiments were carried out with dodecanaldehyde (**4g**) and methyl acetoacetate (**5a**) and 10 mol% of $[\text{PyrriL}][\text{CH}_3\text{COO}]$ (**2**) at 0 °C. After each cycle, the PyrriL **2** was decanted by centrifugation in the reactional flask, the supernatant was removed, and the process was repeated with the addition of new reagents in the reactional flask. The first reuse resulted in a slight decrease in yield. Catalytic activity was maintained well, and no decrease in the activity of PyrriL was observed, even after the fourth reuse. The catalytic performance over four cycles is depicted in Fig. 4.

Our experiments show that the employment of PyrriLs as a catalytic system in the Knoevenagel reaction with aliphatic aldehydes and 1,3-dicarbonyl compounds resulted in good yield of alkylidenes. In addition, this technique can be performed easily, with readily available, inexpensive starting materials, and the products exhibit high stability and can be stored in air without any sign of degradation.

Conclusions

In this work, the synthesis of long-chain alkylidenes (fatty alkylidenes) was demonstrated under PyrriLs catalysis and



solvent-free conditions. The products showed good yields (70–90%) following Knoevenagel condensation, using classic 1,3-dicarbonyl compounds and long-chain aldehydes, in a few hours and using an eco-friendly approach. In addition, experiments with recycling the catalyst [Pyrr][CH₃COO] make this method an attractive alternative to existing methods for the synthetically useful Knoevenagel reaction, and catalytic activity is well maintained after four cycles of catalysis.

We are in the process of synthesising a series of lipophilic γ -amino-butyric acid derivatives *via* long-chain β -alkyl- γ -nitro-esters using fatty alkylidenes **6a–q** as a building block.

Experimental

Apparatus and chemistry

The reagents were purchased from Aldrich Chemical Co. and used without further purification. All organic solvents used for the synthesis were of analytical grade. Column chromatography was performed using a silica gel 60 A (ACROS Organics, 0.035–0.070 mesh). The reactions were monitored using thin-layer chromatography (TLC) performed with plates containing silica gel (Merck 60 GF245), and the spots were visualised using iodine. Yields refer to chromatographically and spectroscopically homogeneous materials. Infrared (IR) spectra were measured on a Shimadzu PRESTIGIE-21 FT-IR spectrophotometer. The NMR spectra were recorded using a Bruker AVANCE III 400 spectrometer (¹H at 400 MHz and ¹³C at 100 MHz) and a Varian VNMRs 300 spectrometer (¹H at 300 MHz and ¹³C at 75.5 MHz) in deuteriochloroform (CDCl₃) as the solvent. The chemical shift data are reported in units of δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. The coupling constants (³J) are reported in Hz and refer to apparent peak multiplicities. High resolution mass spectra (HRMS) were recorded on Waters XEGO G2 Q-TOF Mass Spectrometer.

Synthesis

General procedure for the synthesis of long-chain alkylidene 6a–q. To a round-bottom flask equipped with a magnetic stirring bar were added aldehyde **4a–i** (5 mmol) and 1,3-dicarbonyl **5a–e** (7.5 mmol), and the system was cooled to 0 °C. Immediately, the IL [Pyrr][CH₃COO] PyrrIL 2 (10 mol%) was added, with stirring maintained at 0 °C for 1.5 h. The reaction was monitored by TLC with hexane : ethyl acetate (80 : 20 ratio) as eluent. After completion of the reaction, the raw product was purified by flash column chromatography on a silica gel, with hexane/ethyl acetate (95 : 05) as eluent, to yield alkylidene **6a–q**. The purified products were analysed by proton and carbon NMR, IR, and ESI-MS/MS.

(E/Z)-Methyl-2-acetyl-4-methylpent-2-enoate (6a). Yellow oil. Yield: 83%. IR (film, ν_{\max} cm^{−1}): 1224, 1253, 1365, 1465, 1637, 1699, 1730, 2872, 2966; ¹H NMR (CDCl₃, 400 MHz): δ 6.71 (d, 1H, *J* = 12.0 Hz, isomer *E*), 6.62 (d, 1H, *J* = 12.0 Hz, isomer *Z*), 3.83 (s, 3H, isomer *Z*), 3.78 (s, 3H, isomer *E*), 2.67 (m, 1H, isomers *Z*, *E*), 2.37 (s, 3H, isomer *E*), 2.31 (s, 3H, isomer *Z*), 1.09 (d, *J* = 8.0 Hz, 6H, isomer *Z*), 1.05 (d, 6H, *J* = 4.0 Hz, isomer *E*).

¹³C NMR (CDCl₃, 100 MHz): δ 195.0, 167.0, 148.1, 147.9, 137.5, 52.1, 52.0, 38.9, 38.1, 31.2, 28.3, 28.2, 26.9, 22.4, 22.3. HRMS calculated for C₉H₁₄O₃ [M – H][−] 169.0870; found 169.0858.

(E/Z)-Methyl-2-acetyl-5-methylhex-2-enoate (6b). Yellow oil. Yield: 77%. IR (film, ν_{\max} cm^{−1}): 1224, 1253, 1369, 1436, 1637, 1701, 1726, 2872, 2958; ¹H NMR (CDCl₃, 400 MHz): δ 6.95 (t, 1H, *J* = 8.0 Hz, isomer *E*), 6.88 (t, 1H, *J* = 8.0 Hz, isomer *Z*), 3.84 (s, 3H, isomer *Z*), 3.79 (s, 3H, isomer *E*), 2.36 (s, 3H, isomer *E*), 2.32 (s, 3H, isomer *Z*), 2.21 (t, 2H, *J* = 8.0 Hz, isomer *Z*), 2.15 (t, 2H, *J* = 8.0 Hz, isomer *E*), 1.82 (m, 1H, isomer *Z*, *E*), 0.96–0.93 (m, 6H, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.0, 167.0, 148.1, 147.9, 137.5, 52.1, 52.0, 38.9, 38.2, 31.2, 28.3, 28.2, 26.9, 22.4, 22.4. HRMS calculated for C₁₀H₁₆O₃ [M – H][−] 183.1032; found 183.1029.

(E/Z)-Methyl-2-acetyloct-2-enoate (6c). Yellow oil. Yield: 80%. IR (film, ν_{\max} cm^{−1}): 1240, 1251, 1379, 1462, 1637, 1722, 2860, 2956; ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (t, 1H, *J* = 8.0 Hz, isomer *E*), 6.87 (t, 1H, *J* = 8.0 Hz, isomer *Z*), 3.83 (s, 3H, isomer *Z*), 3.79 (s, 3H, isomer *E*), 2.37 (s, 3H, isomer *E*), 2.32 (s, 3H, isomer *Z*), 1.57–1.44 (m, 2H, isomer *Z*, *E*), 1.38–1.22 (m, 6H, isomer *E*, *Z*), 0.93 (m, 8H, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.2, 167.0, 149.5, 149.2, 137.7, 136.9, 52.1, 52.1, 31.4, 30.1, 29.2, 28.1, 26.9, 22.4, 22.4, 13.9. HRMS calculated for C₁₁H₁₈O₃ [M – H][−] 197.1172; found 197.1174.

(E/Z)-Methyl-2-acetyldec-2-enoate (6d). Yellow oil. Yield: 89%. IR (film, ν_{\max} cm^{−1}): 1247, 1253, 1365, 1436, 1637, 1714, 2856, 2954; ¹H NMR (CDCl₃, 400 MHz): δ 6.95 (t, 1H, *J* = 8.0 Hz, isomer *E*), 6.88 (t, 1H, *J* = 8.0 Hz, isomer *Z*), 3.85 (s, 3H, isomer *Z*), 3.80 (s, 3H, isomer *E*), 2.38 (m, 8H, isomer *E*, *Z*), 1.57–1.44 (m, 2H, isomer *Z*, *E*), 1.38–1.22 (m, 8H, isomer *E*, *Z*), 0.93–0.86 (m, 3H, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.2, 166.9, 149.4, 149.2, 136.9, 52.0, 31.7, 30.1, 29.4, 29.2, 28.9, 28.6, 28.4, 26.8, 22.6, 14.0. HRMS calculated for C₁₃H₂₂O₃ [M + H]⁺ 225.1485; found 225.1488.

(Z)-Methyl-2-acetylundec-2-enoate (6e). Yellow oil. Yield: 72%. IR (film, ν_{\max} cm^{−1}): 1226, 1381, 1438, 1637, 1726, 2856, 2954; ¹H NMR (CDCl₃, 400 MHz): δ 6.95 (t, 1H, *J* = 8.0 Hz, isomer *E*), 6.88 (t, 1H, *J* = 8.0 Hz, isomer *Z*), 3.85 (s, 3H, isomer *Z*), 3.80 (s, 3H, isomer *E*), 2.38–2.23 (m, 8H, isomer *E*, *Z*), 1.51 (m, 2H, isomer *E*, *Z*), 1.28 (m, 10H, isomer *E*, *Z*), 0.91–0.87 (m, 3H, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.2, 167.0, 149.2, 136.9, 52.1, 31.8, 30.1, 29.4, 29.3, 28.4, 26.9, 22.7, 14.1. HRMS calculated for C₁₄H₂₄O₃ [M – H][−] 239.1653; found 239.1660.

(E/Z)-Methyl-2-acetyldodec-2-enoate (6f). Yellow oil. Yield: 90%. IR (film, ν_{\max} cm^{−1}): 1220, 1361, 1381, 1462, 1635, 1695, 1730, 2854, 2927; ¹H NMR (CDCl₃, 400 MHz): δ 6.93 (t, 1H, *J* = 8.0 Hz, isomer *E*), 6.85 (t, 1H, *J* = 4.0 Hz, isomer *Z*), 3.76 (s, 3H, isomer *Z*), 3.71 (s, 3H, isomer *E*), 2.29–2.15 (m, 8H, isomer *E*, *Z*), 1.41 (m, 2H, isomer *E*, *Z*), 1.22 (m, 12H, isomer *E*, *Z*), 0.81 (t, 3H, *J* = 8.0 Hz, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.1, 166.9, 165.0, 149.4, 149.2, 137.7, 136.8, 135.2, 63.6, 52.4, 52.0, 32.5, 31.8, 31.2, 29.4, 29.1, 28.6, 29.2, 28.8, 26.8, 22.6, 14.1. HRMS calculated for C₁₅H₂₆O₃ [M – H][−] 253.1709; found 253.1812.

(E/Z)-Methyl-2-acetyltetradec-2-enoate (6g). Yellow oil. Yield: 80%. IR (film, ν_{\max} cm^{−1}): 1219, 1361, 1379, 1463, 1637, 1697, 1730, 2854, 2926; ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (t, 1H, *J* =



8.0 Hz, isomer *E*), 6.86 (t, 1H, *J* = 8.0 Hz, isomer *Z*), 3.83 (s, 3H, isomer *Z*), 3.78 (s, 3H, isomer *E*), 2.37–2.22 (m, 8H, isomer *E*, *Z*), 1.53–1.40 (m, 2H, isomer *Z*, *E*), 1.26 (m, 16H, isomer *E*, *Z*), 0.88 (t, 3H, *J* = 8.0 Hz, isomer *E*, *Z*). ¹³C NMR (CDCl₃, 100 MHz): δ 195.2, 166.9, 149.2, 137.8, 136.8, 135.2, 63.6, 52.0, 33.4, 31.9, 31.2, 30.1, 28.4, 28.6, 26.9, 19.9, 14.1. HRMS calculated for C₁₇H₃₀O₃ [M + H]⁺ 283.2268; found 283.2270.

3-Dodecylidenepentane-2,4-dione (6h). Yellow oil. Yield: 70%. ¹H NMR (CDCl₃, 400 MHz): δ 6.68 (t, 1H, *J* = 8.0 Hz), 2.32 (s, 3H), 2.23 (q, 2H, *J* = 8.0 Hz), 1.48 (m, 2H), 1.26 (s, 16H), 0.88 (t, 3H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 203.5, 190.8, 197.1, 146.9, 145.2, 137.3, 123.5, 33.0, 31.9, 31.7, 29.6, 29.3, 28.9, 28.7, 26.0, 24.0, 22.7, 14.1. HRMS calculated for C₁₇H₃₀O₂ [M – H][–] 265.2173; found 265.2161.

3-Hydroxy-2-(1-hydroxydodecyl)-5,5-dimethylcyclohex-2-enone (6i). White solid. Yield: 73%. ¹H NMR (CDCl₃, 400 MHz): δ 12.48 (s, 1H), 3.91 (t, 1H, *J* = 8.0 Hz), 2.34–2.23 (m, 4H), 2.00 (m, 2H), 1.22 (m, 18H), 1.07 (s, 3H), 1.06 (s, 3H), 0.88 (t, 3H, *J* = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 189.9, 189.5, 116.6, 47.0, 46.2, 31.9, 31.1, 29.9, 29.6, 29.5, 29.3, 29.3, 29.1, 29.0, 26.7, 22.6, 14.1. HRMS calculated for C₂₀H₃₆O₃ [M + H]⁺ 325.2698; found 325.2786.

Diethyl 2-dodecylidenemalonate (6j). Yellow oil. Yield: 70%. ¹H NMR (CDCl₃, 400 MHz): δ 6.92 (t, 1H, *J* = 8.0 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 4.16 (q, 2H, *J* = 7.0 Hz), 2.21 (m, 2H), 1.22 (m, 24H), 0.81 (t, 3H, *J* = 6.85 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 164.1, 149.6, 128.6, 61.2, 31.9, 29.7, 29.6, 28.3, 22.7, 14.1. HRMS calculated for C₁₉H₃₄O₄ [M + H]⁺ 327.2530; found 327.2551.

2,2-Dimethyl-5-(3-methylbutylidene)-1,3-dioxane-4,6-dione (6k).²⁶ Yellow oil. Yield: 90%. IR (film, ν_{max} cm^{–1}): 3479, 3004, 2956, 2860, 1789, 1733, 1637, 1476, 1286, 1202, 1001, 912, 799; ¹H NMR (300 MHz, CDCl₃): δ 7.96 (t, 1H, *J* = 7.5 Hz), 2.86 (t, 2H, *J* = 7.5 Hz), 1.96 (sept, 1H, *J* = 7.5 Hz), 1.75 (s, 6H), 1.01 (d, 6H, *J* = 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 167.9, 161.8, 159.8, 118.6, 104.8, 39.7, 28.6, 27.6 (2C), 22.5 (2C).

5-Hexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (6l). Yellow oil. Yield: 95%. IR (film, ν_{max} cm^{–1}): 3446, 3009, 2936, 2855, 1795, 1746, 1624, 1560, 1357, 1301, 1195, 1017, 928, 799; ¹H NMR (300 MHz, CDCl₃): δ 7.95 (t, 1H, *J* = 7.5 Hz), 2.96 (q, 2H, *J* = 7.5 Hz), 1.76 (s, 6H), 1.62 (m, 2H), 1.38 (m, 4H), 0.92 (t, 3H, *J* = 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 169.6, 165.6, 162.5, 160.4, 118.6, 105.4, 32.3, 31.7, 29.5, 28.3, 23.2, 14.7. HRMS calculated for C₁₂H₁₈O₄ [M – H][–] 225.1132; found 225.1124.

2,2-Dimethyl-5-octylidene-1,3-dioxane-4,6-dione (6m). Yellow oil. Yield: 92%. IR (film, ν_{max} cm^{–1}): 3446, 3009, 2936, 2855, 1795, 1746, 1624, 1560, 1357, 1301, 1195, 1017, 928, 799; ¹H NMR (300 MHz, CDCl₃): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.30 (m, 10H), 1.61 (quint, 2H, *J* = 6.0 Hz), 1.76 (s, 6H), 2.96 (q, 2H, *J* = 6.0 Hz), 7.95 (t, 1H, *J* = 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 14.7, 23.2, 28.3, 28.8, 29.6, 30.0, 31.8, 32.3, 105.4, 118.7, 160.5, 162.5, 165.6, 169.7. HRMS calculated for C₁₄H₂₂O₄ [M – H][–] 253.1445; found 253.1439.

5-Decylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (6n). Yellow pale paste solid. Yield: 85%. IR (film, ν_{max} cm^{–1}): 3009, 2928, 2847, 1792, 1752, 1738, 1639, 1467, 1381, 1296, 1201, 1002, 925, 799. ¹H NMR (300 MHz, CDCl₃): δ 7.93 (t, 1H, *J* = 7.5 Hz), 2.94 (q, 2H, *J* = 9.0 Hz), 1.74 (s, 6H), 1.59 (m, 2H), 1.26 (m, 10H), 0.88 (t, 3H, *J* = 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 169.7, 162.6,

160.5, 118.7, 105.5, 32.5, 31.8, 30.1, 30.0, 29.9, 28.9, 28.8, 28.3 (2C), 23.3, 14.7. HRMS calculated for C₁₆H₂₆O₄ [M – H][–] 281.1758; found 281.1749.

5-Dodecylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (6o). White solid, mp 67–69 °C. Yield: 85%. IR (film, ν_{max} cm^{–1}): 3398, 3009, 2920, 2847, 1802, 1748, 1738, 1641, 1568, 1462, 1381, 1309, 1203, 1009, 912, 807, 718. ¹H NMR (CDCl₃, 300 MHz): δ 7.96 (t, 1H, *J* = 7.2 Hz), 2.96 (m, 2H), 1.76 (s, 6H), 1.62 (m, 2H), 1.28 (m, 16H), 0.91 (t, 3H, *J* = 7.0 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 169.7, 162.2, 160.5, 118.7, 105.4, 32.5, 31.8, 31.6, 30.2 (2C), 30.1 (2C), 29.2 (2C), 28.8, 28.3, 23.3, 14.7. HRMS calculated for C₁₈H₃₀O₄ [M – H][–] 309.2071; found 309.2061.

5-Hexadecylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (6p). White solid, mp 81–83 °C. Yield: 80%. IR (film, ν_{max} cm^{–1}): 3001, 2920, 2855, 1795, 1746, 1730, 1641, 1462, 1381, 1301, 1195, 1001, 799, 718. ¹H NMR (300 MHz, CDCl₃): δ 7.93 (t, 1H, *J* = 7.5 Hz), 2.94 (q, 2H, *J* = 6.0 Hz), 1.74 (s, 6H), 1.60 (m, 2H), 1.28 (m, 24H), 0.88 (t, 3H, *J* = 6.0 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 169.0, 161.9, 159.8, 118.0, 104.7, 31.9, 31.1, 29.6 (4C), 29.5 (2C), 29.4 (2C), 29.3 (2C), 29.2, 28.1, 27.6 (2C), 14.0. HRMS calculated for C₂₂H₃₈O₄ [M – H][–] 365.2697; found 365.2690.

2,2-Dimethyl-5-octadecylidene-1,3-dioxane-4,6-dione (6q). White solid, mp 78–79 °C. Yield 83%. IR (film, ν_{max} cm^{–1}): 3001, 2920, 2847, 1786, 1738, 1624, 1471, 1390, 1293, 1195, 1009, 799, 718. ¹H NMR (300 MHz, CDCl₃): δ 7.95 (t, 1H, *J* = 7.5 Hz), 2.95 (q, 2H, *J* = 6.0 Hz), 1.76 (s, 6H), 1.61 (m, 2H), 1.27 (m, 28H), 0.90 (t, 3H, *J* = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 168.5, 161.4, 159.3, 117.5, 104.3, 31.4, 30.7, 29.2 (4C), 29.1 (2C), 29.0 (2C), 28.9 (2C), 28.8 (2C), 27.7, 27.2 (2C), 22.4, 13.6. HRMS calculated for C₂₄H₄₂O₄ [M – H][–] 393.3010; found 393.2995.

Acknowledgements

The authors are grateful for the financial support of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Apoio à Pesquisa do Estado do Rio Grande do Sul (FAPERGS/PRONEM), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). Fellowships from CAPES and CNPq (D. Russowsky and M. G. Montes D'Oca) are also acknowledged.

Notes and references

- Y. Hayashi, Y. Miyamoto and M. Shoji, *Tetrahedron Lett.*, 2002, **43**, 4079.
- R. Tanikaga, N. Konya, K. Hamamura and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3211.
- E. Knoevenagel, *Ber. Dtsch. Chem. Ges.*, 1894, **27**, 2345.
- R. Menegatti, in *Green Chemistry – Environmentally Benign Approaches*, ed. M. Kidwai and N. K. Mishra, InTech, Rijeka, 2012, ch. 2, pp. 13–32.
- R. Antonioletti, P. Bovicelli and S. Malancona, *Tetrahedron*, 2002, **58**, 589.
- D. C. Forbes, A. M. Law and D. W. Morrison, *Tetrahedron Lett.*, 2006, **47**, 1699.
- T. Sakai, K. Miyata, S. Tsuboi and M. Utaka, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 4072.



- 8 C. Milite, S. Castellano, R. Benedetti, A. Tosco, C. Ciliberti, C. Vicidomini, L. Bouilly, G. Franci, L. Altucci, A. Mai and G. Sbardella, *Bioorg. Med. Chem.*, 2011, **19**, 3690.
- 9 J.-C. Jung, E. Lim, Y. Lee, D. Min, J. Ricci, O.-S. Park and M. Jung, *Molecules*, 2012, **17**, 2091.
- 10 G. Papori and D. Babulal, *Tetrahedron Lett.*, 2009, **50**, 897.
- 11 E. Priede, S. Brica, E. Bakis, N. Udris and A. Zicmanis, *New J. Chem.*, 2015, **39**, 9132.
- 12 H. S. Pawar, A. S. Wagh and A. M. Lali, *New J. Chem.*, 2016, **40**, 4962.
- 13 H. Yujiro, M. Yuji and S. Mitsuru, *Tetrahedron Lett.*, 2002, **43**, 4079.
- 14 D. I. Magee, S. Ratshonka, J. McConaghy and M. Hood, *Can. J. Chem.*, 2012, **90**, 450.
- 15 S. Keskin, D. Kayrak-Talay, U. Akman and O. Hortaçsu, *J. Supercrit. Fluids*, 2007, **43**, 150.
- 16 S. Balalaie, A. Poursaeed, M. J. Khoshkholgh, H. R. Bijanzadeh and E. Wolf, *C. R. Chim.*, 2012, **15**, 283.
- 17 F. A. Khan, J. Dash, R. Satapathy and S. K. Upadhyay, *Tetrahedron Lett.*, 2004, **45**, 3055.
- 18 D. W. Morrison, D. C. Forbes and J. H. Davis Jr, *Tetrahedron Lett.*, 2001, **42**, 6053.
- 19 S. Zhao, X. Wang and L. Zang, *RSC Adv.*, 2013, **3**, 11691.
- 20 M. Anouti, M. Caillon-Caravanier, Y. Dridi, H. Galiano and D. Lemordant, *J. Phys. Chem. B*, 2008, **112**, 13335.
- 21 T. G. M. Treptow, F. Figueiró, E. H. F. Jandrey, A. M. O. Battastini, C. G. Salbego, J. B. Hoppe, P. S. Taborda, S. B. Rosa, L. A. Piovesan, C. R. M. D'Oca, D. Russowsky and M. G. M. D'Oca, *Eur. J. Med. Chem.*, 2015, **95**, 552.
- 22 C. R. M. D'Oca, T. Coelho, T. G. Marinho, C. R. L. Hack, R. D. Duarte, P. A. da Silva and M. G. M. D'Oca, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5255.
- 23 R. D. Duarte, R. Ongaratto, L. A. Piovesan, V. R. de Lima, V. Soldi, A. A. Merlo and M. G. M. D'Oca, *Tetrahedron Lett.*, 2012, **53**, 2454.
- 24 D. S. dos Santos, L. A. Piovesan, C. R. M. D'Oca, C. R. L. Hack, T. G. M. Treptow, M. O. Rodrigues, D. B. Vendramini-Costa, A. L. T. G. Ruiz, J. E. de Carvalho and M. G. M. D'Oca, *Bioorg. Med. Chem.*, 2015, **23**, 340.
- 25 R. C. Brinkerhoff, H. F. Tarazona, P. M. de Oliveira, D. C. Flores, C. R. M. D'Oca, D. Russowsky and M. G. M. D'Oca, *RSC Adv.*, 2014, **4**, 49556.
- 26 O. Bassas, J. Huuskonen, K. Rissanen and A. M. P. Koskinen, *Eur. J. Org. Chem.*, 2009, 1340.

