Crude glycerol from waste cooking oil treatment as an alternative solvent in synthesis of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate

A H Cahyana, B Ardiansah and H Hanifah
Department of Chemistry, Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Indonesia, Kampus UI Depok, Depok 16424, Indonesia

Corresponding author’s e-mail: herrykim@ui.ac.id

Abstract. Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, a 1,4-DHP derivative, has been synthesized from benzaldehyde, ethyl acetate and ammonium acetate via a one-pot three component reaction in crude glycerol as solvent. Crude glycerol was obtained from the treatment of waste cooking oil. The product was obtained in 69 % yield when the reaction was conducted at 90 °C for 1 h under reflux in 10 mL glycerol.

Keywords: waste cooking oil, hydrolysis, glycerol, solvent, 1,4-dihydropyridine.

1. Introduction
Expeditious and sustainable processes in producing organic compounds are concerning numerous synthetic chemists, where the structural complexity of products frequently requires multistep synthetic pathways, manifolded reagents, sumptuous reaction media and tedious post-reaction work-up, leading to highly exhausting experimental protocols [1]. Currently, organic chemists have concentrated considerable attention towards more environmentally friendly synthetic methodologies that are applicable in laboratory as well as industrial scale [2]. In this status, multicomponent reactions (MCRs) have become an efficient strategy in contemporary synthesis of complex organic molecules from simple precursors because they can achieve conversion in one-step reaction without isolation of any intermediate [3]. MCRs provide a great benefit of time-saving one-pot syntheses, satisfactory yields, high atom economy, and energy-saving, thus allowing a rapid investigation of a working hypothesis [4]. Consequently, developing new multicomponent protocol is an interesting field of the study to generate molecular diversities which have a widespread of applications.

1,4-Dihydropyridine (1,4-DHP) skeleton is an integral part of pharmacophores in medicinal chemistry [5]. Commercially available drugs having this moiety, such as amlodipine and nivaldipine (figure 1) are evidence of the importance of 1,4-DHP [6]. Derivatives of 1,4-DHP have exhibited a broad spectrum of pharmacological properties, such as cocaine-dependent regulators [7], hepatoprotective [8], HIV-1 protease inhibitors [9], vasodilators [10] and antitumor [11] activities. First introduced by Arthur Hantzsch in 1882, recently many multicomponent reactions in 1,4-DHPs syntheses have been developed, such as using Au(PPh)Cl/AgOTf [12], montmorillonite [13], magnetic guanidinylated chitosan nanobiocomposite [14], V,O/ZrO [15], nano-silica supported tin tetrachloride [16] and [3,6-DOMDA]OTf ionic liquid [17]. Despite good results were obtained, some reported methods have at least one limitation, such as usage of excess and toxic organic solvents, expensive metal-based catalysts and the use of high reaction temperatures. Hence, development of
new reaction conditions for synthesis of 1,4-DHP derivatives is still an interesting research area. In the present work, we report preparation of crude glycerol from the treatment of waste cooking oil and its use as an alternative solvent for catalyst-free one-pot multicomponent reaction in 1,4-DHP synthesis.

2. Materials and methods

2.1. Materials

Waste cooking oil was collected from the cafeteria in the faculty. All chemicals were synthesis grade and used without purification, such as benzaldehyde, cinnamaldehyde, ethyl acetoacetate and ammonium acetate. Fourier Transform Infrared (FTIR) analysis was performed on Shimadzu Prestige-21 spectrophotometer. UV-Vis spectra were noted on Shimadzu 2450 double beam spectrophotometer. Gas Chromatography and Mass Spectrometry (GC-MS) analysis was conducted on Shimadzu GC-MS QP Mass Spectrometer 2010A.

2.2. Methods

2.2.1. Preparation of glycerol from waste cooking oil. Waste cooking oil was filtered using filter paper prior to use. The filtered waste cooking oil (20 g) and potassium hydroxide 1N in ethanol (100 mL) were stirred at 60 °C for 60 min. After the reaction mixture was cooled down to room temperature, hydrochloric acid 3N (50 mL) was slowly inserted and stirred. The mixture will separate into two phases. Crude glycerol was found at lower phase. Finally, glycerol was collected and ready to be used as solvent in 1,4-DHP synthesis.

2.2.2. Synthesis of 1,4-DHP in glycerol. In a 50 mL round-bottom flask equipped with condenser, benzaldehyde (1 mmol), ammonium acetate (1 mmol) and ethyl acetoacetate (2 mmol) in prepared glycerol (10 mL) were stirred and refluxed (80–100 °C). The reaction progress was observed using TLC. After the process, the temperature of the compound was reduced to room temperature, and then cold water (50 mL) was added. The obtained product was separated by filtration. Then, crude product was recrystallized from ethanol to get pure compound, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (compound 1).

3. Results and discussion

Glycerol was prepared from hydrolysis of waste cooking oil using potassium hydroxide. Base-catalyzed hydrolysis of triglyceride in waste cooking oil was performed under reflux system at 80-100°C in ethanol to produce glycerol and soaps. Then, acidic work-up to the mixture produces two separated phases, glycerol and free fatty acids (figure 2). Glycerol was then recovered and ready to be used as solvent.

Screening of best reaction conditions was performed by using benzaldehyde, ethyl acetoacetate and ammonium acetate via a one-pot multicomponent reaction in crude glycerol (10 mL) as solvent. Reaction time was varied from 1 to 3 h, whereas temperature from 80 to 100 °C (table 1). At 80 °C for 1 h, yield of product was found to be 25%. Surprisingly, when temperature was increased to 90 °C, the product was obtained in 69%. However, increasing temperature to 100 °C cannot improve the product yield. Unfortunately, prolong reaction time (2 or 3 h) at any temperature gave 1,4-DHP in the range of 26–40% yield only.
Table 1. Optimization of reaction conditions for MCR

| Entry | Time (h) | T (ºC) | Yield (%) |
|-------|----------|--------|-----------|
| 1     | 1        | 80     | 25        |
| 2     | 1        | 90     | 69        |
| 3     | 1        | 100    | 30        |
| 4     | 2        | 80     | 28        |
| 5     | 2        | 90     | 40        |
| 6     | 2        | 100    | 28        |
| 7     | 3        | 80     | 27        |
| 8     | 3        | 90     | 38        |
| 9     | 3        | 100    | 26        |

* Ph-CHO (1 mmol), ethyl acetoacetate (2 mmol), NH4OAc (1 mmol)
* isolated yield

Figure 2. (a) reaction mixture (b) glycerol after separation

Figure 3. (a) FTIR (b) UV-Vis (c) GC and (d) Mass spectra of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate

A 1,4-DHP derivative, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, was characterized by means of FTIR, UV, Vis and GC-MS (figure 3). In FTIR, a sharp peak appeared at 3337 cm⁻¹ is due to N-H stretching vibration from secondary amine. Peaks around 2900-2980 cm⁻¹ indicate the presence of C-H sp³ vibration in the molecule (figure 3a). From UV-Vis analysis, it was found that the molecule has maximum lambda at 237 and 354 nm (figure 3b), as characteristic for n to π* and π to π*, respectively. The product has retention time at 12.37 min (figure 3c), and has m/z value of 329.1 (figure 3d).
4. Conclusions
Glycerol obtained from hydrolysis of waste cooking oil can be used as an alternative solvent in synthesis of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, a derivative of 1,4-DHP. The mildness of the synthesis and experimental simplicity using non-toxic solvent make this protocol efficient for multicomponent reaction in 1,4-dihydropyridine synthesis.

Acknowledgements
This work was supported by PITTA Grant 2018 from Universitas Indonesia with contract No. 234/UN2.R3.1/PPM.00/2018.

References
[1] Filho J FA, Lemos B C, de Souza A S, Pinheiro S and Greco S J 2017 Tetrahedron 73 6977–7004
[2] Goel V, Bajwan A, Chauhan S and Goel S 2018 Chem. Sci. Trans. 7 343–7
[3] Patil S, Pawar P B, Jadhav S D and Deshmukh M B 2013 Asian J. Chem. 25 9442–6
[4] Dömling A 2006 Chem. Rev. 106 17–89
[5] Velena A, Zarkovic N, Troselj K G, Bisenieks E, Krauze A, Poikans J and Duburs G 2016 Oxidative Medicine and Cellular Longevity 2016 ID 1892412
[6] Khedkar S A and Auti P B 2014 Mini-Rev. Med. Chem. 14 282–90
[7] Johnson B A, Devous Sr M D, Ruiz P and Ait-Daoud N 2001 Am. J. Psychiatry 158 1191–8
[8] Wei Y, Lu Y, Zhu Y, Zheng W, Guo F, Yao B, Xu S, Wang Y, Jin L and Li Y 2018 Biochim. Biophys. Acta 1862 2261–70
[9] Hilgeroth A, Dressler C, Neuhoff S, Spahn-Langguth H and Langguth P 2000 Pharmazie 55 784–5
[10] Di Stilo A, Visentin S, Cena C, Gasco A M, Ermondi G and Gasco A 1998 J. Med. Chem. 41 5393–401
[11] Mohamed M F, Darweesh A F, Elwahy A H M and Abdelhamid I A 2016 RSC Adv. 6 40900–10
[12] Wang S, Chen H, Zhao H, Cao H, Li Y and Liu Q 2013 Eur. J. Org. Chem. 2013 7300–4
[13] Liu Y P, Liu J M, Wang X, Cheng T M and Li R T 2013 Tetrahedron 69 5242–7
[14] Maleki A, Firouzi-Haji R and Hajizadeh Z 2018 Int. J. Biol. Macromol. 116 320–6
[15] Bhaskaruni S V H S, Maddila S, van Zyl W E and Jonnalagadda S B 2018 Catal. Today 309 276–81
[16] Bamoniri A, Mirjalili B B F and Fouladgar S 2016 J. Taiwan Inst. Chem. Eng. 63 396–403
[17] Baghery S and Zolfigol M A 2017 J. Mol. Liq. 232 174–81