RESEARCH LETTER

Eco-friendly synthesis of esters under ultrasound with p-toluenesulfonic acid as catalyst

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The present work describes the efficient ultrasound-assisted synthesis of saturated aliphatic esters from synthetic aliphatic acids in methanol or in ethanol, using p-toluenesulfonic acid as a catalyst. The esters were isolated in good yields after short reaction times under mild conditions. The compounds were analyzed by high resolution mass spectrometry (HRMS), which give a fragmentations pathway common for these molecules.

Keywords: aliphatic esters; sonochemistry; HRMS; ultrasound

1. Introduction

Esters and derivatives are widespread in nature and are widely used in industry. The rapid increasing demand for esters in food (1), cosmetics (2), pharmaceutical (3), and lubricants (4) industries makes it necessary to find alternative ways instead of reactions which are too scarce or too expensive for commercial applications. Also, the long-chain esters of acids are being exploited industrially as biodiesel and as waxes (5). The industrial process for ester syntheses are based on direct chemical esterification of fatty acids with alcohol in the presence of inorganic catalysts at high-temperatures (6). However, these chemical procedures are tedious, nonselective, and consume a large amount of energy. In connection, the current situation of environmental degradation requires the development of efficient and cleaner methodologies with regard to energy consumption and reduction of waste.

Ultrasound has increasingly been used in organic chemistry in the last years. Compared with the traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out in high yields, shorter reaction time, and milder conditions under ultrasound irradiation. Recently, we have reported a convenient and inexpensive ultrasound-assisted preparation of functionalized arylacetylenes (7), pyrazoles (8, 9), thiazoles (10, 11), isoxazoles (12), and dihydropyrimidinones (13).

The favorable effects of ultrasound irradiation are playing an increasing role in process chemistry, especially in cases where classical methods require drastic conditions or prolonged reactions times. Specialy, the origin of sonochemical effects in liquids is the phenomenon of acoustic cavitation (14, 15).

Ultrasound is transmitted through a medium via pressure waves by inducing vibrational motion of the molecules which alternately compress and stretch the molecular structure of the medium due to a time-varying pressure. Therefore, the distance among the molecules varies as the molecules oscillate around their mean position. If the intensity of ultrasound in a liquid is increased, a point is reached at which the intramolecular forces are not able to hold the molecular structure intact. In consequence, it breaks down, and a cavity is formed. This cavity is a denominated cavitation bubble and this process is called cavitation, and the point is where it starts the cavitation threshold. A bubble responds to the sound field in the liquid by expanding and contracting (16, 17).

Cavitation is a process in which mechanical activation destroys the attractive forces of molecules

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We report here that the efficient methodology to synthesize alkyl esters with p-TSA as catalyst and sonication leads to process improvement.

For the identification of compounds for the first time is employed high resolution mass spectrometry (HRMS) in electrospray ionization-quarupole time of flight (ESI-QTOF), providing a fragmentation pathway which can be used for identifying general esters.

**2. Method**

**2.1. Apparatus and analysis**

The compounds were dissolved in a solution of 50% (v/v) chromatographic grade acetonitrile (Tedia), 50% (v/v) deionized water, and 0.1% formic acid. The solutions were infused directly and individually into the electrospray ionization (ESI) source by means of a syringe pump (Harvard Apparatus) at a flow rate of 10 μL min⁻¹. ESI(+)-MS and tandem ESI(+)-MS/MS were acquired using a hybrid high-resolution and high-accuracy (5 μL/L) MicrOTOF-Q II mass spectrometer (Bruker Daltonics) under the following conditions: capillary and cone voltages were set to +3500 V and +40 V, respectively, with a desolvation temperature of 200°C. For ESI(+)-MS/MS, the energy for the collision-induced dissociations (CID) was optimized for each component. Diagnostic ions were identified on the comparison of their ESI(+)-MS/MS dissociation patterns with theoretical mass dates. For data acquisition and processing, Micro-TOF software (Bruker Daltonics) was used. The data were collected in the m/z range of 50–400 at the speed of two scans per second, providing the resolution of 50,000 FWHM (full width at half maximum) at m/z 200. The infrared (IR) spectra were obtained on a Shimadzu IR Prestige-21 spectrometer (Bruker Daltonics) under the following conditions: capillary and cone voltages were set to +3500 V and +40 V, respectively, with a desolvation temperature of 200°C. For ESI(+)-MS/MS, the energy for the collision-induced dissociations (CID) was optimized for each component. Diagnostic ions were identified on the comparison of their ESI(+)-MS/MS dissociation patterns with theoretical mass dates. For data acquisition and processing, Micro-TOF software (Bruker Daltonics) was used.

**2.2. Synthesis of esters by ultrasound irradiation**

In a flask, the fatty acid (4.0 mmol) and p-TSA (2.0 mmol) were mixed with ethanol (27.6 mL) or methanol (16.8 mL) and sonicated for 20 minutes at room temperature (25°C). After the time indicated, the alcohol was evaporated under reduced pressure. The solid residue was dissolved into deionized water (35 mL), the product was extracted into ethyl ether (3 × 15 mL), and the combined organic fractions were dried (Na₂SO₄). The solvent was evaporated under vacuum to give the pure esters.
2.3. Compound characterization by HRMS and IR data

Methyl octanoate: m/z 159.1397 [C₉H₁₉O₂]+, 117.0926 [C₆H₁₃O₂]+, 103.0772 [C₄H₉O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Ethyl octanoate: m/z 173.1554 [C₁₀H₂₁O₂]+, 145.1240 [C₈H₁₇O₂]+, 103.0774 [C₅H₁₁O₂]+, 89.0612 [C₄H₉O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Methyl decanoate: m/z 187.1699 [C₁₁H₂₃O₂]+, 117.0929 [C₆H₁₃O₂]+, 103.0769 [C₅H₁₁O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1120–1200, 2800–2960.

Ethyl decanoate: m/z 201.1862 [C₁₂H₂₅O₂]+, 173.1552 [C₁₀H₂₁O₂]+, 117.0928 [C₆H₁₃O₂]+, 103.0771 [C₅H₁₁O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1120–1200, 2800–2960.

Methyl dodecanoate: m/z 215.2009 [C₁₃H₂₇O₂]+, 201.1849 [C₁₂H₂₅O₂]+, 187.1689 [C₁₁H₂₃O₂]+, 173.1543 [C₁₀H₂₁O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Ethyl dodecanoate: m/z 251.1972 [C₁₄H₂₈O₂ + Na]+=, 229.2166 [C₁₄H₂₉O₂]+, 201.1854 [C₁₂H₂₅O₂]+, 149.0240 [C₉H₁₇O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Methyl tetradecanoate: m/z 243.2322 [C₁₅H₃₁O₂]+, 229.2162 [C₁₄H₂₉O₂]+, 201.1846 [C₁₂H₂₅O₂]+, 103.0764 [C₈H₁₃O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Ethyl tetradecanoate: m/z 257.2480 [C₁₆H₃₃O₂]+, 229.2161 [C₁₄H₂₉O₂]+, 201.1845 [C₁₂H₂₅O₂]+, 173.1530 [C₁₀H₂₁O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1120–1200, 2800–2960.

Methyl hexadecanoate: m/z 271.2635 [C₁₇H₃₅O₂]+, 257.2481 [C₁₆H₃₃O₂]+, 229.2174 [C₁₄H₂₉O₂]+, 201.1852 [C₁₂H₂₅O₂]+, 103.0733 [C₈H₁₃O₂]+. IR: \( \nu \) (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

Table 1. Ultrasound-assisted ester synthesis by p-TSA catalysis.

| Compound | Product structure | Sonochemistry | Literature |
|----------|------------------|---------------|------------|
| 2a       | ![Image]         | 20, 80        | 21 (35), 73 (35) |
| 2b       | ![Image]         | 20, 81        | 3.5 (36), 95 (35) |
| 2c       | ![Image]         | 20, 77        | 48 (37), 71 (37) |
| 2d       | ![Image]         | 20, 88        | 8 (38), 86 (38) |
| 2e       | ![Image]         | 20, 87        | 4.5 (36), 94 (36) |
| 2f       | ![Image]         | 20, 73        | 6 (39), 65 (39) |
| 2g       | ![Image]         | 20, 80        | 48 (37), 79 (37) |
| 2h       | ![Image]         | 20, 98        | 30 (40), 90 (40) |
| 2i       | ![Image]         | 20, 82        | 48 (37), 64 (37) |
| 2j       | ![Image]         | 20, 91        | 4.5 (36), 90 (36) |

*aYields of isolated products.

*bLiterature.
Ethyl hexadecanoate: m/z 307.2635 [C18H37O2+Na]+, 285.2807 [C18H37O2]+, 257.2431 [C16H33O2]+, 229.2163 [C14H29O2]+, 201.1852 [C12H25O2]+, 149.0240 [C8H5O2]+.

IR: ν (cm\(^{-1}\)) 1720–1760, 1160–1200, 2800–2960.

3. Results and discussion

In this work, we have combined acid catalyzed with ultrasound to prepare some esters by the eco-friendly and rapid process. The experimental procedure for these reactions is remarkably simple and does not require the use of expensive catalysts. The mixture of alcohol and p-TSA was reacted with a variety of fatty acid, leading to esters. In particular, by monitoring gas chromatography-flame ionization detector (GC-FID), it was shown that only 20 minutes (ultrasound – 20KHz) are sufficient to convert the fatty acids into short-chain esters. It was not possible to correlate the results with groups of chemical reagents; however, the yields of the products were satisfactory in comparison with the literature (73–98%, Scheme 1, Table 1). The reaction mechanism for the preparation of esters 2 is similar with the Fischer synthesis (33). A possible explanation is that the product was obtained from acid carboxylic due to the attack of the alcohol in acid media (p-TSA) and subsequent water elimination (Scheme 2).

Relating with this work, to analyze the products 2 ESI-MS and ESI-MS/MS were used, which have been important tools to characterize and identify the synthetic compounds. The measurements were made by a direct infusion (DI) in HRMS equipment Micro-QTOF II.

To respond in positive mode, 0.1% of formic acid was introduced into the sample solution. The
instrument’s accurate mass measurement gives the elemental composition of parent and fragment ions. As is summarized in Table 2, mass accuracy is also easily obtained for all the characteristic fragment ions, thus providing two sets of important information for unequivocal identification. Since the widely accepted accuracy threshold for the confirmation of elemental compositions was established as 10 ppm, this usually provides highly reliable identification of the target compounds (34).

The QTOF-MS/MS provided HRMS and MS/MS data, which allowed the confirmation of chemical formulas based on its ions beyond the elucidation of the fragments \( m/z \). The \([M+Na]^+\) ions for the investigated esters were hardly observed. The \([M+H]^+\) ions were selected as the precursor ions for CID fragmentation to produce MS/MS spectra. The fragmentation behavior follows an order losing alky groups (Scheme 3). This is a characteristic fragmentation which was observed for all compounds obtained here. In accordance with the chain ester size is formed ions with different stability giving different spectra. Therefore, the combination uses of information provided by the two instruments were helpful to elucidate the structures of the studied compounds.

4. Conclusion

In conclusion, the procedure described here is an economical and environmental methodology for esterification reactions with pharmaceutical and industrial importance. Significant advantages of the method include (1) the catalyst is inexpensive; (2) the reaction is easy to execute; (3) the workup is very simple; (4) the required reaction times are shorter (20 minutes); (5) the reaction can be conducted at ambient temperature; and (6) the products are isolated in good yields (73–98%) and high purities. The analyses based on HRMS are easy and give a fragmentation pathway for the direct identification of similar compounds.

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References

(1) Piccicuto, S.; Blecker, C.; Brohee, J.C.; Mbampara, A.; Lognay, G.; Deroanne, C.; Paquot, M.; Marlier, M. Biotechnol. Agron. Soc. Environ. 2001, 5, 209–219.
(2) Vaze, S. Chem. Eng. World. 1996, 31, 115–116.
(3) Hopkins, H.; Small, L.V.D. J. Pharm. Sci. 1960, 49, 220–224.
(4) Lauer, D.A. In Synthetics, Mineral Oils, and Bio-Based Lubricants; Rudnick, L.R., Ed.; CRC: Boca Raton, FL, 2006, pp 441–458.
(5) Larios, A.; Garcia, H.S.; Oliart, R.M.; Valerio-Alfaro, G. Appl. Microbiol. Biotechnol. 2004, 65, 373–376.
(6) Farris, R.D. J. Am. Oil Chem. Soc. 1979, 56, 770A–773A.
(7) Stefani, H.A.; Cell, R.; Dörfl, F.A.; Pereira, C.M.P.; Gomes, F.P.; Zeni, G. Tetrahedron Lett. 2005, 46, 2001–2003.
(8) Pizzuti, L.; Piovesan, L.A.; Flores, A.F.C.; Quina, F.H.; Pereira, C.M.P. Ultrason. Sonochem. 2009, 16, 728–731.
(9) Pizzuti, L.; Martins, P.L.; Ribeiro, B.A.; Quina, F.H.; Pinto, E.; Flores, A.F.C.; Venzke, D.; Pereira, C.M.P. Ultrason. Sonochem. 2010, 17, 34–37.
(10) Venzke, D.; Flores, A.F.C.; Quina, F.H.; Pizzuti, L.; Pereira, C.M.P. Ultrason. Sonochem. 2010, 18, 370–374.
(11) Neuenfeldt, P.D.; Duval, A.R.; Drawanz, B.B.; Rosales, P.F.; Gomes, C.R.B.; Pereira, C.M.P.; Cunico, W. Ultrason. Sonochem. 2011, 18, 65–67.
(12) Nascimento, F.; Baltazar, M.; Pizzuti, L.; Gressler, V.; Rivelli, D.; Barros, S.B.M.; Pereira, C.M.P. Lett. Drug Des. Discov. 2009, 6, 323–326.
(13) Stefani, H.A.; Oliveira, C.B.; Almeida, R.B.; Pereira, C.M.P.; Braga, R.C.; Cella, R.; Borges, V.C.; Savengnago, L.; Nogueira, C.W. Eur. J. Med. Chem. 2006, 41, 513–518.
(14) Parkar, P.A.; Choudhary, H.A.; Moholkar, V.S. Chem. Eng. J. 2012, 187, 248–260.
(15) Choudhury, H.A.; Goswami, P.P.; Malani, R.S.; Moholkar, V.S. *Ultrason. Sonochem.* 2014, 21, 1050–1064.
(16) Choudhury, H.A.; Chakma, S.; Moholkar, V.S. *Ultrason. Sonochem.* 2014, 21, 169–181.
(17) Choudhury, H.A.; Malani, R.S.; Moholkar, V.S. *Chem. Eng. J.* 2013, 231, 262–272.
(18) Tuchtenhagen, C.P.; Dias, D.; Muller, B.V.; Ritter, M.; Santos, M.A.Z.; Oliveira, D.; Crizel, M.G.; Mesko, M.F.; Santos, V.; Pereira, C.M.P. *Rev. Virtual Quím.* 2014, 6, 884–897.
(19) Karemi-Jaberi, Z.; Pooladian, B. *Green Chem. Lett. Rev.* 2012, 5, 187–193.
(20) Thanusu, J.; Kanagarajan, V.; Gopalakrishnan, M. *Green Chem. Lett. Rev.* 2012, 5, 65–72.
(21) Das, S.; Thakur, A.J. *Green Chem. Lett. Rev.* 2011, 4, 131–135.
(22) Kalva, A.; Sivasankar, T.; Moholkar, V.S. *Ind. Eng. Chem. Res.* 2009, 48, 534–544.
(23) Deshmane, V.G.; Gogate, P.R.; Pandit, A.B. *Ultrason. Sonochem.* 2009, 16, 345.
(24) Fiametti, K.G.; Sychoski, M.M.; Cesaro, A.; Furigo, A.; Bretanha, L.C.; Pereira, C.M.P.; Treichel, H.; Oliveira, D.; Oliveira, J.V. *Ultrason. Sonochem.* 2011, 18, 981–987.
(25) Santi, V.; Cardellini, F.; Brinchi, L.; Germani, R. *Tetrahedron Lett.* 2012, 53, 5151–5155.
(26) Hwu, J.R.; Hsu, C.; Jain, M.L.; *Tetrahedron Lett.* 2004, 45, 5151–5154.
(27) Pan, W.; Chang, F.; Wei, L.; Wu, M.; Wu, Y. *Tetrahedron Lett.* 2003, 44, 331–334.
(28) Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron* 2006, 62, 1309–1317.
(29) Hobuss, C.B.; Venzke, D.; Pacheco, B.S.; Souza, A.O.; Santos, M.A.Z.; Moura, S.; Quina, F.H.; Fiametti, K.G.; Oliveira, J.V.; Pereira, C.M.P. *Ultrason. Sonochem.* 2012, 19, 387–389.
(30) Pereira, C.M.P.; Martins, M.A.P.; Moura, S.; Fiss, G.F.; Frizzo, C.P.; Emmerich, D.; Zanatta, N.; Bonacorso, H.G. *Arkivoc* 2006, xiii, 187–194.
(31) Venzke, D.; Flores, A.F.C.; Quina, F.H.; Pizzuti, L.; Pereira, C.M.P. *Ultrason. Sonochem.* 2011, 18, 370–374.
(32) Souza, P.O.; Ferreira, L.F.; Pires, N.R.X.; Sanches, P.J.; Duarte, P.A.; Pereira, C.M.P.; Mesko, M.F. *Rev. Bras. Farmacogn.* 2012, 22, 825–837.
(33) Carey, F.A. *Organic Chemistry*; McGraw-Hill Higher Education: Jefferson, USA, 2000.
(34) Lacorte, S.; Fernandez-Alba, A.R. *Mass Spectrom. Rev.* 2006, 25, 866–880.
(35) Mori, N.; Togo, H. *Tetrahedron* 2005, 61, 5915–5925.
(36) Li, X.; Eli, W. *J. Mol. Catal. A: Chem.* 2008, 279, 159–164.
(37) Gulati, R.; Arya, P.; Malhotra, B.; Prasad, A.K.; Saxena, R.K.; Kumar, J.; Watterson, A.C.; Parmar, V.S. *Arkivoc* 2003, iii, 159–170.
(38) Qiao, K.; Hagiwara, H.; Yokoyama, C. *J. Mol. Catal. A: Chem.* 2006, 246, 65–69.
(39) Li, C.; Yang, J.; Wang, P.; Liu, J.; Yang, Q. *Micropor. Mesopor. Mat.* 2009, 123, 228–233.
(40) Sun, S.Y.; Xu, Y.; Wang, D. *Bioresour. Technol.* 2009, 100, 2607–2612.