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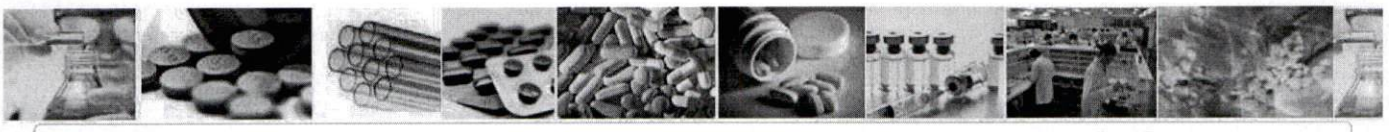

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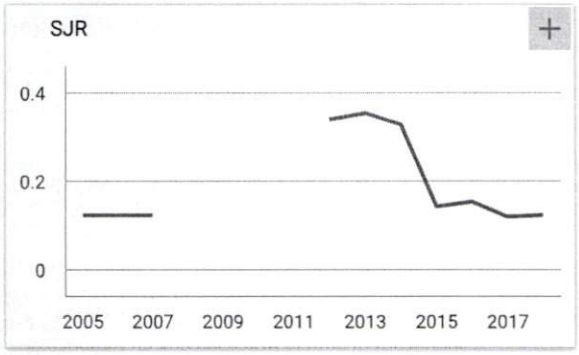
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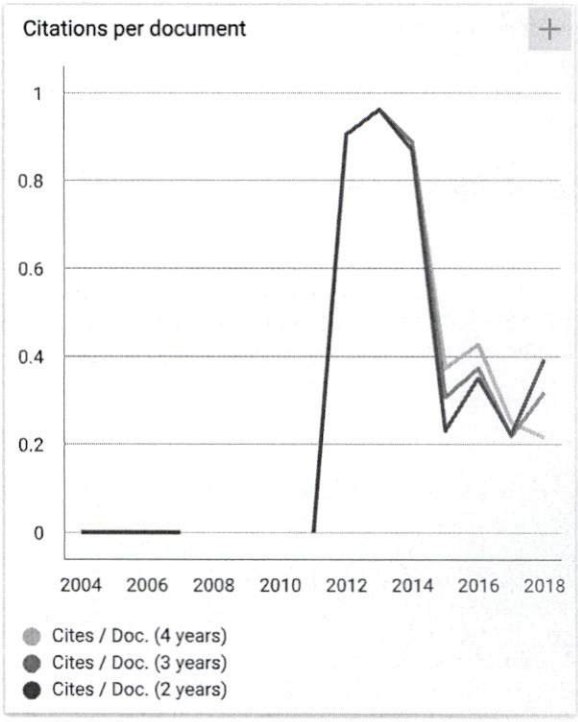
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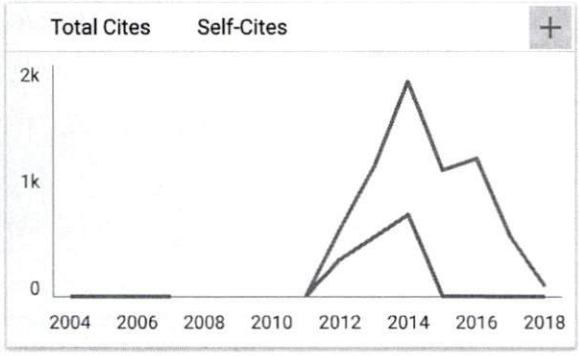
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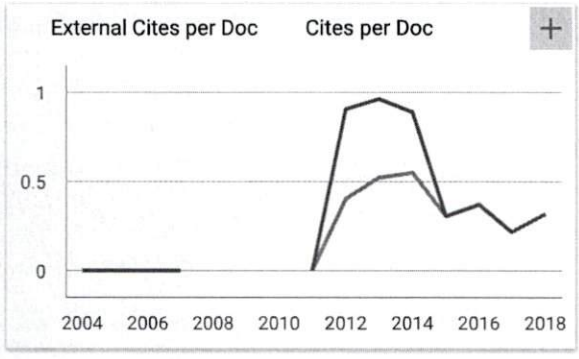
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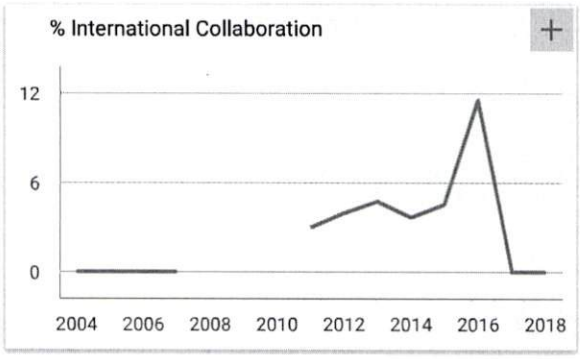
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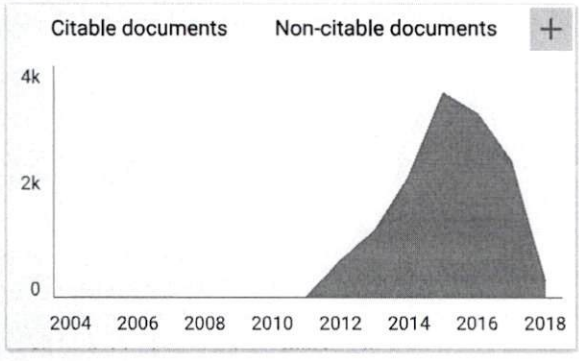
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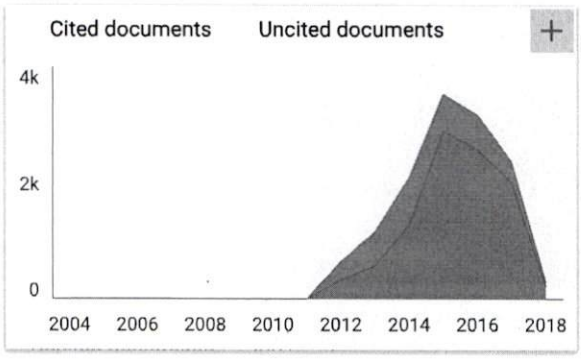
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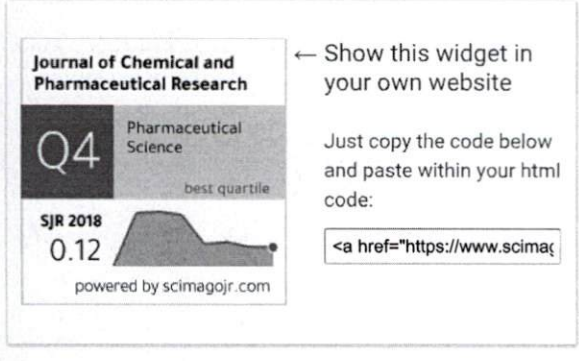
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Research Article

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The Influence of Ratio Pyridine and Triethylamine Catalysts on Synthesis 2-Phenyl-Benzo[D] [1,3] Oxazine-4-On Derivatives

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Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Airlangga, Indonesia

ABSTRACT

The aim of this research was to compare the effect of pyridine and triethylamine catalyst ratios on the synthesis of 2-phenyl-benzo(d)[1,3] oxazine-4-one derivatives. The catalysts used were triethylene amine (100%), pyridine: triethylamine (1: 4 mol); Pyridine: triethylamine (1: 1 mol) and pyridine (100%). Using pyridine (100%) as a catalyst could increase the percentage of the synthesis of 2-phenyl-benzo[d][1,3] oxazine-4-one derivatives to 2 times greater than pyridine: triethylamine (1: 4 mol) as a catalyst. Using pyridine (100%) as a catalyst in the synthesis of 2-phenyl-benzo[d] [1,3]oxazine-4-one derivatives were more effective and efficient by obtaining the following results we obtained 80% for 2-phenyl-4H-benzo[1,3]oxazin-4-one and 86% for 2-(3,4-dichlorophenyl)-4H-benzo[1,3]oxazin-4-one and 82% for 2-(2,4-dichlorophenyl)-4H-benzo[1,3]oxazin-4-one and 46% for 2-(4-nitrophenyl)-4H-benzo[1,3]oxazin-4-one.

Keywords: Catalysts; Triethylene amine; Pyridine; Benzoxazine

INTRODUCTION

Benzoxazine is a heterocyclic compound that has the potential of biological activity to be developed as new drugs. Some of benzoksazine derivatives had been reported as antihypertensive [1], antimicrobial [2], antifungal [3,4], antimicrobial [5-7] andanticancer activity [8,9]. Research on the synthesis of benzoxazine derivatives from the starting material of anthranilic acid was reacted with benzoyl chloride derivatives has been widely practiced [10-12]. The general procedure of synthesis was used pyridine as solvent and catalyst to obtain benzoxazine derivatives [11]. In this research aims to compare triethylamine and pyridine as solvents and catalysts to obtain optimal yield percentages for benzoksazine derivatives.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from Sigma Aldrich and Merck. Reactions were monitored with TLC using pre-coated aluminum sheets with GF254 silica gel, 0.2 mm layer thickness (E. Merck). Eluen for TLC using n-hexane : ethyl acetate (5:2) and the spots were visualized in UV chamber. Melting points of the synthesized compounds were measured with an Electrothermal melting point apparatus. IR spectra were obtained using a Perkin Elmer Spectrum One spectrophotometer using KBr disks. ^{1}H- NMR and ^{13}C-NMR spectra were obtained on JEOL JNM-ECS 400 (1H-NMR: 400 MHz, 13C-NMR: 100 MHz) instrument from Institute of Tropical Disease Airlangga University. We used DMSO-d6 as solven for ^{1}H-NMR and ^{13}C-NMR analysis. Chemical shifts were measured relative to internal standard TMS (d: 0).

Chemical shifts are reported in ∂ scale (ppm). MS spectra were measured with a JEOL JMS 600 spectrometer by using the ESI methods.

General Synthesis

Anthranilic acid (0.05 mol) was dissolved in some of rasioTriethylamine: Pyridine. There are four treatment condition, the first using 100% pure Triethylamine 5 ml; second using Triethylamine 4.3 mL and Pyridine 0.5 mL to make rasioTriethylamine : Pyridine with (1 : 4 mole). Third using Triethylamine 5 mL and Pyridine 3 mL to make rasioTriethylamine : Pyridine with (1 : 1 mole) and fourth using 100% pure Pyridine 5 ml. Some of benzoyl chloride derivatives (0.075 mol) such as 3,4-dichloro benzoyl chloride; 2,4-dichloro benzoyl chloride; 4-nitro benzoyl chloride was added slowly with constant stirring at 0°C temperature. The mixture was stirred for 1.5 hours at 0°C temperature followed by treatment with 10% $NaHCO_3$. Addition of sodium bicarbonate solution was continued until the effervescence due to the evolution of carbon-dioxide ceased. The separated solid was allowed to settle down and filtered off. It was washed with cold water repeatedly until there was no smell of pyridine and unreacted benzoyl chloride derivatives. The solid obtained was recrystallized with ethanol 96% to obtain the compounds. Completion of the reaction was determined by TLC using n-hexane: ethyl acetate (5:2) as mobile phase.

RESULTS AND DISCUSSION

Reaction on Anthranilic Acid with Some of benzoyl chloride derivatives such as 3,4-dichloro benzoyl chloride; 2,4-dichloro benzoyl chloride; 4-nitro benzoyl chloride was dissolved in basic and free-water solvent, obtained 2-phenyl-(4*H*)-benzo[1,3]oxazin-4-one derivatives. The mechanism of the reaction, The first step of the reaction is addition of the nucleophilic amine (-NH_2) Anthranilic acid to the electrophilic carbonyl group from acyl chloride. The base is important because it removes the proton from the -NH_2 as it attacks the carbonyl group. The intermediate product will collapses again by an elimination reaction, this time losing chloride ion, and forming the amide compound (Figure 1) [11,13].

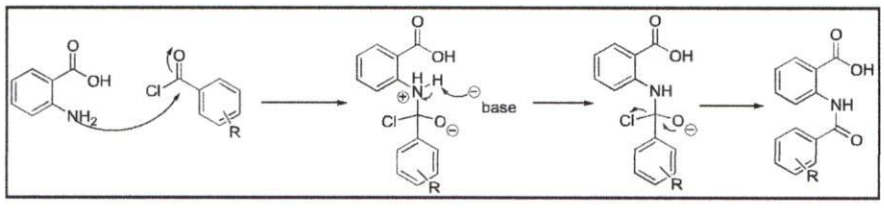

Figure 1: The first mechanism of the reactions

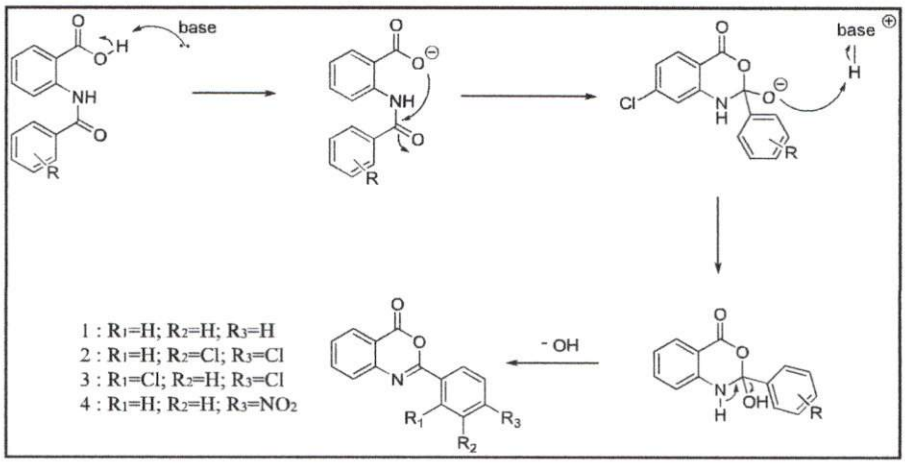

Figure 2: The second mechanism of the reactions to obtain 2-phenyl-(4H)-benzo[1,3]oxazin-4-one derivatives

The second step of the reaction is The base more important because it removes the proton from the –OH and forming ion –O:⁻ as strong nucleophile. ion –O:⁻ will attack to the electrophilic carbonyl group from amide group [11]. Following the mechanism of second step of reaction (Figure 2), finally we obtained 2-phenyl-(4*H*)-benzo[1,3]oxazin-4-one derivatives. There are four compounds (Figure 2).

Detailed physicochemical and spectral data of the obtained compounds 2-phenyl-(4*H*) benzo[1,3]oxazin-4-one derivatives are as follows :

Compound 1 is 2-phenyl-4*H*-benzo [1,3]oxazin-4-one:
Obtained in white crystals, mp: 115-117°C. FT-IR (KBr) cm^{-1}: 1765 (C=O lacton); 1620 and 1474 (C=C aromatic); 3040 (=C-H aromatic); 1614 (C=N); 1315 (C-N).^{1}H-NMR (DMSO, δ, ppm) : δ 8.34 – 8.28 (2H, m); δ 8.24 (1H, dd, J=7.9Hz, 1.2 Hz); δ 7.85-7.79 (1H, m); δ 7.71-7.67 (1H, m); δ 7.60-7.55 (1H, m); δ 7.51 (3H, ddd, J=7.3 Hz; 2.6 Hz; 1.3 Hz). ^{13}C-NMR (DMSO, δ, ppm) : δ 159.7; δ 157.2; δ 147.1; δ 136.7; δ 132.7; δ 130.3; δ 128.8; δ 128.5; δ 128.4 (2C); δ 128.30; δ 127.3 (2C). ESI-MS m/z, $[M+H]^+$=224. All these spectral data are in agreement with the structure of compound 1 (Figures 3 and 4).

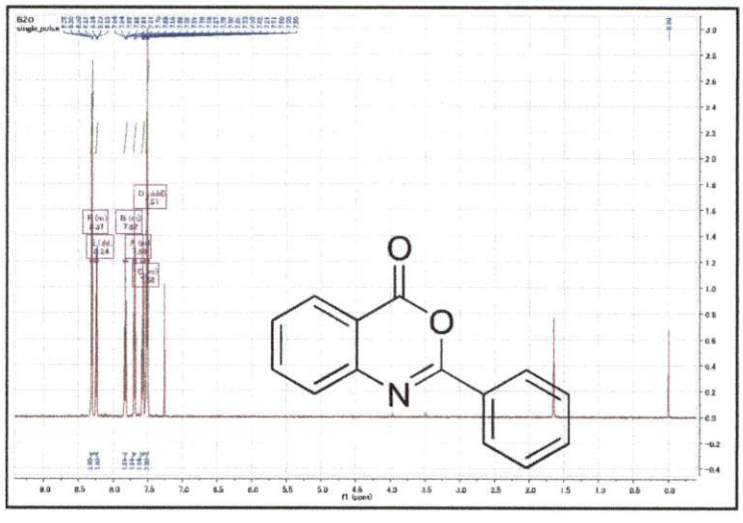

Figure 3: 1H-NMR spectrum of compound 1 in (400 MHz, DMSO-d6)

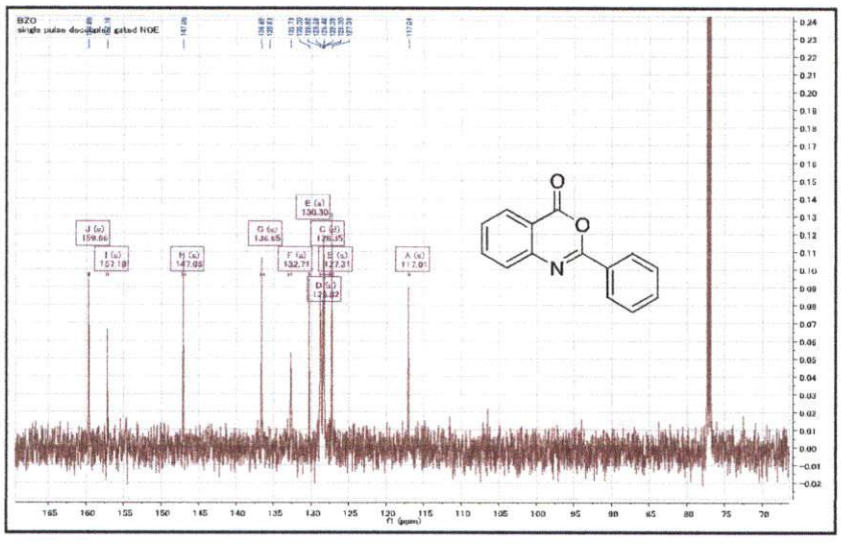

Figure 4: 13C-NMR spectrum of a compound 1 in (100 MHz, DMSO-d6)

Compound 2 is 2-(3,4-dichlorophenyl)-4*H*-benzo[1,3]oxazin-4-one:
Obtained in white powders, mp : 120-121°C.FT-IR (KBr) cm^{-1}: 1760 (C=O lakton); 1621 and 1474 (C=C aromatic); 3090 (=C-H aromatic); 1620 (C=N); 1324 (C-N); 1076 (C-O-); C-Cl (770). ^{1}H-NMR (DMSO-d6, δ, ppm) : δ 8.26 (1H,d, J=2.2 Hz, Atom H from C5 aromatic); δ 8.13 (1H, dd, J= 8.0 Hz; 1.6 Hz, Atom H from C_6 aromatic); δ 8.09 (1H, dd, J= 8.0 Hz; 2.0 Hz, Atom H from C_7 aromatic); δ 7.94 (1H, ddd, J=8.0 Hz; 1.6Hz; 0.8 Hz; Atom H from C_8 aromatic); δ 7.84 (1H, d, J=8.4Hz, Atom H from $C_{2'}$ aromatic); δ 7.743-7.707 (1H, dd, J=7.6Hz; 0.8Hz, Atom H from $C_{5'}$); δ 7.62 (1H, d, J=7.6Hz; 1.2Hz, Atom H from C_6 aromatic). ^{13}C-NMR (DMSO-d6, δ, ppm) : δ 159.0; δ 155.0; δ 146.4; δ 137.6; δ 136.0 ; δ 132.5; δ 132.0; δ

131.3; δ 129.8; δ 129.7; δ 128.7; δ 128.3; δ 127.6; δ 117.6.ESI/MS m/z values (Rel. abundance) : $[M^{+}]$+= 291.99 (100%); $[M^{+2}]$+=293.99 (65%); $[M^{+4}]$= 295.99 (10%). All these spectral data are in agreement with the structure of compound 2 (Figures 5 and 6).

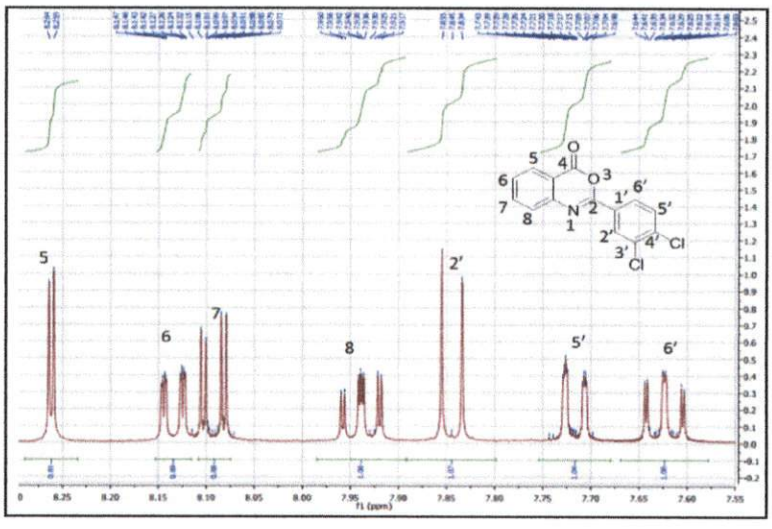

Figure 5: 1H-NMR spectrum of compound 2 in (400 MHz, DMSO-d6)

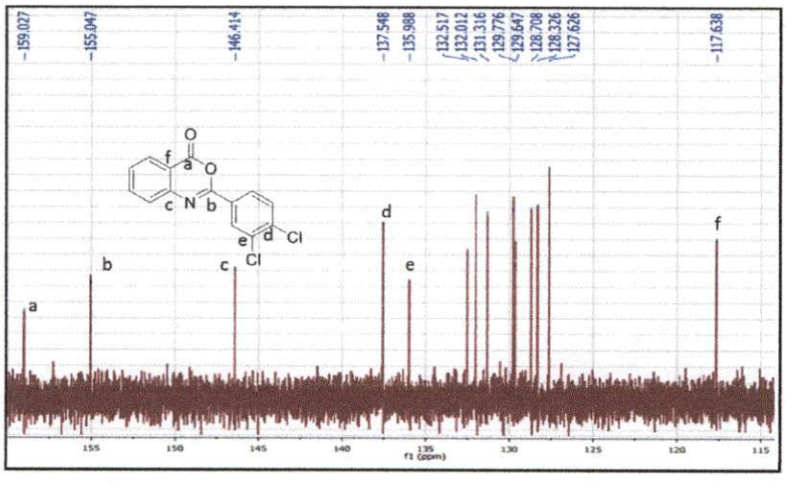

Figure 6: 13C-NMR spectrum of compound 2 in (100 MHz, DMSO-d6)

Compound 3 is 2-(2,4-dichlorophenyl)-4*H*-benzo[1,3]oxazin-4-one:

Obtained in White crystals , mp : 120-121°C. FT-IR (KBr) cm^{-1}: 1767 (C=O lakton); 1623 and 1476 (C=C aromatic); 3090 (=C-H aromatic); 1620 (C=N); 1315 (C-N); 1029 (C-O-C) and 772 (C-Cl). ^{1}H-NMR (DMSO-d6, δ, ppm) : δ 8.15 (1H, dd, J=8.4 Hz; 1.6Hz, Atom H from C_5 aromatic); δ 7.98-7.91 (2H, m, Atoms H from C_6dan C_7 aromatic); δ 7.82 (1H, d, J=2.4Hz, Atom H from C_8 aromatic); δ 7.71-7.60 (3H, m, Atoms H from $C_{2'}$; $C_{5'}$ and $C_{6'}$ aromatic). ^{13}C-NMR (DMSO, δ, ppm) : δ 159.1; δ 155.4; δ 146.2; δ 137.6; δ 137.4; δ 133.6; δ 130.9; δ 130.0; δ 129.5; δ 128.6; δ 128.4; δ 127.7; δ 126.7; δ 117.4. ESI/MS m/z values (Rel. abundance) : $[M^{+}]$+= 291.99 (100%); $[M^{+2}]$+=293.99 (65%); $[M^{+4}]$= 295.99 (10%). All these spectral data are in agreement with the structure of compound 3 (Figures 7 and 8).

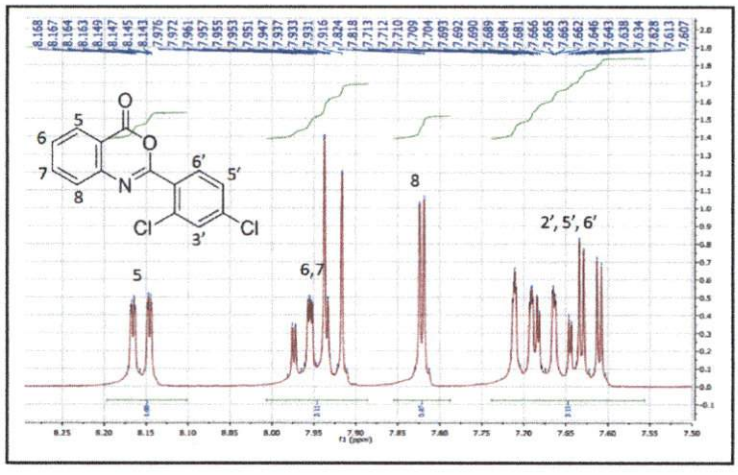

Figure 7: 1H-NMR spectrum of compound 3 in (400 MHz, DMSO-d6)

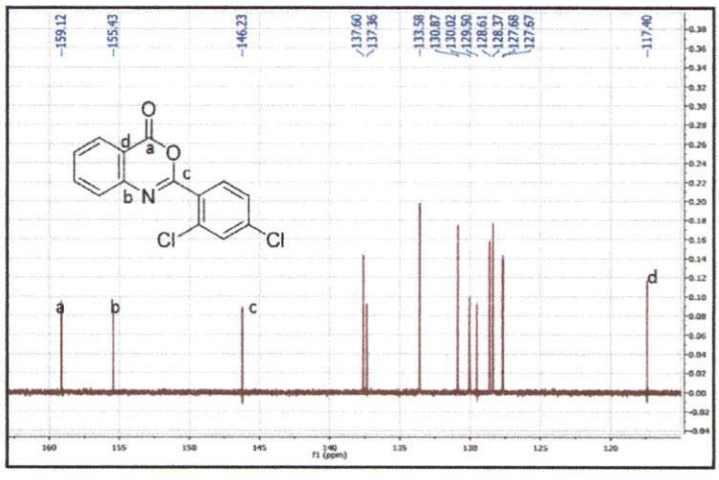

Figure 8: 13C-NMR spectrum of a compound 3 in (100 MHz, DMSO-d6)

Compound 4 is 2-(4-nitrophenyl)-4H-benzo[1,3]oxazin-4-one:

Obtained in yellow powders, mp : 127-128°C FT-IR (KBr) cm^{-1}: 1769 (C=O lacton); 1620 and 1465 (C=C aromatic); 3034 (=C-H aromatic); 1637 (C=N); 1315 (C-N); 1520 and 1356 (-NO_2). 1H-NMR (DMSO-d6, δ, ppm) : δ 8.15 (1H, dd, J=8 Hz, 1.6 Hz); δ 8.08 - 8.06 (1H,m); δ 8.01-7.94 (2H, m); δ 7.75 (2H, d, J=8.0Hz); δ 7.67-7.63 (2H, m). ^{13}C-NMR (DMSO-d6, δ, ppm) : δ 159.0; δ 155.3; δ 150.2; δ 146.4; δ 137.6; δ 136.4; δ 129.7 (2C); δ 128.7; δ 127.8; δ 124.7 (2C); δ 123.0; δ 117.8. ESI-MS m/z, [M^+]= 268.99. All these spectral data are in agreement with the structure of compound 4 (Figures 9 and 10).

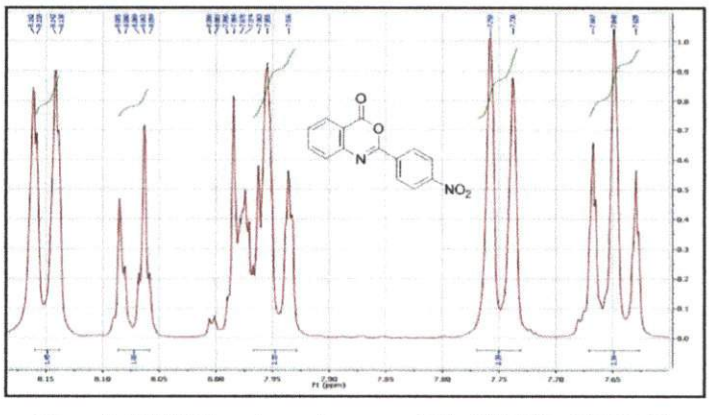

Figure 9: 1H-NMR spectrum of compound 4 in (400 MHz, DMSO-d6)

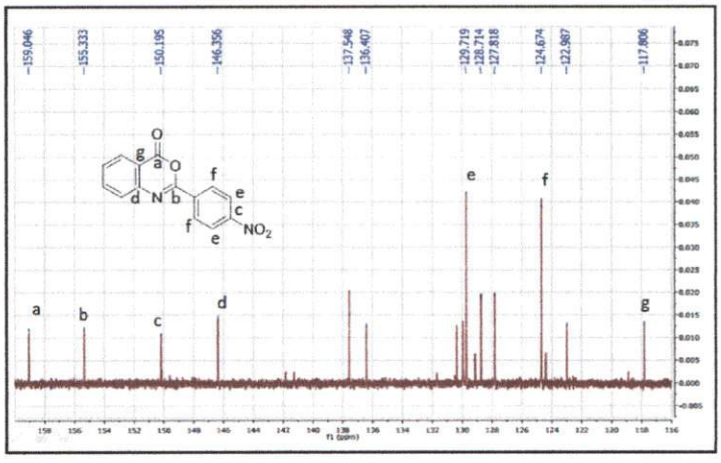

Figure 10: 13C-NMR spectrum of a compound 3 in (100 MHz, DMSO-d6)

The effect of catalyst ratio on triethylamine: pyridine were indicated from the percentage of product yield shown in the Table 1.

Table 1: The influence of catalyst ratio on triethylamine : pyridine to percentages yield

Compound	Yield % for some of rasioTriethylamine : Pyridine in catalyst condition			
	Pure Triethylamine (5 mL)	4:1 mole	1:1 mole	Pure Pyridine
		(4.3 mL ; 0.5 mL)	(5 mL ; 3 mL)	(5 mL)
1	23	30	42	80
2	20	32	48	86
3	22	30	46	84
4	12	18	21	46

Note: yield percentage were average from 3 replicate

Based on the data, using pure Triethylamine as a catalyst yields a lower yield than using pure pyridine as a catalyst. Triethylamine (pKb=3.01) has a stronger base than pyridine (pKb=8.75) is predicted to increase the percentage of yields because the stronger base more easier removes the proton from the $-NH_2$ as it attacks the carbonyl group and more easier removes the proton from the –OH and forming ion $–O:^-$ as strong nucleophile [13,14]. Ion $–O:^-$ will attack to the electrophilic carbonyl group from amide group (Figures 8-11).

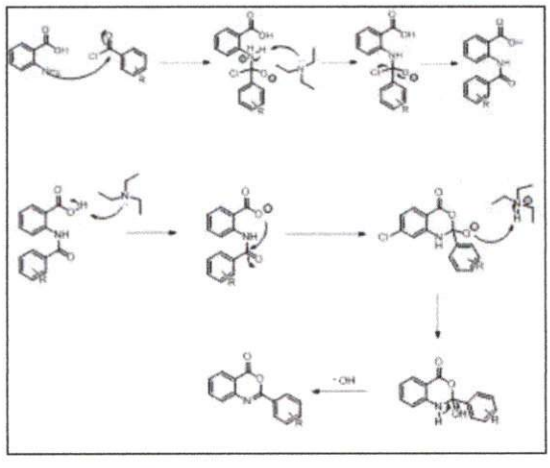

Figure 11: The role of triethylamine as a catalyst in the synthesis of 2-phenyl- (4H) -benzo [1,3] oxazin-4-one derivatives

Although triethylamine is more base than pyridine but using pyridine as a catalyst is more effective in generating higher yield percentages than triethylamine. Based on the data shown in Table 1, the increase of the pyridine to triethylamine ratio were proportional to the increase in the percentages of results. Triethylamine was less effective as a catalyst because the free rotational barrier of triethylamine, there are trimethyl ($-CH_2-CH_3$) blocks the free electron pair on N atom of triethylamine to attract protons (Figure 12) [14,15]. Pyridine was more effective as a catalyst because pyridine has a planar structure and the electron pairs on N atoms are not impeded and do not participate in resonance (Figure 13) [15].

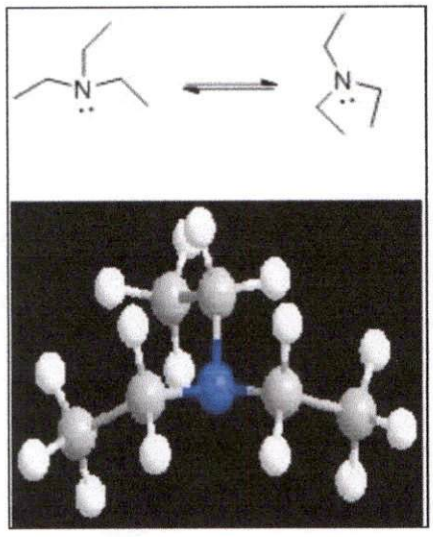

Figure 12: The free rotational barrier of triethylamine

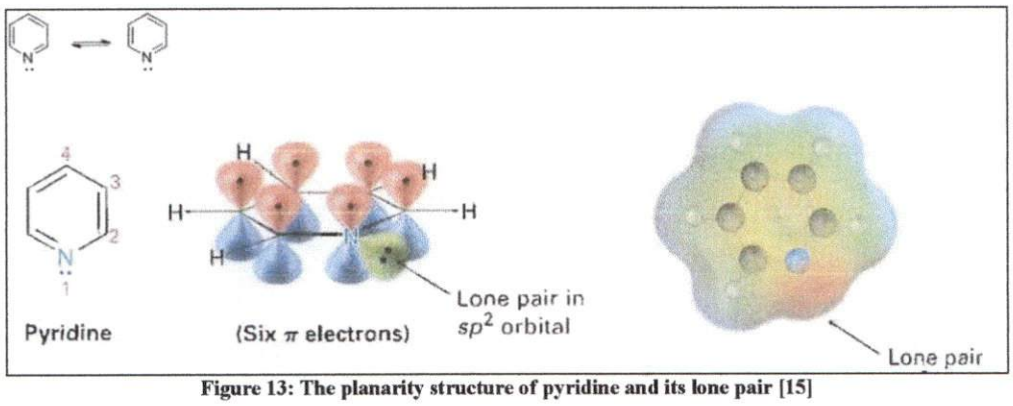

Figure 13: The planarity structure of pyridine and its lone pair [15]

The yield of compound 4 was lower than the other because of the influence of nitro functional groups on 4-nitrobenzoyl chloride as the electron withdrawing groups causing the aromatic to be more positive so that the carbonyl of benzoyl chloride was less positive than the chloro group at 2,4-dichloro benzoyl chloride and 3,4-dichlorobenzoyl chloride because halogens functional groups are the electron donating groups. More aromatic rings $\delta +$ and near $\delta +$ Carbonyl C atoms are mutually repulsive so that they are less stable which is visualized in Figure 14 [13]. The nucleophilic hydrazine hydrate attack on carbonyl from 4-nitrobenzoyl chloride is more difficult due to the presence of a nitrofuntional group as the electron withdrawing groups [13].

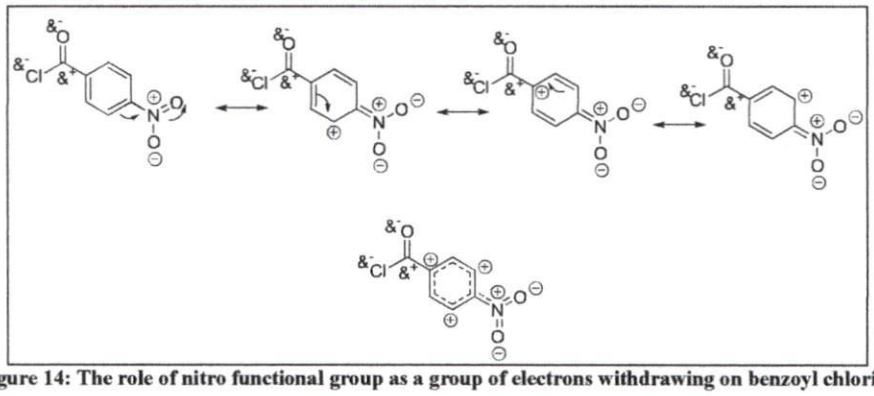

Figure 14: The role of nitro functional group as a group of electrons withdrawing on benzoyl chloride

CONCLUSION

Using pure pyridine as a catalyst in the synthesis of 2-phenyl-benzo[d] [1,3] an oxazin-4-one derivatives obtains 4 times greater product percentage than using pure triethylamine as a catalyst.

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