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Comparison of the Lipoamide Synthesis by Direct Amidation and via Amidation of Fatty Acid Methyl Esters

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Abstract

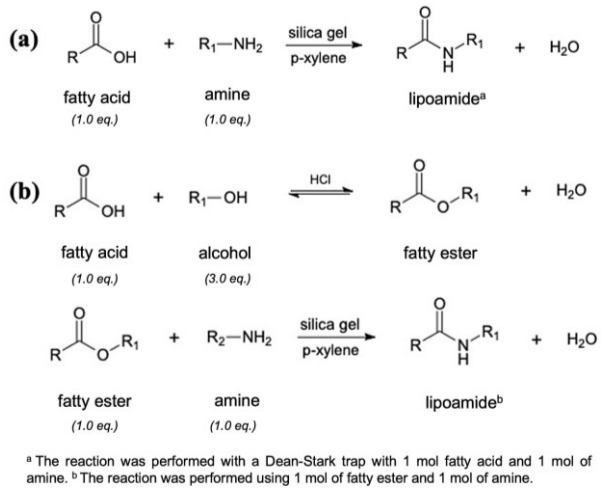
In this research, the preparation of lipoamide through direct amidation of fatty acid and via amidation of fatty acid methyl ester (FAME) was compared. The reactivity of aromatic amines and cyclohexylamine for the synthesis of lipoamide was investigated in this research. The performance of saturated and unsaturated fatty acids was also compared. The synthesis of lipoamides via direct amidation was conducted under reflux using a Dean-Stark trap and silica gel as the catalyst. On the other hand, the amidation of FAME was carried out without catalysts and solvent. Both reactions were run simultaneously for 18 hours at the same temperature. The reaction was monitored using TLC, and then the product was purified using column chromatography and characterized using FTIR and ^{1}H NMR. The TLC data, FTIR, and ^{1}H NMR spectra confirmed that both reaction pathways produced the same lipoamide as the product. Both reaction pathways were compatible with aromatic and nonaromatic amines and saturated and unsaturated fatty acids. The reaction yield of lipoamide from direct amidation was around 70-80% and two-fold higher than lipoamide synthesis via amidation of FAME. Therefore, direct amidation of fatty acid was preferred for the synthesis of lipoamides compared to via amidation of FAME.

1. Introduction

Oleochemicals are derived from oils and fats of vegetable and animal origin [1]. Basic oleochemicals include fatty acids, fatty acid methyl esters (FAME), fatty alcohols, and fatty amines [1, 2, 3]. Another attractive oleochemical is called fatty amide or lipoamide. Naturally, lipoamides are recognized as self-defense agents in plants [4] and bioregulators [5] and also have antimicrobial activity against yeast, mold, and pathogenic bacteria [6]. Lipoamide provides an excellent alternative for construction industry applications [7]. Betancourt-Jimenez *et al.* [7] also reported bio-based lipoamide as an alternative to paraffin and fatty acid esters for phase change materials (PCM). Lipoamide also has been considered as a non-ionic surfactant [8].

Amide compounds are generally found in many synthetic polymers and active pharmaceutical ingredients. Various biological activities are exhibited by amides conjugated with different aliphatic, aromatic, and heterocyclic rings. Biological activities that have been reported for amide compounds are anti-tuberculosis [9], anticonvulsant [10], analgesic, and anti-inflammatory [11], insecticide [12], antifungal [13], and antitumor [14].

Considering the huge benefits and applications of amide compounds and lipoamide, research on the formation of amide bonds has attracted the attention of many researchers. The formation of amide bonds can be achieved by various reaction pathways. Several studies have described direct amidation of carboxylic acids using several catalysts such as boron-derived catalysts [15], phosphorus and silicon-derived catalysts [16, 17], organo-catalyzed reactions [18, 19], and metal-catalyzed reactions [20, 21, 22]. Silica gel-based catalysts have also been employed for direct amidation of carboxylic acids [23]. Silica gel worked effectively as a catalyst and solid support in amidation reactions. The silica gel utilized water removal during the reaction and elevated the reaction yield [24].



[a] The reaction was performed with a Dean-Stark trap with 1 mol fatty acid and 1 mol of amine. [b] The reaction was performed using 1 mol of fatty ester and 1 mol of amine.

Scheme 1. Synthesis of lipoamides through direct amidation of (a) fatty acid and (b) via amidation of FAME

Amides can also be prepared by amidation of activated carboxylic acid derivatives such as acyl chlorides, anhydrides, and ester with amine compounds [25, 26, 27]. In situ activation of carboxylic groups can also be carried out using coupling reagents such as *N*,*N*-dicyclohexylcarbodiimide (DCC) [28], silicon compounds [29], activated phosphate [30], $Sn[N(TMS)_2]_2$ [31], Cl_3CCN/Ph_3P [32], $ArB(OH)_2$ [33], chlorosulfonyl isocyanate [34], and 2-mercaptopyridine-1-oxide-based uranium salts [35]. DCC is an example of a challenging coupling agent [22] due to the difficulty of removing its by-product from the reaction mixture. Esters are often used as intermediate compounds in amide synthesis because the ester synthesis method is inexpensive and easy to carry out. The rate of esterification reaction can be influenced by several parameters, including the molar ratio of reactants, temperature, time, catalyst, and esterification reagent [19].

Research on amides continues to develop. This research aims to compare two reaction pathways for lipoamide synthesis, i.e., direct amidation of fatty acid and via amidation of FAME (Scheme 1). These methods provide a robust alternative to well-established ones that appear more general and straightforward for lipoamide synthesis than those currently in use. Therefore, innovative methods for synthesizing lipoamide through understandable approaches are needed. Stearic and oleic acids were employed as a model for unsaturated and saturated fatty acids. The reactivity of aromatic amines and cyclohexylamine were also compared. Aniline, *p*- anisidine, and *p*-nitroaniline were carefully selected as aromatic amines to investigate the effect of electron-withdrawing and electron-donating groups.

2. Experimental

This research compared the preparation of lipoamide through direct amidation of fatty acid and via amidation of FAME. The synthesis of lipoamides via direct amidation was conducted under reflux using a Dean-Stark trap and silica gel as the catalyst. On the other hand, the amidation of FAME was carried out without catalysts and solvent. Both reactions ran simultaneously for 18 hours at the same temperature (130-140°C).

2.1. Materials and Instruments

The materials used in this study were stearic acid (Pudak Scientific). Other reagents: oleic acid, aniline, cyclohexylamine, *p*-anisidine, *p*-nitroaniline, dry methanol, HCl 37%, anhydrous sodium sulfate, dichloromethane, toluene, acetic acid glacial, and silica gel 60 (0.063-0.200 mm) for column chromatography were purchased from Merck (Darmstadt, Germany), *p*- xylene 99% (Loba Chemie), 2',7'-dichlorofluorescein and TLC silica gel 60 F_{254} were purchased from Sigma-Aldrich, ethyl acetate and hexane with technical grade. FTIR (SHIMADZU IRPrestige-21) and ^{1}H NMR (Bruker Avance Neo-Ascend 500) were used for characterization.

2.2. Synthesis of Fatty Acid Methyl Ester (FAME)

The mixture of fatty acid (stearic acid or oleic acid; 10 g), dry methanol (methyl stearate; 8.52 mL, methyl oleate; 8.59 mL), and 0.5% conc. HCl (methyl stearate; 0.159 mL, methyl oleate; 0.16 mL) was refluxed and stirred for 6 hours. The mole ratio of fatty acid and methanol was 1:6 [36]. The reaction was stopped by evaporating the excess of methanol. The reaction mixture was dissolved in hexane and washed twice using water to remove residual methanol and HCl. The organic phase was collected, washed with brine, and dried using anhydrous Na_2SO_4. The formation of fatty acid methyl esters was identified by TLC using hexane-ethyl acetate (3:1) as the eluent system. The conversion ratio of fatty acid to FAME was calculated based on the free fatty acid (% FFA) value before and after the reaction. The % FFA value was determined by alkalimetric titration using NaOH solution.

$$\%\ FFA = \frac{mL\ NaOH \times N\ NaOH \times Mr\ fatty\ acid\ and/or\ methyl\ ester}{g\ sample \times 1000} \times 100\% \quad (1)$$

$$\%\ Conversion = \frac{\%\ FFA\ fatty\ acid - \%\ FFA\ methyl\ ester}{\%\ FFA\ fatty\ acid} \times 100\% \quad (2)$$

2.3. Amidation of FAME

The mole ratio of FAME and amine for this reaction was 1:1. Methyl stearate (1 g; 0.0033 mol), aniline (0.30 g), cyclohexylamine (0.37 g), *p*-anisidine (0.37 g), *p*- nitroaniline (0.31 g). Methyl oleate (1 g; 0.0032 mol), aniline (0.29 g), cyclohexylamine (0.36 g), *p*-anisidine (0.36 g), *p*-nitroaniline (0.30 g). The mixture was heated under reflux conditions for 18 hours at 130-140°C [8]. The formation of products was monitored by TLC using toluene-ethyl acetate (95:5). The reaction mixture was dissolved in hexane and washed twice with water. The organic phase was collected, washed with 1 M HCl and brine, and dried using anhydrous Na_2SO_4. The purification of lipoamides was carried out using column chromatography using a hexane-ethyl acetate system.

2.4. Direct Amidation of Fatty Acid

The mixture of fatty acids and amines (1:1 mol), 20 mL *p*-xylene, and 20% silica gel-reaction mixture as catalysts was refluxed with a Dean-Stark trap for 18 hours at 138°C [23]. Stearic acid (3 g; 0.0105 mol), aniline (0.95 g), cyclohexylamine (1.20 g), *p*-anisidine (1.18 g), and *p*- nitroaniline (1 g). Oleic acid (3 g; 0.0106 mol), aniline (0.96 g), cyclohexylamine (1.21 g), *p*-anisidine (1.19 g), and *p*-nitroaniline (1.01 g). The reaction was

monitored by TLC using toluene-ethyl acetate (95:5). The organic phase was collected, washed with 1 M HCl and brine, and then dried using anhydrous Na_2SO_4. Purification of lipoamides was carried out by column chromatography using toluene-ethyl acetate (98:2). The ratio of silica gel and sample was 30:1.

3. Results and Discussion

3.1. Synthesis of Fatty Acid Methyl Ester (FAME)

The esterification of fatty acids facilitated the activation of the carboxyl group toward amines in the synthesis of lipoamides. In this study, the esterification of stearic acid and oleic acid was performed under acidic conditions, utilizing 0.5% concentrated hydrochloric acid (HCl) as the catalyst. Dry methanol was used in excess to shift the equilibrium to the formation of the product. In addition, excess dry methanol enhanced the solubility of fatty acids. The synthesis of FAME was monitored using thin-layer chromatography (TLC), which indicated a higher Rf value than the starting fatty acid.

The structure of FAME was confirmed using FTIR spectroscopy. Figure 1 displays the FTIR spectra of FAME compared with the corresponding fatty acid as the starting material. The FTIR spectra of FAME did not show a typical strong and broad O-H stretch absorption peak associated with carboxylic acids (fatty acids). On the other hand, a new absorption peak corresponding to the C-O ester bond (1173 cm^{-1}) was detected in the FTIR spectra of FAME. In addition, the C=O absorption has shifted to a larger wavenumber value. The C=O absorption of stearic acid was observed at 1715 cm^{-1} while the C=O absorption of methyl stearate and methyl oleate were respectively at 1746 and 1739 cm^{-1}. The C=O ester tends to absorb light at a higher wavenumber/frequency (1735-1755 cm^{-1}) [37].

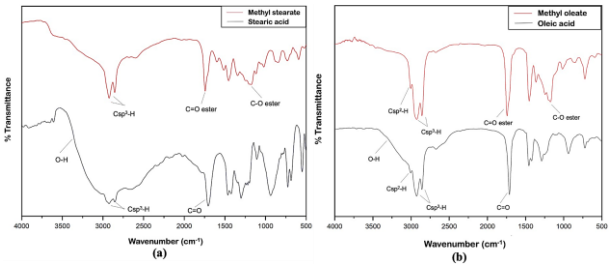


Figure 1. FTIR spectra of (a) methyl stearate and (b) methyl oleate compared to its corresponding fatty acid

In the preliminary study, Masyithah *et al.* [8] reported the results of GC analysis, revealing that the purity of the methyl ester produced was 84.08%. Kang *et al.* [38] also reported the FTIR spectra analysis results, indicating that carboxylic acid (fatty acid) absorption had developed into a new C-O ester absorption peak, suggesting that the fatty acid derivatives were fully converted into esters. The conversion ratio of fatty acid to FAME was calculated based on the free fatty acid (% FFA) value before and after the reaction. This method has good repeatability and is widely utilized for refined oils [39]. The conversion ratio in the synthesis of methyl stearate was 89.56%, and in the synthesis of methyl oleate was 90.70%. The higher the conversion percentage data, the more effectively fatty acids can be converted into methyl esters via the esterification pathway. The data indicated that esterification under acidic conditions was satisfactory for preparing FAME.

3.2. Synthesis Reaction of Lipoamides

Synthesis of lipoamides was conducted using two separate pathways, i.e., direct amidation of fatty acid and via amidation of FAME. The reactivity of saturated and unsaturated fatty acids toward aromatic amine and cyclohexylamine was examined in this research. Direct amidation was performed using silica gel as a catalyst to accelerate the dehydration of fatty amine salt to form the amide bond [40]. The removal of water was facilitated by the Dean-Stark trap. Water removal prevented the hydrolysis of lipoamide and promoted the formation of lipoamide. A solvent with a high boiling point is required to eliminate the water from the reaction mixture. *p*- Xylene was selected as the reaction solvent for this research.

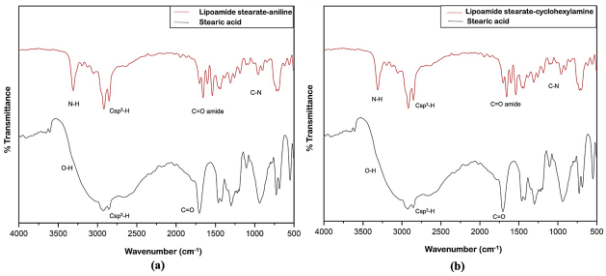


Figure 2. FTIR spectra of (a) lipoamide stearate-aniline and (b) lipoamide stearate-cyclohexylamine compared to stearic acid

Table 1. FTIR data of synthesized lipoamides stearate by direct amidation of fatty acid or via amidation of FAME

Functional group	Wavenumber (cm^{-1})*				
	S	LSA	LSS	LSPA	LSPN
N-H	-	3327	3329	3301	3304
O-H	2500-3300	-	-	-	-
Csp^3-H	2927	2915	2924	2920	2924
C=O	1715	1510-1700	1510-1700	1510-1700	1510-1700
C-N	-	666-800	666-800	666-800	666-800

* S = stearic acid
LSA = lipoamide stearate-aniline
LSS = lipoamide stearate-cyclohexylamine
LSPA = lipoamide stearate-*p*-anisidine
LSPN = lipoamide stearate-*p*-nitroaniline

Table 2. FTIR data of lipoamides oleate by direct amidation of fatty acid or via amidation of FAME

Functional group	Wavenumber (cm^{-1})*				
	O	LOA	LOS	LOPA	LOPN
N-H	-	3327	3329	3301	3304
O-H	2500-3300	-	-	-	-
Csp^2-H	3010	3004	3004	3008	3008
Csp^3-H	2927	2930	2928	2917	2918
C=O	1715	1510-1700	1510-1700	1510-1700	1510-1700
C-N	-	666-800	666-800	666-800	666-800

* O = oleic acid
LOA = lipoamide of oleate-aniline
LOS = lipoamide of oleate-cyclohexylamine
LOPA = lipoamide of oleate-*p*-anisidine
LOPN = lipoamide of oleate-*p*-nitroaniline

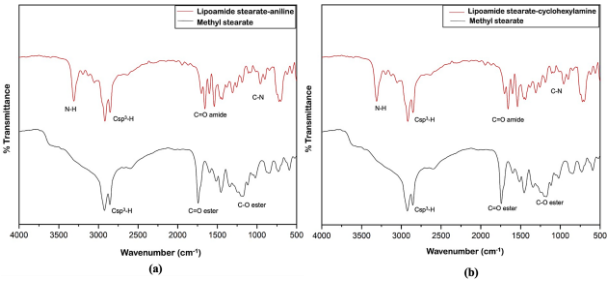


Figure 3. FTIR spectra of (a) lipoamide stearate-aniline and (b) lipoamide stearate-cyclohexylamine compared to methyl stearate

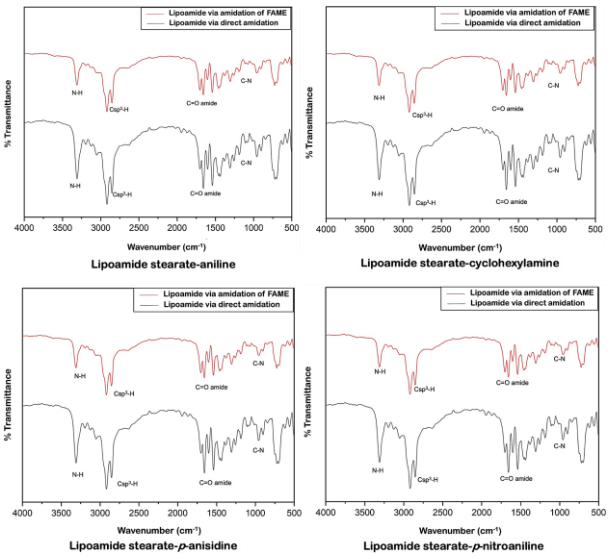


Figure 4. FTIR spectra of lipoamides stearate synthesized via direct amidation compared with lipoamides obtained via amidation of FAME

Yang *et al.* [41] reported that the direct amidation using toluene as a solvent only produced a yield of 28%. In other words, the higher boiling point of *p*-xylene (b.p. 138°C) was advantageous for forming amide bonds compared to toluene (b.p. 111°C). In addition, using 20% silica gel as a catalyst enhances the rate of steps without actually engaging in it. On the other hand, the amidation of FAME was conducted without solvent and catalyst. The unreacted amines from both reactions were removed by extraction using 1 M HCl to make the product purification easier. The physical form of lipoamide obtained after the purification of products of both reaction pathways was similar. All lipoamides were solid at room temperature. The TLC profiles conveyed that the lipoamide was formed during the reaction. The spot of lipoamide obtained from direct amidation was seen at higher Rf values than the fatty acid as the starting material (for comparison, the TLC profiles lipoamides are summarized in Supplementary Table S.1-S.4).

3.3. FTIR Spectra

The synthesized lipoamide was characterized using FTIR. The two representative FTIR spectra of lipoamides from direct amidation are presented in Figure 2, while Figure 3 shows the FTIR spectra of lipoamides obtained via the amidation of FAME. The successful synthesis of lipoamide via direct amidation was indicated by the absence of strong and broad O-H absorption in the lipoamide products (Figure 2). Furthermore, the FTIR spectra confirmed the formation of lipoamide via the amidation of FAME, as evidenced by the disappearance of the C-O ester absorption peak in the product lipoamides (Figure 3).

The formation of all lipoamide from both reaction pathways was verified by the appearance of a new single peak N-H absorption at 3300 cm^{-1} and C-N absorption at around 666-800 cm^{-1}. These findings are consistent with previous studies on lipoamide, which reported the presence of N–H stretch/bend vibrations at 3500 cm^{-1}, 3280 cm^{-1}, and 3300 cm^{-1} [42, 43]. Furthermore, the existence of multiple peaks at around 1510-1700 cm^{-1} validated the amide structure of lipoamides [42].

FTIR spectra of lipoamides from direct amidation and via amidation of FAME were combined to ensure that both reaction pathways produced the same lipoamide. The FTIR spectra of lipoamides stearate are presented in Figure 4, and the FTIR spectra of lipoamides oleate are displayed in Figure 5. The FTIR spectra showed that the lipoamide from both reaction pathways was the same. The detailed FTIR peak list of all lipoamides is presented in Table 1 and Table 2.

Table 3. Reaction yield of lipoamides stearate and oleate obtained from direct amidation of fatty acid and via amidation of FAME using several amine compounds

Sample	Amine compound	Yield (%)	
		Direct amidation	Amidation of FAME
Lipoamide oleate	aniline	80.33	31.18
	p-anisidine	80.04	32.76
	p-nitroaniline	71.75	31.63
	cyclohexylamine	76.82	36.17
Lipoamide stearate	aniline	79.77	31.84
	p-anisidine	80.83	33.88
	p-nitroaniline	78.05	24.39
	cyclohexylamine	78.27	36.51

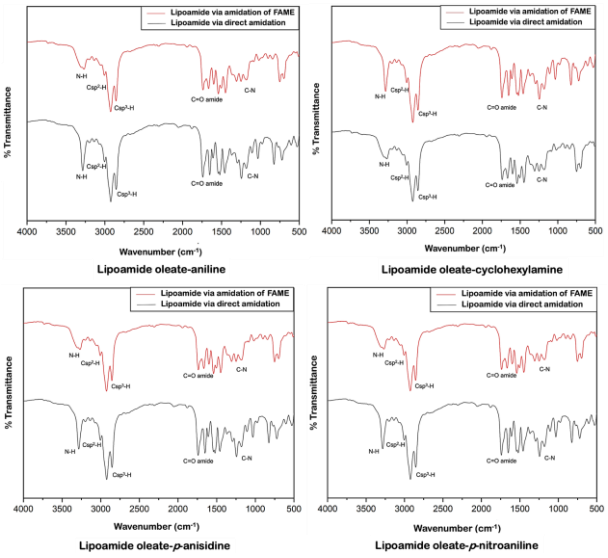


Figure 5. FTIR spectra of lipoamides oleate synthesized via direct amidation compared with lipoamides obtained via amidation of FAME

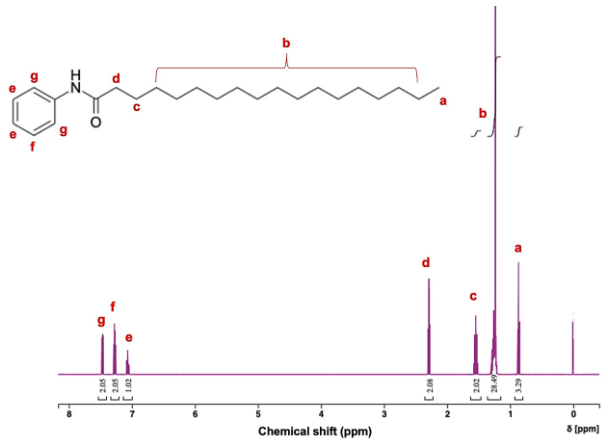


Figure 6. ^{1}H NMR spectra of lipoamide stearate-aniline

3.4. Reaction Yield

Table 3 represents the yield of lipoamide from direct amidation and via amidation of FAME. In general, the reaction pathway impacted the yield of lipoamide. The yield of lipoamides produced by direct amidation was two-fold higher than that produced via amidation of FAME. The type of fatty acid and amine did not significantly influence the yield. Theoretically, cyclohexylamine should have stronger nucleophilicity than aniline. However, the steric hindrance of cyclohexyl chair conformation around the amine group of cyclohexylamine may slightly reduce the reactivity of the amine group. The presence of NO_2 substituent on aniline lowered the yield of the lipoamide obtained from direct amidation. The strong electron-withdrawing properties of NO_2 decreased the basicity of *p*-nitroaniline. Therefore, the acid-base reaction between fatty acid and amine during the formation of lipoamide was obstructed.

Following these results, direct amidation of fatty acid was preferred for synthesizing lipoamides over amidation of FAME. Table 4 summarizes the effectiveness of both methods. The yield of lipoamides produced by direct amidation was two-fold higher than that produced via amidation of FAME. This is because direct amidation converts fatty acids directly into lipoamides in a single-step reaction, whereas amidation of FAME involves two steps. In addition, the direct amidation requires a shorter synthesis time for producing lipoamides.

3.5. ^{1}H NMR Spectra

Lipoamide stearate-aniline was chosen as a representative for characterization using ^{1}H NMR. The ^{1}H NMR characterization was performed to strengthen the evidence for the formation of lipoamide. ^{1}H NMR spectra of lipoamide stearate-aniline (Figure 6) confirmed the structure of the lipoamide. The detailed data ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) of lipoamide stearate-aniline was δ (ppm) 0.86 (3H, *J* = 7.00 Hz), 1.15-1.36 (28H, m), 1.54 (2H, *J* = 7.67 Hz), 2.29 (2H, *J* = 7.37 Hz), 7.07 (1H, *J* = 7.76 Hz), 7.27 (2H, *J* = 8.08 Hz), and 7.47 (2H, dd, *J* = 8.46, 1.12 Hz). Proton-type H_E, H_F, and H_G from the aniline structure display the largest chemical shift values in the downfield area at around 7 to 8 ppm. The electronegativity of atom O carbonyl also shifted the peak of proton H_C and H_D in the downfield area, respectively, at 1.54 and 2.29 ppm compared to the other protons. The electronegative atoms surrounding the proton affect the chemical shift of the proton signal [44].

Table 4. Comparison of lipoamide synthesis by direct amidation and via amidation of FAME

Method	Time	Catalyst	Reaction condition	Yield
Direct amidation	all lipoamides were run simultaneously for 18 hours at 130- 140°C, but lipoamides with *p*- anisidine only 12 hours	silica gel	one step reaction	70-80%
Amidation of FAME	all lipoamides were run simultaneously for 18 hours at 130- 140°C, but lipoamides with *p*- anisidine only 12 hours	without catalyst	two-step reaction	20-30%

4. Conclusion

In conclusion, we have compared two methods for preparing lipoamides: direct amidation of fatty acid and amidation of FAME. Both methods were suitable for preparing lipoamides from unsaturated and saturated fatty acids using aromatic amines or cyclohexylamine. The type of fatty acid and amine did not significantly affect the reaction yield. Direct amidation of fatty acids was preferred because the yield was two times higher than the synthesis of lipoamides via amidation of FAME. The yield of lipoamide from direct amidation was quite satisfactory at around 70-80%.

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