Malaysian Journal of Analytical Sciences, Vol 21 No 5 (2017): xxx - xxx
DOI: https://doi.org/10.17576/mjas-2017-2105-zz

MALAYSIAN JOURNAL OF ANALYTICAL SCIENCES

Published by The Malaysian Analytical Sciences Society

ISSN
1394 - 2506

SYNTHESIS AND X-RAY SINGLE CRYSTAL STUDY OF 3-DIBUTYNYL AND 4-DIPENTYNYL PYRIDINE-2,6-DICARBOXYLATE

(Sintesis dan Kajian Sinar-X Hablur Tunggal 3-dibutinil dan 4-dipentinil piridina-2,6-dikarboksilat)

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Received: 7 March 2017; Accepted: 19 July 2017

Abstract

Two pyridine-2,6-dicarboxylates each containing butynyl and pentynyl at position 2 and 6 were synthesized by esterification of 2,6-pyridinedicarbonyl dichloride with *N*-alkyne alcohol. All compounds were characterized by using nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR) and mass spectrometry (MS) techniques. Crystallographic studies showed that both compounds, 3-dibutynyl pyridine-2,6-dicarboxylate **(3a)** and 4-dipentynyl pyridine-2,6-dicarboxylate **(3b)** crystallized in monoclinic system with same space group of C 2/c.

Keywords: diester macrocyclic, esterification, X-Ray structural study

Abstrak

Dua sebatian piridina dikarboksilat, 3-dibutinil dan 4-dipentinil pada kedudukan 2 dan 6 telah berjaya disintesiskan dengan tindak balas pengesteran di antara 2,6-piridinadikarbonil diklorida dengan *N*-alkuna alkohol. Setiap sebatian berjaya dicirikan dengan teknik spektroskopi resonans magnetik nuklear (RMN), infra merah (IR) dan spektrometri jisim (MS). Kajian kristalografi menunjukkan sebatian 3-dibutinil piridina-2,6-dikarboksilat **(3a)** dan 4-dipentinil piridina-2,6-dikarboksilat **(3b)** terhablur dalam sistem monoklinik dengan kumpulan ruang C 2/c.

Kata kunci: makrosiklik diester, tindak balas pengesteran, kajian struktur sinar-X

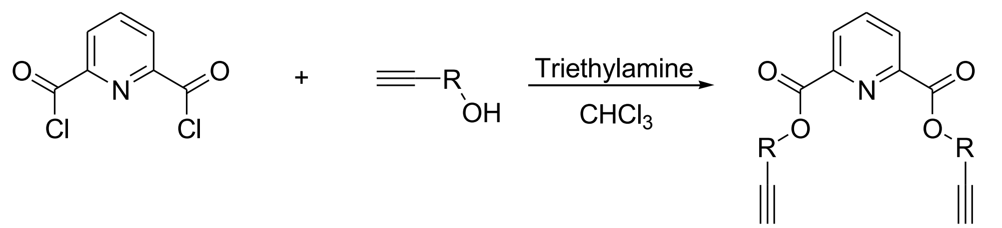
Introduction

The synthesis study of macrocyclic has been rapidly developed for almost 40 years [1]. The design of this compound can be varies depending on the linker being used such as pyridine, benzene or aliphatic chain. The side chain can be functional group of ester, ether, thiourea, alkyne and alkene [2-7]. Various derivatives have been reported due to straightforward preparation and potential in biological activities and medicine.

Macrocyclic compound is an important reference compound in chemistry studies such as complexation to metal due to existence electron donating atom in the ligand [8-9]. Some of macrocyclic derivatives have been reported showing great capability in antibacterial, anticancer and HIV treatment [10-14]. Besides that, macrocyclic compounds contained alkene or alkyne ligands have been studied in recent trend of metathesis reaction. This reaction has been shown to facilitate several complicated reaction steps especially in natural product synthesis such as lactones and marine alkaloid nakadomarin A [15].

Esters are commonly synthesized from the condensation reaction between carboxylic acid and alcohol with the loss of water. The esters can also be prepared by other reactions using acid anhydrides, acid chloride, unsaturated hydrocarbon, amides, nitriles, ethers, aldehydes, ketones, alcohols, and ester itself. The synthesis of these macrocyclic were carried out by esterification reaction with acyl chloride and alkyne alcohol in the presence of triethylamine as a base. The nitrogen's lone pair of triethylamine assisted the deprotonation of hydrogen at hydroxyl to initiate the esterification reaction.

This is demonstrated in the present work where pyridine acyl chloride was reacted with alkyne alcohol to form pyridine bridged diester macrocyclic followed by 3- and 4-dialkyne to form 3-dibutynyl pyridine-2,6-dicarboxylate **3a** and 4-dipentynyl pyridine-2,6-dicarboxylate **3b**, respectively (Scheme 1). With the help of X-ray structure, we could see either the presence of lone pair of nitrogen pyridine, position of the ester on ring or the *sp* hybridization of alkyne would give effect on geometry of the isomers. Following this, the designing of next product for future study, especially in complexation or metathesis reaction become facile. Thus, the synthesis, characterization and X-ray structures of the isomers are presented.



1 **2** **3a/3b**

3a R= CH_2CH_2

3b R= $CH_2CH_2CH_2$

Scheme 1. Synthesis of N-dialkyne pyridine-2,6-dicarboxylate, 3a and 3b at ambient temperature with percentage yield of 76% and 63%

Materials and Methods

Materials

2,6-pyridinedicarbonyl dichloride, 3-butyn-1-ol, 4-pentyn-1-ol, triethylamine, chloroform, cyclohexane and ethyl acetate were purchased from Sigma Aldrich. Other chemicals were analytical grades and used as received.

Instruments

The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (Merck Kieselgel $60F_{254}$ UV indicator). Column chromatography was performed using silica gel Merck Kieselgel (230-400 mesh). The NMR spectra were recorded by Bruker spectrometer at 400 MHz for ^1H NMR using tetramethylsilane (TMS) as internal standard and 100 MHz for ^{13}C NMR. The coupling constant (J) are given in Hz. IR spectra were recorded in the range of 4000-370 cm^{-1} using a Perkin Elmer Spectrum GX with samples prepared as KBr pellets. The melting point was determined by using Barnstead Electrothermal IA9000 Series Melting Point Apparatus with oven temperature range ambient to 400 °C. The Mass spectrometry was recorded by Bruker MicroToF Q with method of direct infuse and source type electro-spray ionization (ESI).

Synthesis of *N*-dialkyne pyridine-2,6-dicarboxylate

2,6-pyridinedicarbonyl dichloride (4.9 mmol, 1g) was dissolved in 25 mL chloroform inside the one-neck round bottom flask. Alkyne alcohol solution (9.8 mmol) is added into the mixture followed with 2.1 mL of triethylamine. The mixture was stirred at 0 °C for 10 minutes and continued stir at room temperature for 18 hours. The mixture

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then dried under vacuum and the residue purified by flash chromatography (cyclohexane/ethyl acetate) to give colorless crystal upon evaporation. The crystals are suitable for X-ray study.

Results and Discussion

Representative data for synthesis 3-dibutynyl pyridine-2,6-dicarboxylate, 3a

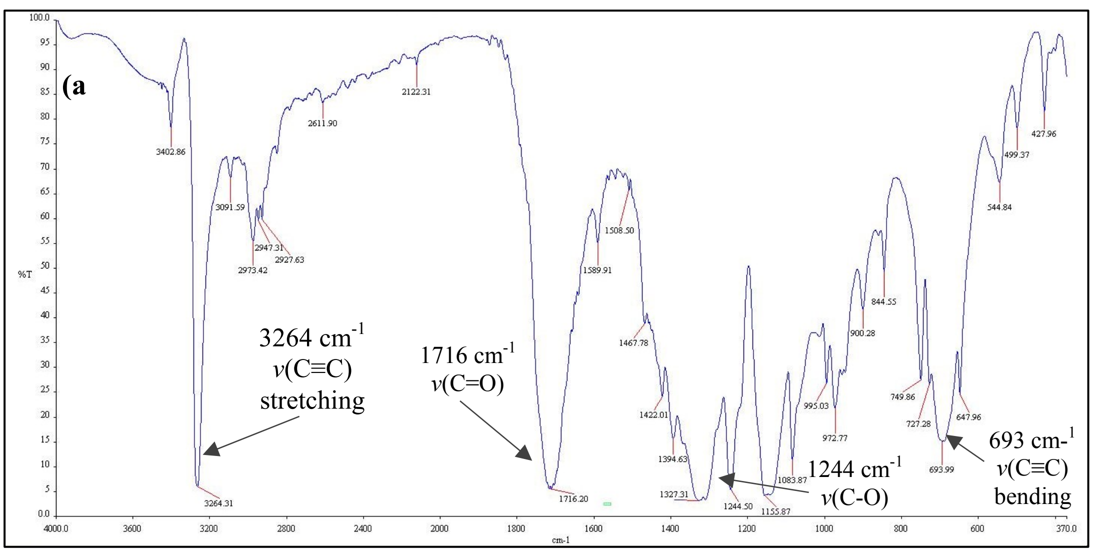
The compound was obtained as colorless crystal in 76% yield after recrystallization. Mp 86 - 87 °C. IR (KBr pellets) υ/cm^{-1}: 3264 (stretching C≡C), 1716 (C=O), 1327 (Ar-N), 1244 (C-O), 693 (bending C≡C).; ^{1}H NMR (400 MHz; $CDCl_3$) $\delta_{H\ 2.06}$ (2H, s, C≡CH), 2.73 (4H, t, J= 6.8, 2xC*H_2*C≡C*H*), 4.52 (4H, t, J= 7.2, 2xOCH_2CH_2C≡CH), 8.02 (1H, t, J=7.6, ArH), 8.30 (2H, d, J=7.6, 2xArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 18.9 (CH_2C≡CH), 63.6 (O-*C*H_2), 70.3 (*C*≡CH), 79.5 (*C*≡CH), 128.2 (Ar*C*H), 138.4 (Ar*C*H), 148.1 (Ar*C*), 164.1 (*C*=O). HRMS (ES^+) m/z calculated for $C_{15}H_{13}NO_4Na$ $[M+Na]^+$ 294.2578, found 294.0740.

Representative data for synthesis 4-dipentynyl pyridine-2,6-dicarboxylate, 3b

The compound was obtained as colorless crystalline in 63% yield after recrystallization. Mp 80 - 82 °C. IR (KBr pellets) υ/cm^{-1}: 3278 (stretching C≡C), 1736 (C=O), 1288 (Ar-N), 1237 (C-O), 693 (bending C≡C). ^{1}H NMR (400 MHz; $CDCl_3$) $\delta_{H\ 2.01}$ (2H, s, C≡CH), 2.09 (4H, **t**, J= 8, 2xC*H_2*C≡C*H*), 2.41 (4H, q, J= 4, 2xCH_2CH_2C≡CH), 4.54 (4H, t, J=8, 2xO-$CH_2CH_2CH_2$C≡CH), 8.02 (1H, t, J=8, ArH), 8.27 (2H, d, J=8, 2xArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 15.27 (CH_2C≡CH), 27.45 (O-CH_2-CH_2)64.70 (O-CH_2), 69.26 (C≡CH), 82.87 (C≡CH), 127.90 (ArCH), 138.25 (ArCH), 148.44 (ArC), 164.51 (C=O). HRMS (ES+) m/z calculated for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$ 322.3109, found 322.1158.

Characterization

The infrared spectra for both ester macrocyclic isomers, **3a** and **3b** showed the presence of the stretching frequency at 3264 and 3278 cm^{-1} due to the existence of terminal alkyne. The peak at 1716 and 1740 cm^{-1} are the stretching frequencies for the *ν* (C=O). For the peak at 1327 and 1288 cm^{-1} are referred to aromatic amine of the pyridine and peak at 1244 and 1237 cm^{-1} are for the ether group. Sharp peak at 693 and 654 cm^{-1} are referring to bending mode of the terminal alkyne. Figure 1(a) display the IR spectrum of **3a** and (b) for compound **3b**.



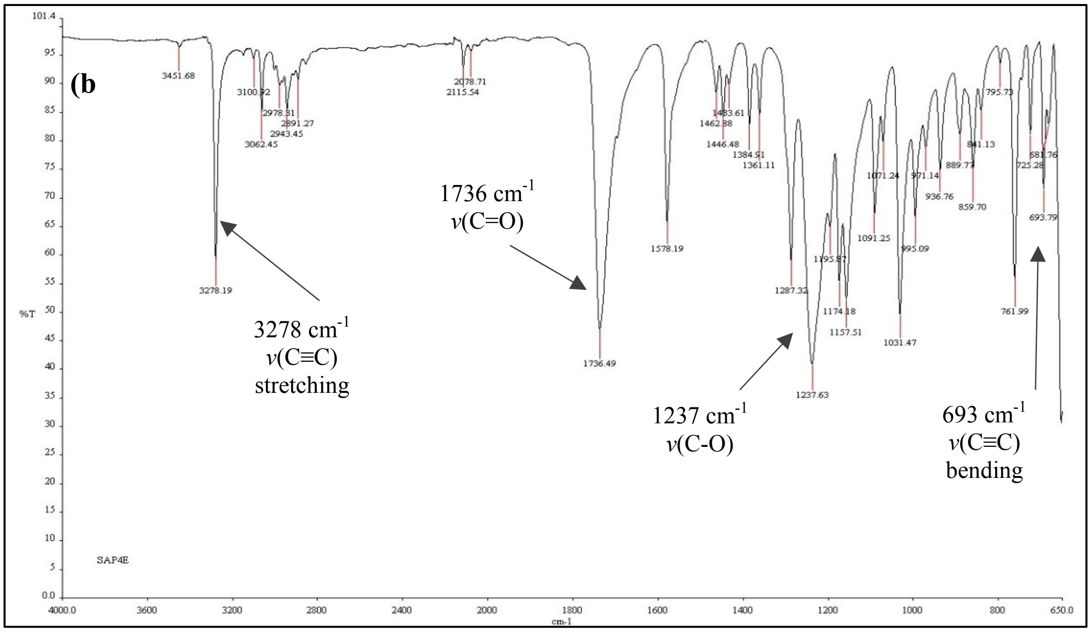


Figure 1. The IR spectrum of (a) **3a** and (b) **3b**

The chemical shifts of the pyridine rings protons for the both isomers are similar and appeared as a dublet at 12.0 and a triplet at 11.0 ppm, respectively. The terminal alkynes protons for the compounds **3a** and **3b** were found in the range of 1.0-2.0 ppm. The chemical shifts of the methylene protons near the alkyne ($-CH_2C{\equiv}CH$) appeared at the range of 2.07-5.02 ppm while the methylene protons's chemical shifts are found at 4.50 ppm. In the ^{13}C NMR spectra, the carbon chemical shifts of C=O is found at 174.0 ppm, respectively for the both isomers. The aromatic pyridine carbon chemical shifts of the isomers appeared in the range of 124.5-136.0 ppm. The chemical shift for the terminal alkyne observed at the range of 21.1-43.8 ppm. The value of molecular ion peak found in mass spectrometry for **3a** and **3b** are agreed with the expected molecular weight, respectively.

X-ray crystallographic study

The colorless crystals of **3a** and **3b** are crystallized in monoclinic system with same space group of C 2/c. The crystallographic data are summarized in Table 1.

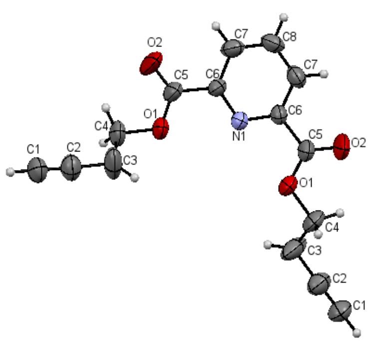
Table 1. Crystal data and structure refinement for the compounds **3a** and **3b**.

Crystal Parameters	**3a**	**3b**
CCDC deposition number	1535752	1536022
Empirical formula	$C_{15}H_{11}NO_4$	$C_{17}H_{17}NO_4$
Formula weight	269.25	299.31
Temperature	303(2) K	303(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	C 2/c	C 2/c
Unit cell dimensions	a = 13.2710(16) Å	a = 24.577(4) Å
	b = 11.7023(14) Å	b = 6.3136(9) Å
	c = 8.9657(10) Å	c = 10.5608(14) Å
	α = 90°	α = 90°
	β = 102.672(4)°	β = 99.562(5)°
	γ = 90°	γ = 90°

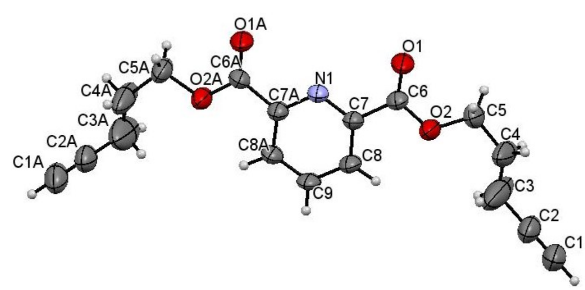
Table 1 (cont'd). Crystal data and structure refinement for the compounds **3a** and **3b**.

Crystal Parameters	**3a**	**3b**
Volume	1358.5(3) Å^3	1616.0(4) Å^3
Z	4	4
Density (calculated)	1.316 Mg/m^3	1.230 Mg/m^3
Absorption coefficient	0.097 mm^{-1}	0.088 mm^{-1}
F(000)	560	632
Crystal size	0.480 x 0.300 x 0.130 mm^3	0.480 x 0.160 x 0.080 mm^3
Theta range for data collection	3.053 to 24.972°	3.334 to 24.966°
Index ranges	-15<=h<=15, -13<=k<=13, -9<=l<=10	-28<=h<=28, -7<=k<=7, -12<=l<=12
Reflections collected	18132	16291
Independent reflections	1197 [R(int) = 0.0714]	1420 [R(int) = 0.0988]
Completeness to theta	99.9 %	99.9 %
Max. and min. transmission	0.988 and 0.955	0.993 and 0.959
Refinement method	Full-matrix least-squares on F^2	Full-matrix least squares on F^2
Data / restraints / parameters	1197 / 0 / 92	1420 / 1 / 101
Goodness-of-fit on F^2	1.071	1.372
Final R indices [I>2sigma(I)]	R1 = 0.0734, wR2 = 0.1969	R1 = 0.1094, wR2 = 0.2461
R indices (all data)	R1 = 0.1031, wR2 = 0.2305	R1 = 0.1695, wR2 = 0.2763
Largest diff. peak and hole	0.391 and -0.322 e.Å^{-3}	0.735 and -0.587 e.Å^3

Figure 2 shows the structure molecular with labels of the molecules **3a** and **3b**. Both molecules with the pyridine linker and both side chains groups, respectively adopt a cis-cis against the C=O bond. The two molecules have asymmetric unit of ½ independence molecule generated since they are centrosymmetric across the N1/C8 and N1/C9 atoms.



3a



3b

Figure 2. ORTEP diagrams of compund 3a and 3b drawn at 50% probability displacement ellipsoids

Compound **3a** possess a planar geometry by its pyridine ring N1/(C6-C8)/C6a-C7a) with the ester C4-C5/O1-O2 and C4a-C5a/O1a-O2a with maximum deviation of 0.016 Å for atom C4. The pyridine and ester groups are perpendicular with the alkyne side chain with dihedral angle to the ester at C5/O1/C4/C3 with -139.8(4)°. As for compound **3b**, all atoms are in planar with maximum deviation at C8 with 0.052(4) Å. The bond lengths and angles are in normal ranges for both compounds (Table 2).

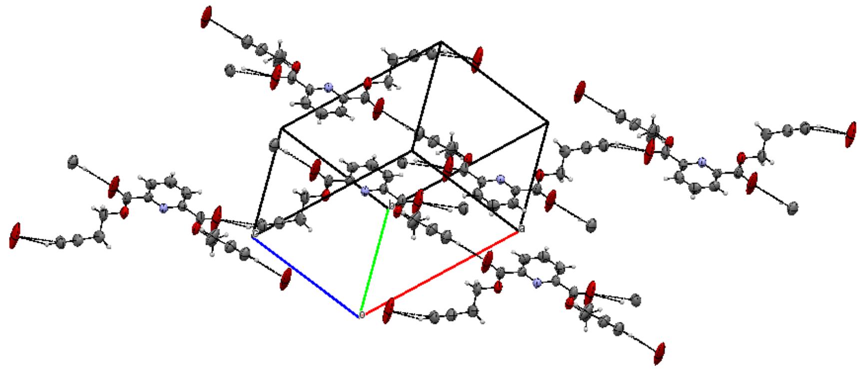
Table 2. Selected Bond Lengths (Å) and Bond Angles (°) for Compounds **3a** and **3b**

Compound 3a		**Compound 3b**	
Bond	**Dist.**	**Bond**	**Dist.**
O1—C5	1.300 (4)	O1—C6	1.193(5)
O1—C4	1.456 (4)	O2—C6	1.327(5)
O2—C5	1.177 (4)	O2—C5	1.458(6)
N1—C6#1	1.332(3)	N1—C7	1.337(5)
N1—C6	1.333 (3)	N1—C7#1	1.337(5)
C1—C2	1.166 (5)	C1—C2	1.127(8)
C2—C3	1.463 (5)	C2—C3	1.405(10)
C3—C4	1.455 (6)	C3—C4	1.504(8)
C5—C6	1.492 (4)	C4—C5	1.449(9)
C6—C7	1.386 (5)	C6—C7	1.493(6)
C7—C8	1.360 (4)	C7—C8	1.391(6)
C8—C7#1	1.360 (4)	C8—C9	1.369(6)
		C9—C8#1	1.369(6)
Angle	**(°)**	**Angle**	**(°)**
C5—O1—C4	116.5 (3)	C6—O2—C5	117.1(4)
C6#1—N1—C6	115.8 (4)	C7—N1—C7#1	117.1(5)
C1—C2—C3	178.1 (4)	C1—C2—C3	169.7(10)
C4—C3—C2	112.2 (3)	C2—C3—C4	115.9(8)
C3—C4—O1	108.2 (3)	C5—C4—C3	123.2(7)
O2—C5—O1	123.4(3)	C4—C5—O2	109.7(5)
O2—C5—C6	121.5(3)	O1—C6—O2	122.6(5)
O1 —C5 —C6	115.2(3)	O1—C6—C7	126.1(4)
N1 —C6 —C7	123.8(3)	O2—C6—C7	111.3(4)
N1 —C6 —C5	119.0(3)	N1—C7—C8	123.0(5)
C7 —C6 —C5	117.2(3)	N1—C7—C6	115.3(4)
C8 —C7 —C6	118.9(3)	C8—C7—C6	121.6(4)
C7#1—C8 —C7	118.7(4)	C9—C8—C7	119.0(5)
		C8#1—C9—C8	118.9(6)

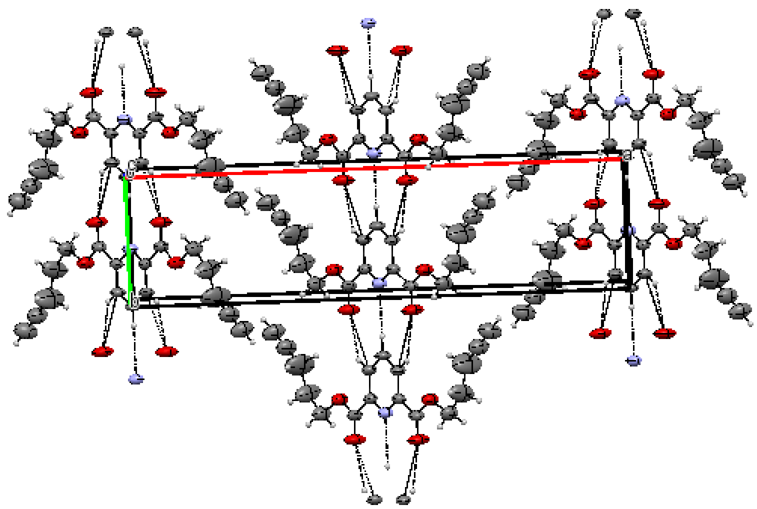
In the crystal structure, the **3a** molecule is linked by C1—H1···O2 intermolecular hydrogen bond. In contrast with molecule **3b**, linked by nitrogen of pyridine with the hydrogen methine of C9 pyridine, N1···H9—C9 and oxygen carbonyl and hydrogen methine of C8 pyridine, C8—H8···O1 (Table 3). The intermolecular hydrogen bond for molecule **3a** and **3b** formed a network of polymorph at b-axis and c-axis (Figure 3).

Table 3. Hydrogen Bond Lengths (Å) and Bond Angles for Compounds **3a** and **3b**

Compound	**D—H····A**	**D—H**	**H····A**	**D····A**	**D—H····A**	**Symmetry code**
3a	C1—H1····O2#2	0.93	2.25	3.131(6)	159	½-x, ½+y, -1/2-z
3b	C8—H8····O1$1#2	0.93	2.51	3.182(6)	129.3	-x+2, y, -z+1/2
	C9—H9····N1#2	0.93	2.60	3.531(8)	180	2x, y-1, z



3a



3b

Figure 3. Polymorph network of molecule at b-axis (**3a**) and c-axis (**3b**). The dash line indicates the intermolecular hydrogen bond

Conclusion

The ester macrocyclic 3-dibutynyl-2,6-pyridine dicarboxylate and 4-dipentynyl-2,6-dicarboxylate were successfully synthesized by condensation reaction and fully characterized using spectroscopic techniques. Both compounds were crystallized in the solvent system of cyclohexane and ethyl acetate for purification and afforded colorless and needle-liked crystals. The observation on CCDC data has no record on these compounds. Both compounds have monoclinic system with space group of C 2/c but different geometry as **3b** showed fully geometry planar. The intermolecular hydrogen bond gave the compounds a polymorph network in the crystal structure. The terminal alkynes on both compounds are suitable metathesis reaction. Thus, further study on the metathesis reaction and optimization to obtain cyclic compounds are in progress.

Acknowledgement

The authors thank the Ministry of Higher Education of Malaysia and Universiti Kebangsaan Malaysia for the research grant GUP-2016-059. The assistance of Mr Mohammad Fadzlee bin Ngatiman at Centre of Research and

Instrumentation Management. One of the authors, Nawwar Hanun would like to thank the Ministry of Higher Education of Malaysia for the Mybrain15 scholarship.

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