The Study of the Reaction of Morpholine with Aryl halide and Aliphatic halide

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Declaration

No portion of the work referred to in this desertion has been submitted in support of an application for another degree of qualification of this or any other university or institution of higher learning.

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List of Abbreviations

Copper(I)Iodide	CuI
Dimethyl Formamide	DMF
Ethanol	EtOH
Deuterated chloroform	$CDCl_3$
Gas chromathography mass spectroscopy	GC-MS
Gram	g
Hour	h
Hydrogen	H_2
Infrared	IR
Milliliter	mL
Nitrogen	N
Nuclear Magnetic Resonance	NMR
Oxygen	O
Percentage	%
Potassium Carbonate	K_2CO_3
Sodium Hydroxide	NaOH
Ultraviolet	UV
Zinc	Zn

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ABSTRACT:

This study was aimed to synthesized the morpholine derivatives by the cross coupling reaction between morpholine and an aryl halide. The reaction of morpholine with 4-bromobenzaldhyde and 4-bromoanisole. When morpholine reacted with 4-bromoanisole, the reaction was failed but morpholine reacted with 4-bromobenzaldehyde produced 4-morpholine-4-yl-benzaldehyde, which showed that the reaction was successful. The reaction of morpholine with 4-bromobenzaldehyde was compared in the presence and absence of the copper(I) iodide which act as a catalyst. The GC result showed that the conversion of the product without catalyst was much more higher than the reaction with catalyst under the same condition. The side product also was discovered in the reaction without catalyst, the morpholine actually was attacked to the carbon in the carbonyl group of 4-bromobenzaldehyde to produce 4-bromobenzoic acid,morpholide.

Keywords: Morpholine, 4-bromobenzaldehyde, bromoanisole,
4-morpholine-4-yl-benzaldehyde, 4-bromobenzoic acid morpholide

ABSTRAK:

Kajian ini bertujuan untuk mensintesis derivatif morpholine daripada tindak balas gandingan kacukan antara morpholine dan halida aryl. Tindak balas morpholine dengan 4-bromobenzaldehid dan 4-bromoanisole. Morpholine bertindak balas dengan 4-bromoanisole, tindak balas tersebut telah gagal tetapi apabila morpholine bertindak balas dengan 4-bromobenzaldehid dihasilkan 4-morpholine-4-yl-benzaldehid yang menunjukkan bahawa tindak balas tersebut telah berjaya . Tindak balas morpholine dengen 4-bromobenzaldehid juga telah dibandingkan diantara kehadiran dan ketiadaan tembaga(1)iodida yang bertindak sebagai pemangkin. Hasil GC menunjukkan bahawa hasil tindak balas tanpa pemangkin adalah jauh lebih tinggi daripada tindak balas dengan pemangkin dengan mengunakan teknik sintesis yang sama. Kompaun sampingan juga telah ditemui apabila tindak balas tanpa pemangkin, morpholine sebenarnya telah diganti kepada hidrogen dalam kumpulan aldehid dalam 4-bromobenzaldehid untuk menghasilkan asid 4-bromobenzoic, morpholid.

Kata Kunci: Morpholine, 4-bromobenzaldehid, bromoanisol, 4-morpholine-4-yl-benzaldehid, asid 4-bromobenzoic morpholid

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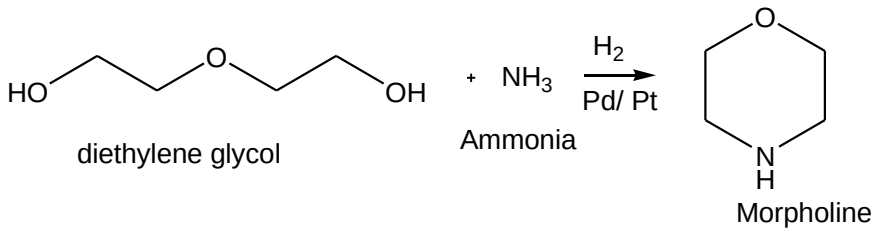
1.0 INTRODUCTION

1.1 Morpholine

Morpholine with the common name of diethylenimide oxide, is a colourless, hygroscopic and versatile organic liquid compound, which produced from the reaction of diethylene glycol and ammonia in the presence of hydrogen and Pd/Pt as a catalyst at 150-400 ºC and 30-400 atm (**Scheme 1.1**) (Mjos, 1978). This compound is soluble in water due to the presence of dipole-dipole bonds among the molecules and therefore, morpholine shows the highest boiling point compared to piperazine and piperadine, which are structurally similar to morpholine.



Scheme 1.1: Synthesis of Morpholine

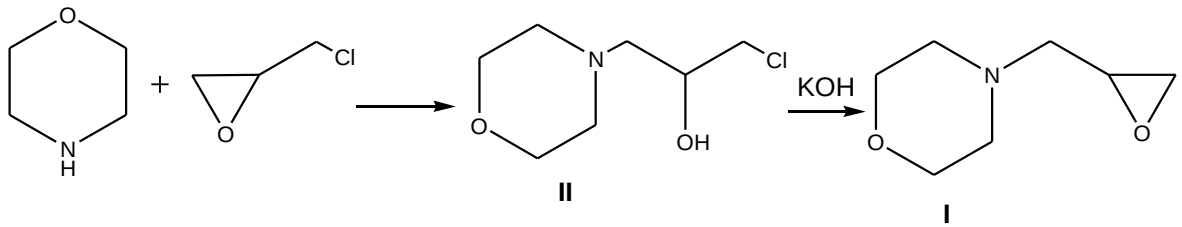
Morpholine usually used as a catalyst in a reaction and as a preservative for the diesel production, which can produce a quality fuel without any sediment and harmless to the engines. In addition, morpholine can be used as a corrosion inhibitor for the steam boiler system. It is also act as an intermediate for the coagulation of the rubber and as a separating agent in many important reactions (Huntsman, 2005). For example, adding morpholine into styrene containing hydrocarbon will isolate the styrene by azeotropic distillation. Due to this properties, morpholine derivatives are claimed as an effective separating agent of low viscosity components from mineral, animal, vegetable and fish oils (Huntsman, 2005).

Derivatives of the fatty acid in morpholine act as a emulsifiers in the manufacture of waxes and polishes. Besides that, it was also used as a bactericides, pharmaceutical chemicals, and

antioxidants for lubricating oils. Morpholine derivatives specifically being used in the textile industry, where they act as textile lubricants and sizing emulsifiers (Hunstman, 2005).

Beresford (2004) reported that morpholine used in the form of morpholine fungicides that had protective and systemic activity. The study also stated that morpholines fungicides were used for controlling powdery mildew diseases on large range of crops and it was used for the treatment of cereal foliar diseases. For example, black sigatoka was a disease occurred in bananas, this disease treated by applied morpholine fungicides.

Morpholine derivatives had also an important role in curing several diseases. The heterocyclic ring had morpholine nucleus with various of biological activity. Morpholine derivative such as 2-aryl-1(4-morpholinophenyl)-4-(3,4-disubstitutedbenzylidine)imidazolin-5-one were reported as anti-inflammatory, analgesic, anaesthetic, anti HIV, anticancer, appetite suppressant, antidepressant, anti microbial activities etc. (Priya et al., 2011). Morpholine derivatives also was reported as antimicrobial agent by the reaction of some mannich base. The study showed that different compound had different rate of antimicrobial and antifungal activity towards some microorganisms (Idhayadhulla et al., 2011). 4-(oxiran-2-ylmetyl)morpholine (**I**) is an example of morpholine derivative compound formed from the reaction between 1-chloro-2,3-epoxypropane and morpholine (**Scheme 1.2**), the compound (**I**) was used as stimulant of β-adrenoceptive systems. (Mesropyan et al., 2005)



Scheme 1.2 : Synthesis of 4-(Oxiran-2-ylmetyl)morpholine

The morpholine based derivative compounds showed luminescent properties depended on the functional groups present in the structure because it is an amino ether.

1.1 PROJECT OVERVIEW

Morpholine was found as one of the component in the turmeric powder extraction using hexane. The extraction that containing morpholine showed luminescent when it was placed under the UV light. Since turmeric powder is the main ingredients in Indian curry cuisine, thus, the component in the turmeric powder are believed less harmful to human. In the view of this, morpholine is potentially used in the field of bio imaging to view the cells. However, it is not easy to synthesize the morpholine in normal organic synthesis methods. It is always involved catalyst in the reaction for example copper(I) iodide (CuI) and palladium (Pd). In this study, the synthesis reactions of morpholine were investigated using gas chromatorgraphy-mass spectroscopy (GCMS).

1.2 OBJECTIVES

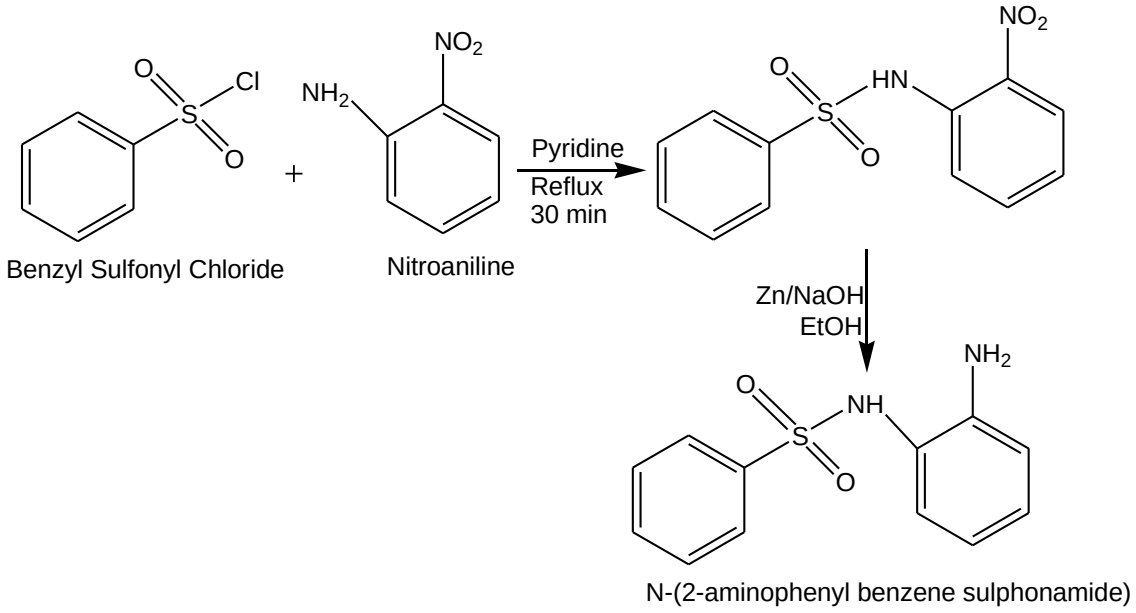
1. To study the cross coupling reaction of morpholine with aryl halides and aliphatic halide in the presence and absence of catalyst.

2. To study the formation of 4-arylmorpholine using gas chromatography mass spectroscopy (GC-MS)

2.0 LITERATURE REVIEWS

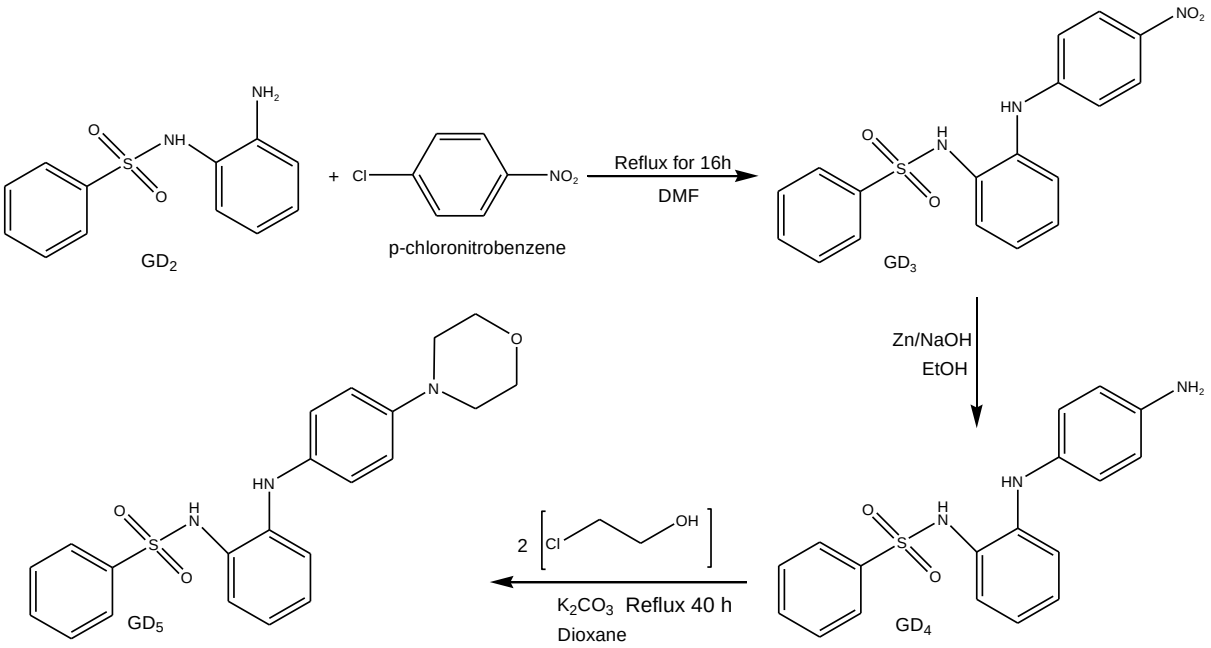
2.1 Synthesis of Morpholine

Synthesis of the morpholine compounds have been studied by Singh & Bansal in 2004. This compound was synthesized by using 2-chloroethanol as an intermediate. The reaction pathways are shown in **Scheme 2.1** and **Scheme 2.2**. **Scheme 2.1** shown the intermediate sulfonamide compound was prepared from the reaction between sulfonyl chloride and amines. The reaction was initiated by hydrolyzed the acid chloride and yielded the sulfonamide in pyridine. The reaction was time dependent, which may affect the outcome result of the reaction. For example, if the reaction is more than 30 minutes, it may result a disulfonyl substituted nitroaniline, which has a similar Rf value in TLC with the intermediate sulfonamide compound. Sometimes, reduction agents such as zinc were used in order to obtain a better yield of sulfonamide.



Scheme 2.1: Synthesis of sulfonamide intermediate

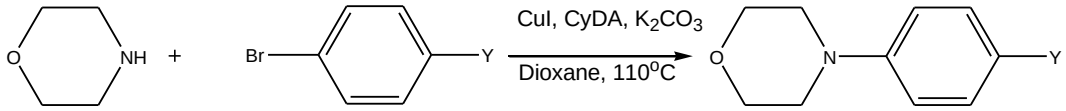
After obtaining the intermediate sulphonamide compound, it was undergo coupling reaction with *p*-chloronitrobenzene and N-{2-4-nitrophenyl)amino)phenyl}benzene sulphonamide was precipitated out (**Scheme 2.2**). The reaction was continued by reduction using Zn/NaOH of the *N*-{2-[4-(nitrophenyl)amino] phenyl}benzene sulphonamide, GD_3, to produced *N*-{2-[4-(aminophenyl)amino] phenyl}benzene sulphonamide, GD_4. Compound GD_4 was coupled with 2-chloroethanol to form *N*-{2-[4{4-morpholino}aniline]phenyl}benzene sulfonamide, GD_5, which was a morpholine being substituted.



Scheme 2.2: Synthesis of morpholine containing sulfonamide compound

Cross coupling reaction involved formation of C-N bonding using copper(I) iodide as an active catalyst studied by Beletskaya and Cheprakov (2004). The reaction was carried out between aryl halide and secondary heterocyclic amine such as morpholine. The reaction carried out under milder condition in the presence of K_2CO_3 as a base for the reaction and *rac trans* cyclohexanediamine as a ligand which used as softening for the reaction. The copper(I) iodide plays role as the catalyst in the reaction which promote the bonding of carbon in aryl compound

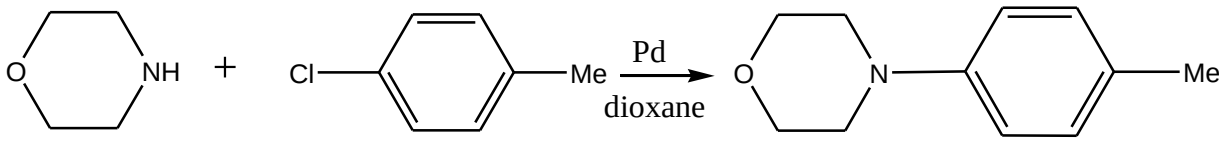
with nitrogen in heterocyclic compound (**Scheme 2.3**). The halide that attached to the aryl compound usually bromine, which it was good leaving group instead of chlorine.



Y-OCH_3, SCH_3, phenyl compound

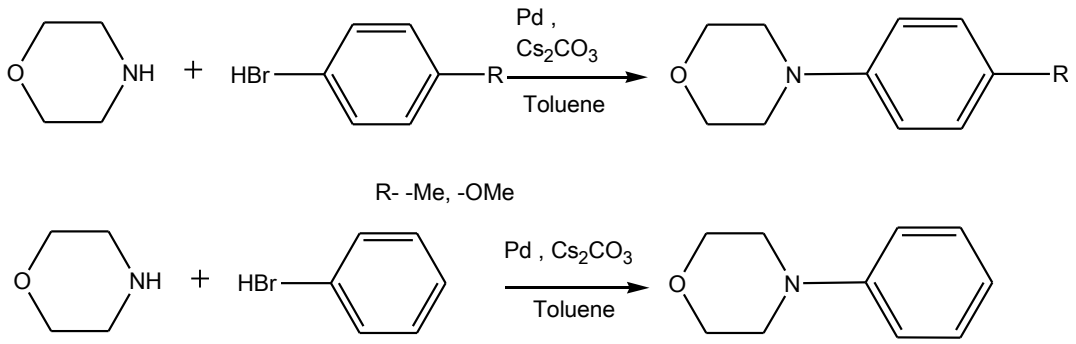
Scheme 2.3: Synthesis of morpholine derivatives using cross-coupling reaction

Apart of using copper(I) iodide, the cross-coupling reaction mediated by palladium catalyst between morpholine and chlorotoluene to form 4-tolyl-morpholine was also reported (Hiller et al., 2001) (**Scheme 2.4**). The group conducted the reaction by using supporting ligands such as 1-iodopropane.hydrochloride which was believed to enhance the efficiency of a catalytic system. Potassium butan-1-olate was used as a base in order to neutralize the HX formed in course of coupling reaction. 1,4- dioxane used as a solvent in the reaction which give higher yield (86%) of the product.



Scheme 2.4: Synthesis of 4-tolyl-morpholine

Another similar reaction to Hiller et al. (2001) was reported by Lundgren et al. (2010). In Lundgren method, the cross coupling reaction was mediated by palladium as catalyst(**Scheme 2.5**). Unlike Hiller, the reaction used more appropriate base such as Cs_2CO_3 or $LiN(SiMe_3)_2$ and toluene as the solvent, which resulted the yield of 99%.



Scheme 2.5 : Synthesis of various morpholine derivatives

In 2013, Sahli and coworkers studied the carbon-carbon formation via terpenylations of amines involving hydrogen transfer for morpholine with terpenes under inert condition. Morpholine was reacted with 3,7-dimethyloct-6-en-1-yl to form 4-(3,7-dimetyloct-6-en-1-yl) morpholine which is shown in **Figure 2.1**.

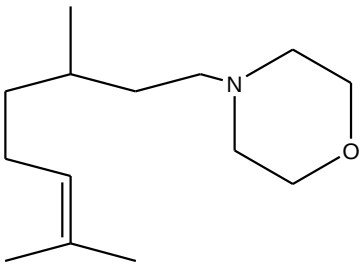
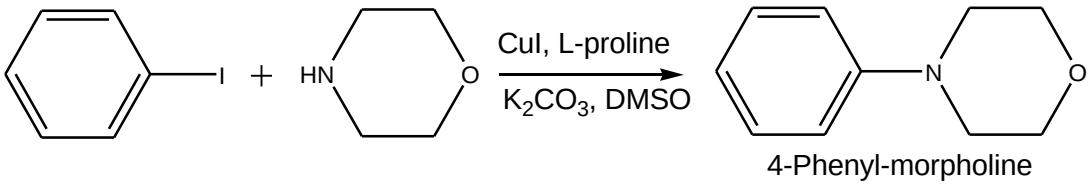


Figure 2.1: The structure of 4-(3,7-dimetyloct-6-en-1-yl)morpholine

Morpholine was reacted with aryl halide compounds to produce phenylmorpholines (**Scheme 2.6**) using copper(I) iodide as catalyst and L-proline act as a promoter. The aliphatic secondary amines had steric hindrance that slowly coupled with the aryl halide compound than the primary aliphatic amines. So the yield of the reaction was 77%, which lower than the reaction involved primary amine with aryl halide. (Zhang et al., 2005).



Scheme 2.6: Synthesis of 4-phenyl-morpholine

2.2 The Reaction of Morpholine

Morpholine has been used to react with dialkylthiocarbamate anion in order to form a Co(III) complex and the molecular structure (**Figure 2.2**) was reported by Zhang and coworkers in 2001.

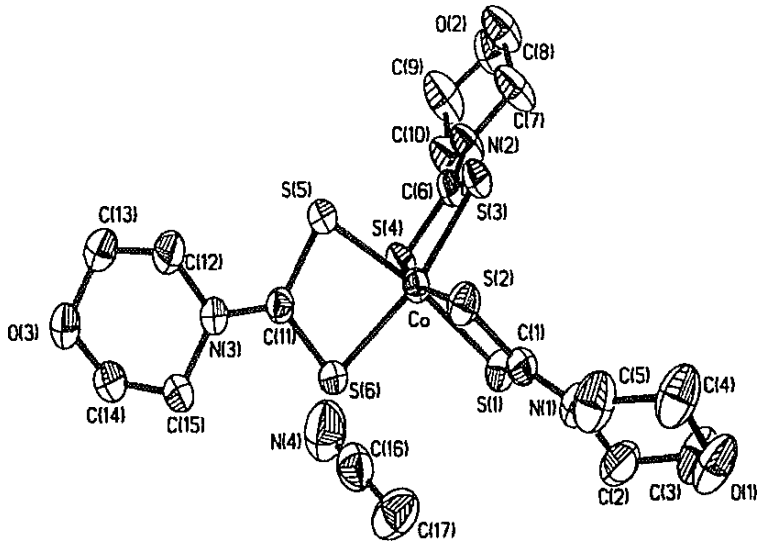


Figure 2.2: Schematic diagram for $[Co(S_2CNC_4H_8O)_3]\cdot CH_3CN$ compound

The Co(III) complex was initiated from the synthesis of $C_4H_8ONCS_2Na$ by reacting with morpholine in CH_3CN at -4 ºC. The solution was added with carbon disulfide and sodium hydroxide, and continued to stir for 4 - 5 hours to give a pure $C_4H_8ONCS_2Na$ with the yield of 92%. Then, the Na salt was then added into the aqueous solution of $[Co(CH_3CO_2)_3]$ and a green precipitate was formed.

The substitution reaction of morpholine to *C*-phenylcalix[4]resorcinarene was reported by Fox and coworkers in 1999 (**Figure 2.3**)

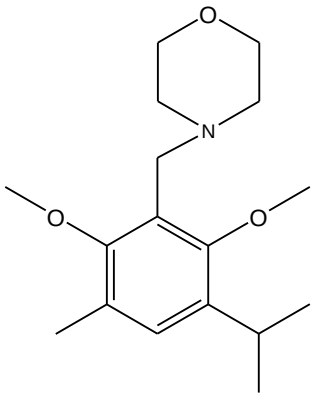
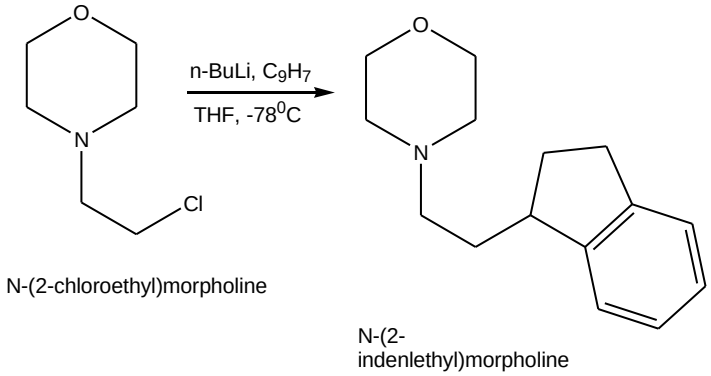


Figure 2.3 : The stucture of *C*-phenylcalix[4]resorcinarene attached by morpholine as substituent

To react the morpholine with *C*-phenylcalix[4]resorcinarene (**Figure 2.3**), the group utilized paraformaldehyde mixed with morpholine in ethanol. The resultant mixture was heated under reflux for 12 hours and orange precipitate was formed. The resulted compound was filtered and purified using recrystallisation in dimethylformamide and ethanol to afford 85% yield.

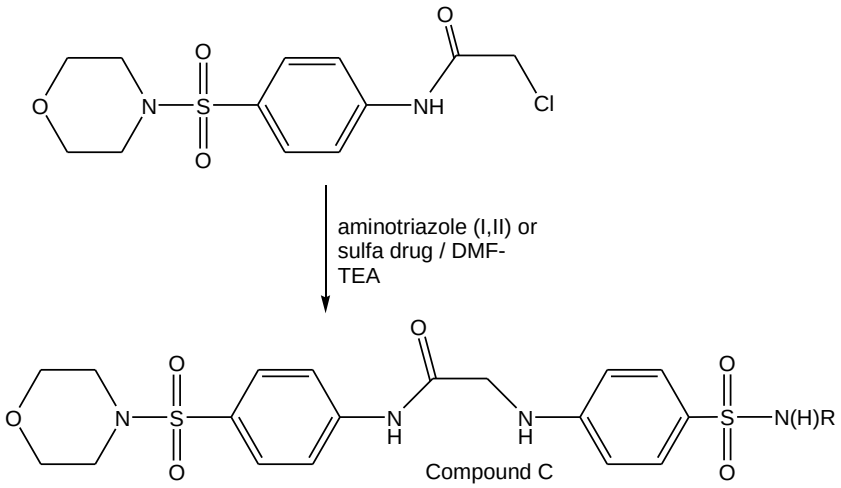
Obuzor and Booth (2011) studied the reaction of *N*-(2-chloroethyl)morpholine to the mixture of n-butyllithium and indene to form 4-(2-indenylethyl)morpholine under argon and reflux condition for 18 hours (**Scheme 2.7**). The final product appears as light brown oil form indicating 4-(2 Indenylethyl)morpholine was successfully synthesized and the yield obtained was 71%.



Scheme 2.7: Schematic diagram of synthesis pathway of 4-(2 Indenylethyl)morpholine.

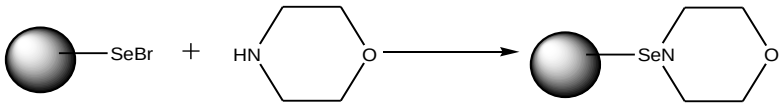
Hassan and coworkers (2011) revealed the reaction between *N*-[4 (chloroacetyl)aminobenzenesulphonyl]morpholine with amine derivatives in acetone or

dimethylformamide, 4-aminotriazoles or sulpha drugs to produce *N*-[4-(substituted glycyl)aminobenzenesulphonyl]-morpholine derivatives (**Scheme 2.8**).



Scheme 2.8: The synthesis of *N*-[4-(substituted glycyl)aminobenzenesulphonyl]-morpholine derivatives

Sheng and coworkers (2003) reported on a synthesis of α-haloaldehydes from 4-(phenylseleno)morpholine with supported by polymer. The reaction involved was polystyrene-supported (4-phenylseleno)morpholine used for the selenenylation of saturated aldehyde and deselenenylation reaction by halogenations (**Scheme 2.9**).

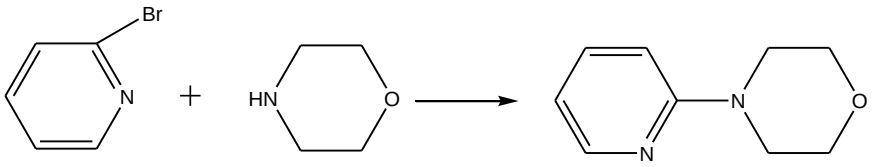


Scheme 2.9: Synthesis of α-Haloaldehyde from 4-(phenylseleno)morpholine

Sperotto and coworkers in 2010 carried out the reaction between morpholine and aryl halides, which is known as C-N coupling reaction by using aminoarenethiolato-copper(I) as a catalyst and the reaction was carried out under schlenk techniques. The aminoarenethiolate was thermally stable catalyst which also soluble in organic solvent. Actually, S,N-coordinating 2-aminoarenethiolate ligand was chosed as a catalyst because to test the basicity and the steric hindrance of the amino arm of S,N-ligand. Dimethyl sulfoxide (DMSO) was used as solvent

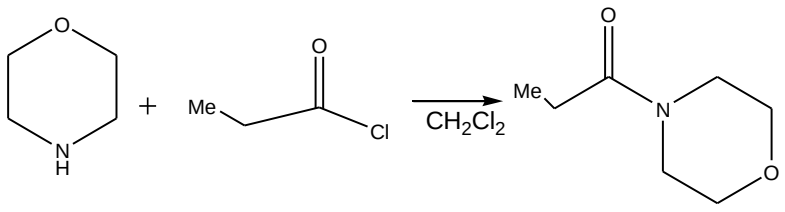
which obtained slightly lower yields. Potassium carbonate was used as bases. The group found that the reaction has some limitations such as the aryl halides attached strongly electron-withdrawing substituents. The reaction between 2-bromopyridine and morpholine to form 4-pyridin-2-yl-morpholine (**Scheme 2.10**).

The group also found that bromobenzene was an effective coupling compound when compared with fluoro-, chloro and iodobenzene which seldom showed conversion to C-N coupling product. It was because the bromo group that bonded with the aromatic ring was a good leaving group than other halogen groups.



Scheme 2.10: Synthesis of 4-pyridin-2-yl-morpholine

The synthesis of 1-morpholinopropan-1-one from by the reaction between morpholine and propan-1-one in the presence of CH_2Cl_2 (**Scheme 2.11**) was studied by Lettan II and coworkers (2007). The reaction was carried out under inert condition using DCM as solvent.

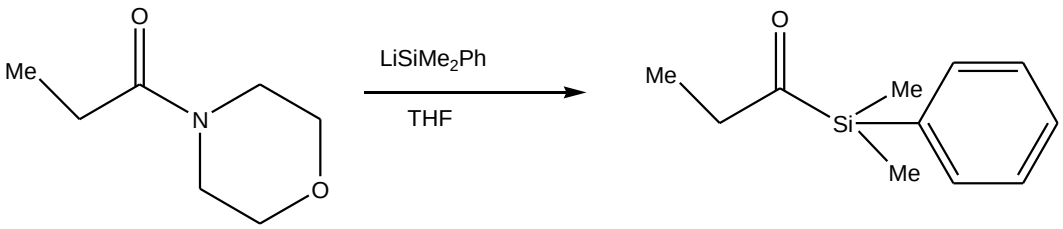


Scheme 2.11: Synthesis of 1-morpholinopropan-1-one

Lettan II and coworkers aimed to synthesized the acylsilanes, the 1-morpholinopropan-1-one was act as an intermediate product to synthesized the acylsilanes. Therefore, over addition of

organometallic reagent to morpholine amide was reduced by the brook rearragement which was the normal nucleophilic attack to the carbon in the carbonyl group.

Previously, the group was found that addition of silyl anions to the amide was produced acylsilanes but it was not the approprite method to produced. So, the addition of the organometallic reagents to alkyl morpholine amide (**Scheme 2.12**) was more economic method and also it was found that the reaction was conducted in the absence of the transition metals and other protecting groups



Scheme 2.12: Synthesis of Acylsilanes from methyl morpholine amide

2.3 Properties of Morpholine

Zemity and coworkers (2006) studied some derivatives of sulfonamide against controlling the population of *Tetranychus urticae*, which is known as two spotted spider mites, it was very harmful for human being. The group found that morpholine sulphonamide (**Figure 2.4**) was very strong against the adult and larval stage of *T.urticae*. So, the study was carried out about the acaricidal activity.

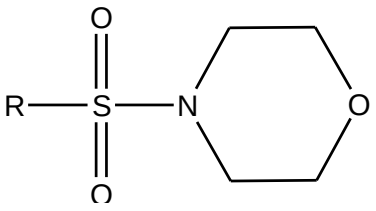
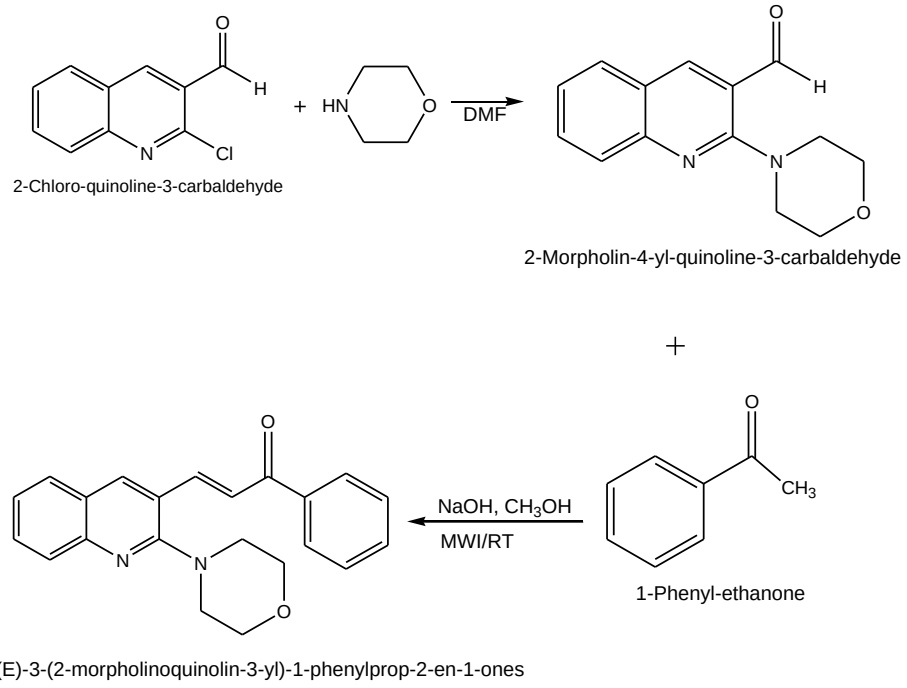


Figure 2.4: Structure of Morpholine sulphonamide

The data was reported by Zemity and coworkers (2006) based on the acaricidal activity of the morpholine sulphonamide activity. The protection against pests was proven by the linkage of morpholine and sulfone. Chlorine group that appended with morpholine resulted highly reactive against pest compared to methyl group. Morpholine sulphonamide derivatives also had great effect against the larvae of *T. urticae*.

The luminescence properties of morpholine derivatives of naphthalimide in polar and non polar solvents was investigated by Grunzinskii and coworkers (1997). The morpholine derivatives show shift of chromic effect in the more polar solvent shifted to lower energy resulted the λ_{max} of absorption was small value of quantum yield and lifetime. On the other hand, non polar solvents showed blue shift of the λ_{max} of absorption, emission and the quantum yield was increase almost tenfold or more compared to polar solvents.

The antibacterial activity of morpholine was studied by Subhashini and coworkers in 2013. (E)-3-(2-morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-ones was synthesized by reacting 2-chloro-quinoline-3-carbaldehyde with morpholine to produce 2-morpholine-4-yl-quinoline-3-carbaldehyde and followed by the reaction with 1-phenyl-ethanone (**Scheme 2.13**).



Scheme 2.13: Synthesis of (E)-3-(2-morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-ones

The biological properties of (E)-3-(2-morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-ones was investigated by using gram negative bacteria was *Escherichia coli* and gram positive bacteria was *Staphylococcus aureus* at 1000, 500 and 250 µg of the concentration of medium in dilutions methods. DMF was used as solvent control which did not show zone of inhibition. 250 µg chosen as optimum concentration medium, the group found that (E)-3-(2-morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-ones has strong antibacterial activity against *Staphylococcus aureus*. On the other hand, the compound was inactive against *Escherichia coli*.

In addition, a study was carried out by Patil and coworkers in 2011 about the synthesis of 2-(3-fluoro-4-yl-morpholin-4-ylphenylimino)-5-benzylidene-3-ethylthiazolidin-4-one (**Figure 2.5**) and investigates the antibacterial activity.

The group was studied an antibacterial activity of 2-(3-fluoro-4-yl-morpholin-4-ylphenylimino)-5-benzylidene-3-ethylthiazolidin-4-one by assayed the compound with the gram positive bacteria namely *Staphylococcus aureus*, *Bacillus subtillis* and gram negative bacteria namely *Escherichia coli* and fungal strain for example *Aspergillus niger* and *Rhizopus otyzae*. The study revealed that the compound has strong activity against *Staphylococcus aureus* and *Bacillus subtillis*. In contrary, the compound has moderate activity against *Escherichia coli*, *Aspergillus niger* and *Rhizopus otyzae*.

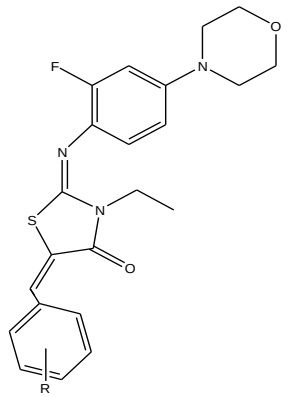


Figure 2.5: the structure of 2-(3-fluoro-4-yl-morpholin-4-ylphenylimino)-5-benzylidene-3-ethylthiazolidin-4-one