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Lactic acid as an invaluable green solvent for ultrasound-assisted scalable synthesis of pyrrole derivatives

Shi-Fan Wang *, Chao-Lun Guo, Ke-ke Cui, Yan-Ting Zhu, Jun-Xiong Ding, Xin-Yue Zou, Yi-Hang Li

Department of Pharmacy, School of Ocean, Hainan University, Haikou 570228, People's Republic of China

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ABSTRACT

Lactic acid has been used as a bio-based green solvent to study the ultrasound-assisted scale-up synthesis. We report here, for the first time, on the novel and scalable process for synthesis of pyrrole derivatives in lactic acid solvent under ultrasonic radiation. Eighteen pyrrole derivatives have been synthesized in lactic acid solvent under ultrasonic radiation and characterized by ^{1}H NMR, IR, ESI MS. The results show, under ultrasonic radiation, lactic acid solvent can overcome the scale-up challenges and exhibited many advantages, such as bio-based origin, shorter reaction time, lower volatility, higher yields, and ease of isolating the products.

1. Introduction

It is well known that the ultrasonic irradiation caused cavitations in the liquid medium where the formation, growth and collapse of micro-bubbles occurred [1]. This can stimulate the reactivity of chemical species, resulting in the acceleration of the heterogeneous reactions more effectively [2]. Compared with traditional methods, ultrasonic-assisted organic synthesis is more convenient [3–5]. Ultrasonic-assisted organic synthesis as a green synthetic approach is a powerful technique that is being used more and more [6,7].

Pyrrole nucleus is widespread in marine natural products [8,9], such as makaluvic acid from the South African Latrunculid Sponge *Strongylodesma aliwaliensis* [10] and the Sceptrin (Fig. 1) which showed good activity against cell motility in a variety of cancer cell lines [11]. It is also present in a large number of pyrrole derived drugs, such as the cholesterol-lowering drug atorvastatin [12] and the antiinflamatory analgesic tolmetin [13,14] (Fig. 2). For this reason, a number of synthetic methods to prepare the compounds containing pyrrole nucleus have been developed [15–18].

One of the most classical and common approaches for the synthesis of pyrrole derivatives is the Knorr condensation reaction which is achieved through the condensation reaction of α-amino carbonyl compounds with 1,3-dicarbonyl compounds [19]. In traditional Knorr condensation reaction, the α-amino carbonyl compound was generated in situ by the nitrosation of 1,3-dicarbonyl compound and then by reducing the nitroso compound using zinc powder under weak acidic conditions. Eventually, the condensation reaction of α-amino carbonyl compounds with 1,3-dicarbonyl compounds was carried out in the medium of glacial acetic acid under reflux conditions to give pyrrole derivatives. The reaction mechanism of traditional Knorr condensation reaction could be shown in Scheme 1.

In traditional Knorr condensation reaction, glacial acetic acid is massively used as solvent and difficult to recycle. Acetic acid has a very strong corroding effect on metal equipments because glacial acetic acid is a volatile acid. Lactic acid (2-hydroxy propionic acid) is a bio-based weak acid that is considered biodegradable, nontoxic and nonvolatile. It is the simplest hydroxyl acid with an asymmetric carbon atom and exists in two optical isomers. The L(+)-isomer is produced in humans and other mammals, whereas both the D(−)- and L(+)-enantiomers are produced in bacterial systems. The majority of the world's commercially produced lactic acid is made by the bacterial fermentation of agricultural crops, such as corns [20–22].

Recently, lactic acid is reported as a useful green solvent to promote some three-component reactions [23]. But it has never been considered as a green bio-based solvent in sonochemical reactions. Our aim was to develop a green, novel and industrially acceptable process for the synthesis of pyrrole derivatives. In order to achieve this, we therefore started a project to investigate the possibility of lactic acid as bio-based green solvent for the scalable sonochemical synthesis of pyrrole derivatives using Knorr condensation reaction.

* Corresponding author.
E-mail address: wangsf777@163.com (S.-F. Wang).

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Herein, we wish to report, for the first time, an eco-friendly, efficient and facile protocol for the scale-up syntheses of pyrrole derivatives in lactic acid medium under ultrasonic radiation.

2. Materials and methods

2.1. Apparatus and analysis

Reaction courses and the resulted products were monitored by thin-layer chromatography (TLC) on the self-made pre-coated silica gel 60 F_{254} plates. Spots were detected by a UV lamp visualized at 254 nm and/or 365 nm. Melting points (°C, uncorrected) were determined on a XT4 MP apparatus (Taike Corp., Beijing, China). Sonication was performed in a Kunshan KQ 500E ultrasonic cleaner (Kun Shan Ultrasonic Instruments Co., Ltd., Jiangsu, China) with a frequency of 40 kHz, an ultrasonic power of 500 W and a heating power of 800 W. The size of the reactor is 530 mm length, 320 mm width and 380 mm depth. In the reactor, the size of the water bath is 500 mm length, 300 mm width and 150 mm depth. The reaction mixture was irradiated at 20–80 °C for appropriate time. The reaction flask was positioned in the maximum energy area in the cleaner with cycled water running to control the desired temperature of the water bath. The IR spectra were recorded on a Thermo iS10 IR spectrometer (KBr pellets) and ^{1}H NMR spectra were recorded in $CDCl_3$ or d^6-DMSO on a Bruker DPX400 spectrometer with TMS and solvent signals allotted as internal standards. Splitting patterns are as follows: *s*, singlet; *d*, doublet; *dd*, double doublets; *t*, triplet; *q*, quartet; *m*, multiplet. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. ESI mass spectra were recorded on the Shimadzu LCMS-IT-TOF mass spectrometer. All reagents are A.R. grade and purchased from Aladdin Industrial Corporation.

2.2. General procedure for the synthesis of α-nitroso carbonyl intermediates

One mole (69 g) of the saturated solution of sodium nitrite was added dropwise into a 500 ml of lactic acid solution containing 1 mol of 1,3-dicarbonyl compound in a large flask under stirring at 0–5 °C. After all of the saturated solution of sodium nitrite had been added, the resulting solution was continued to stir at room temperature for 2 h to give the resulting solution containing the corresponding α-nitroso carbonyl intermediates for later use.

2.3. General procedure for the synthesis of pyrrole derivatives in lactic acid under ultrasound irradiation

For the synthesis of compounds **1**–**18** in lactic acid, 10 mmol of 1,3-dicarbonyl compound in 30 ml of lactic acid was added into the resulting solution containing 10 mmole of α-nitroso carbonyl intermediates in a conical flask. Then, 40 mmol (2.6 g) of zinc powder were added in batches to the resulting mixture under ultrasonic irradiation (40 kHz, 500 W) at 60 °C for 0.5 h until the reaction is accomplished. The reaction mixture was cooled to room temperature to form white solid. The white solid was recrystallized from ethanol or acetone to give corresponding pure pyrrole derivatives.

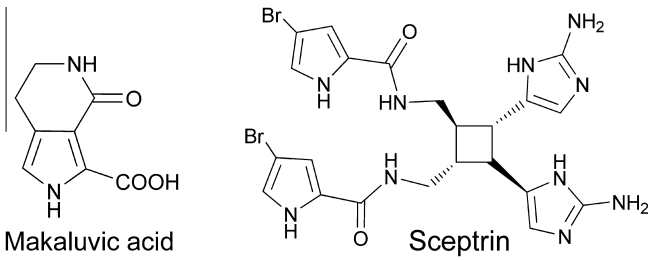

Fig. 1. The structures of makaluvic acid and nakamuric acid.

2.4. General procedure for scale-up synthesis of pyrrole derivatives in lactic acid under ultrasound irradiation

For scale-up synthesis of compounds **1**–**18** in lactic acid, 1 mol of 1,3-dicarbonyl compound in 500 ml of lactic acid was added into the above-mentioned resulting solution containing 1 mol of α-nitroso carbonyl intermediates in a large conical flask. Then, 4 mol (260 g) of zinc powder were added in batches to the resulting mixture under ultrasonic irradiation (40 kHz, 500 W) at 60 °C for 1 h until the reaction is accomplished. The reaction mixture was cooled to room temperature to give the corresponding compounds.

2.4.1. Compound **1**

Crystallized from ethanol to obtain crystals in colorless needles, mp 134–135 °C; IR (KBr) cm^{-1}: 3260 (NH), 2993, 2933 (CH); 1690 (C=O), 1664, 1482, 1437 (C=C in pyrrole ring), 1263 (O—C—O); ^{1}H NMR ($CDCl_3$): δ 1.34–1.36 (*t*, 3H, $CH_2\underline{CH_3}$), 1.37–1.39 (*t*, 3H, $CH_2\underline{CH_3}$), 2.51 (*s*, 3H, CH_3), 2.56 (*s*, 3H, CH_3), 4.26–4.35 (*m*, 4H, $2CH_2$), 9.01 (*s*, 1H, NH); HRMS (ESI) calcd. For $C_{12}H_{17}NO_4$, *m*/*z* 239.1158, found 240.1239 [M+H]$^+$.

2.4.2. Compound **2**

Crystallized from ethanol to obtain crystals in colorless needles, mp 141–143 °C; IR (KBr) cm^{-1}: 3298 (NH), 2989, 2954 (CH); 1703 (C=O), 1669, 1561, 1512 (C=C in pyrrole ring), 1286 (O—C—O); ^{1}H NMR ($CDCl_3$): δ 1.36–1.39 (*t*, 3H, $CH_2\underline{CH_3}$), 2.51 (*s*, 3H, CH_3), 2.56 (*s*, 3H, CH_3), 3.82 (*s*, 3H, OCH_3), 4.30–4.36 (*q*, 2H, CH_2), 9.09 (*s*, 1H, NH); HRMS (ESI) calcd. For $C_{11}H_{15}NO_4$, *m*/*z* 225.1001, found 226.1076 [M+H]$^+$.

2.4.3. Compound **3**

Crystallized from ethanol to obtain crystals in pale yellow needles, mp 109–111 °C; IR (KBr) cm^{-1}: 3298 (NH), 2980, 2929 (CH); 1697 (C=O), 1654, 1568, 1516 (C=C in pyrrole ring), 1280 (O—C—O); ^{1}H NMR ($CDCl_3$): δ 1.37–1.40 (*t*, 3H, $CH_2\underline{CH_3}$), 2.54 (*s*, 3H, CH_3), 2.58 (*s*, 3H, CH_3), 4.76–5.27 (*q*, 2H, $CH_3\underline{CH_2}$), 5.40–5.47 (*d*, 2H, $CH{=}CH\underline{CH_2}$), 5.98–6.08 (*m*, 3H, $CH_2{=}CH$), 9.43 (*s*, 1H, NH); HRMS (ESI) calcd. For $C_{13}H_{17}NO_4$, *m*/*z* 251.1158, found 252.1233 [M+H]$^+$.

2.4.4. Compound **4**

Crystallized from ethanol to obtain crystals in colorless needles, mp 124–126 °C; IR (KBr) cm^{-1}: 3281 (NH), 2976, 2933 (CH); 1692 (C=O),1669, 1561, 1508 (C=C in pyrrole ring), 1286 (O—C—O); ^{1}H NMR ($CDCl_3$): δ 1.36–1.39 (*t*, 3H, $CH_2\underline{CH_3}$), 1.58 (*s*, 9H, $OC(CH_3)_3$), 2.50 (*s*, 3H, CH_3), 2.55 (*s*, 3H, CH_3), 4.30–4.36 (*q*, 2H, $CH_3\underline{CH_2}$), 8.94 (*s*, 1H, NH); HRMS (ESI) calcd. For $C_{14}H_{21}NO_4$, *m*/*z* 267.1471, found 268.1553 [M+H]$^+$.

2.4.5. Compound **5**

Crystallized from ethanol to obtain crystals in colorless needles, mp 115–117 °C; IR (KBr) cm^{-1}: 3290 (NH), 2976, 2941 (CH); 1697 (C=O), 1652, 1570, 1512 (C=C in pyrrole ring), 1289 (O—C—O); ^{1}H NMR (d^6-DMSO): δ 1.29–1.32 (*t*, 3H, $CH_2\underline{CH_3}$), 2.42 (*s*, 3H, CH_3), 2.47 (*s*, 3H, CH_3), 3.33 (*s*, 3H, OCH_3), 3.35–3.66 (*m*, 4H, OCH_2CH_2O), 4.24–4.28 (*q*, 2H, $\underline{CH_2}CH_3$),11.88 (*s*, 1H, NH); HRMS (ESI) calcd. For $C_{13}H_{19}NO_5$, *m*/*z* 269.1263, found 270.1344 [M+H]$^+$.