CHAPTER IV
DEVELOPMENT OF STAR-SHAPED BENZOXAZINE SUPRAMOLECULES

4.1 Abstract

Synthesis of star-shaped structure with four-arm benzoxazine dimers through the reaction between tetra-tosylated pentaerythritol as a core molecule and benzoxazine dimers as arm molecules is focused. A model reaction of phenol with core molecule suggests that the reaction for four-arm substitution is prohibited, and only two-arm star product substituted with phenols was obtained. In case of the reactions between benzoxazine dimers and core molecule, surprisingly, it does not give only two-arm star product, but also show the formation of cyclic benzoxazine dimers when the amount of case catalyst is excess. Furthermore, the mechanism related to this reaction was proposed as a model for substitution reaction of multi-tosylated core molecule and phenolic derivatives.

Keyword: star-shaped structure, benzoxazine molecule, substitution reaction, tosylated compound

4.2 Introduction

The star-shaped molecules are unique in terms of physicochemical performances, such as solution viscosity, and hydrodynamic volume.[1] Thus, the star-shaped structures can be applied in many applications, for example drug carrier,[2] capacitor in solar cells,[3] self-assembled functional membranes,[4] etc. The star-shaped molecules can be generally synthesized by three approaches, (i) the polymerization of monomer initiated by a multifunctional initiator core, so-called core-first approach, (ii) the polymerization of multi-vinyl monomers initiated by a macro-initiator, so-called arm-first approach, and (iii) the coupling reaction of functionalized polymer chains onto a multifunctional linking agent, so-called grafting-to approach.[5] Although the preparation of star-shaped structures are well established, the fact that, the conventional synthesis deal with multi-step reactions, low-yield of obtained products, and complicated purifications.

In recent years, our group has focused on supramolecular chemistry of benzoxazine molecules. Benzoxazine dimer (BZ-d) obtained from ring-opening reaction of benzoxazine monomers (BZ-m) were clarified as supramolecular compounds through hydrogen bond network of di-phenolic structure.[6] The benzoxazine dimers also perform unique reactions for selectively preparing macrocyclic compounds through either esterification[7] or etherification.[8]

Taking the abovementioned points into our consideration, herein, it comes to the question the star-shaped molecule can be prepared in a simple approach through the chemistry of supramolecular benzoxazine or not. The present work focuses on study the synthesis of star-shaped moleulce through the the reaction between benzoxazine dimer and tetra-tosylated core molecule systematically. The mechanism of this reaction is also proposed as model case for star-shaped molecule synthesis via substitution reaction of phenolic-based arm chains and multi-tosylated core molecule

4.3 Experimental Section

4.3.1 Materials

Paraformaldehyde, 2,4-dimethylphenol, p-cresol, p-toluenesulfonyl chloride, methylamine and sodium sulfate anhydrous were purchased from Fluka, Switzerland. Sodium hydroxide, triethylamine, sodium bicarbonate, potassium hydroxide, and isopropanol were obtained from Carlo Erba, Italy. Diethyl ether, 1,4-dioxane, acetonitrile, acetone, chloroform, tetrahydrofuran, dimethyl formamide were provided from Labscan, Ireland. Deuterated chloroform and pentaerythritol were purchased from Sigma-Aldrich, Germany. All chemicals were used as received.

4.3.2 Instruments and Equipment

Finishing reaction points were measured by Tin layer chromatography. Fourier transform infrared spectra (FTIR) were recorded by a Bruker Equinox55 infrared spectrometer in the range 4,000-650 cm^{-1} with 64 scans and resolution of 4 cm^{-1}, ZnSe was used as the background material. Proton nuclear magnetic resonance (^{1}H-NMR) spectra and nuclear overhauser effect spectroscopy (NOESY) spectra were obtained from a Broker Biospin Avance III 500MHz nuclear magnetic resonance spectrometer. Mass spectroscopy was analyzed by a Biosystems/Vestec electrospray ionization time-of-flight mass spectrometer (ESI-TOF MS).

4.3.3 Preparation of Tetratosylated Pentaerythritol, **1**

The tetratosylated pentaerythritol, **1**, was prepared by heating the mixtures of pentaerythritol (0.27g, 2mmol) and sodium hydroxide (0.31g, 8mmol) in acetonitrile solution at 60°C for 1 h. Then, *p*-Toluenesulfonyl chloride (1.53g, 8mmol) was added and the solution was stirred at room temperature for 3 days. The solvent was removed under vacuum to obtain the crude product. The crude product was dissolved in chloroform and washed several times with water and dried over sodium sulfate anhydrous followed by recrystallization in chloroform to obtain white crystal of **1**.

67% yield; R_f = 0.74 (5%MeOH in $CHCl_3$); FT-IR (KBr, cm^{-1}): 1468 cm^{-1} (w, disubstituted benzene), 1367 cm^{-1} (s, O=S=O stretching), 981 cm^{-1} (vs, S-O-C),

884 cm^{-1} (s, C-C-C); ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 2.52 (12H, S-Ar-**CH_3**), 3.92 (8H, C-**CH_2**-O), 7.56 (8H, meta-Ar-**H**), 7.87 (8H, othro-Ar-**H**); ESI (MeOH, m/z): 775.04 (core molecule + $Na)^+$.

4.3.4 Preparation of BZ-m

BZ-m was prepared as reported in the past (Chirachanchai *et al.*, 2009). Methylamine (0.35 mL, 10 mmol) was added dropwisely into paraformaldehyde solution (1.52 mL, 20 mmol) in dioxane. Then, *p*-cresol (1.08 g, 10 mmol) was added and refluxed at 110 °C for 6 h. The solution obtained was dissolved in diethyl ether and extracted with 0.1 N sodium hydroxide solution (10 mLx2) and water (10 mLx2). The product was dried with sodium sulfate anhydrous and the solvent was removed to obtain the yellowish crude product.

90% yield; R_f = 0.62 (5%MeOH in $CHCl_3$); FT-IR (ZnSe, cm^{-1}): 3000–2850 cm^{-1} (w, C-H), 1613 cm^{-1} (m, C=C stretching), 1506 cm^{-1} (s, trisubstituted benzene), 1225 cm^{-1} (vs, C-O-C antisymmetric stretching), 917 cm^{-1} (b, O-C-N); ^{1}H-NMR(500 MHz, $CDCl_3$, ppm): 2.34 (3H, para- **CH_3**), 2.77 (3H, oxazine-**CH_3**), 4.01 (2H, Ar-**CH_2**-N), 4.99 (O-**CH_2**-N), 6.67, 6.90, and 7.03 (3H, Ar-**H**).

4.3.5 Preparation of N,N-Bis(2-hydroxy-5-methyl benzyl) methylamine (BZ-d), 2

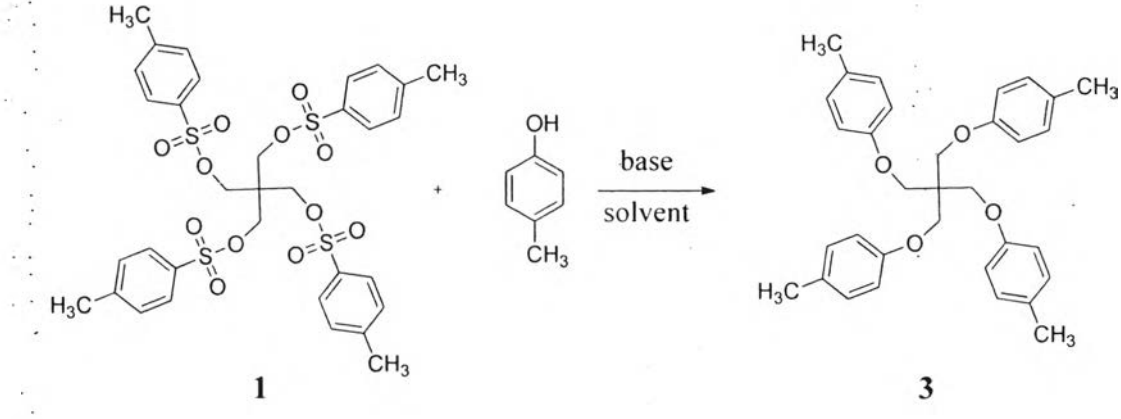
Compound **2** was prepared as reported in the past.[9] In brief, the mixtures of BZ-m and *p*-cresol (molar ratio 1:1) were stirred at 60 °C for 3 h. The mixture was allowed to react until the solution became viscous. The viscous solution was washed with diethyl ether and was dried over sodium sulfate anhydrous. The solvent was removed under vacuum to obtain the crude product. The crude product was recrystallized in isopropanol to obtain white crystal of **2**.

87% yield; R_f = 0.32 (5%MeOH in $CHCl_3$); FT-IR (KBr, cm^{-1}): 3338 cm^{-1} (s, O-H stretching), 3008–2853 cm^{-1} (m, C-H stretching), 1502 cm^{-1} (s, trisubstituted

benzene), 1246 cm^{-1}(m-s, C-OH in plane bending), 950 (w, trisubstituted benzene), 860 cm^{-1}(s, out-of-plane C-H deformations); ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 2.25(6H, para-**CH_3**), 2.30 (3H, N-**CH_3**), 3.78 (4H, Ar-**CH_2**-N), 6.54, 6.91 and 7.03 (6H, Ar-**H**).

*4.3.6 Model Reaction Between **1** and Phenol Derivatives*

Scheme 4.1



Compound **1** and *p*-cresol (molar ratio 1:4/ **1**: *p*-cresol) were reacted in acetonitrile with refluxing in addition of triethylamine (molar ratio 1:4:4) with solid content about 30%. The completion of the reaction was followed by thin layer chromatography (TLC) which indicated the reaction time of 36 h. The solvent was removed and the crude product was recrystallized in the mixed solvent of isopropanol and chloroform (2:1 v/v) to obtain **3**. Similarly, the reactions were carried out by using sodium bicarbonate, potassium hydroxide, sodium hydroxide instead of triethylamine to study the effect of additional base on the reaction.

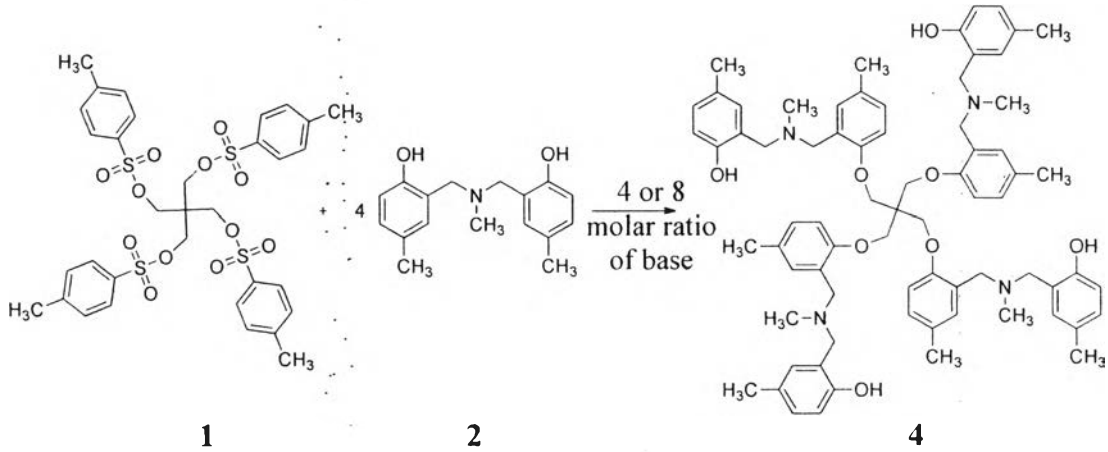
Furthermore, isopropanol and other polar aprotic solvents apart from acetonitrile; tetrahydrofuran, acetone, and dimethyl formamide were used to study the effect of temperatures and types of solvents on the reaction.

41% yield; white crystal product; FT-IR (KBr, cm^{-1}): 3032-2925 cm^{-1} (m, C-H stretching), 1613 cm^{-1} (m, C=C aromatic ring), 1512 cm^{-1} (vs, disubstituted benzene ring of phenol), 1472 cm^{-1} (m, disubstituted benzene ring of tosyl),1365 cm^{-1} (vs, O=S=O streching), 1235 cm^{-1} (s, C-O-C alkyl aryl ethers), 1054 cm^{-1} (m,

R(alkyl)-C-O streching), 982 cm^{-1} (s, S-O-C), 884 cm^{-1} (s, C-C-C), 860 cm^{-1}(s, out-of-plane C-H deformations); ^{1}H-NMR ($CDCl_3$, ppm): 2.31 (6H, Ar-**CH_3**), 2.38 (6H, Ar-**CH_3**), 3.903 (4H, **CH_2**-O-S), 4.232 (4H, **CH_2**-O-Ar), 6.57 (4H, O-othro-Ar-**H**), 7.04 (4H, O-meta-Ar-**H**), 7.19 (4H, S-othro-Ar-**H**), 7.68 (4H, S-meta-Ar-**H**)); ESI (MeOH, m/z): 647.16 (2-arms phenol + Na)$^+$.

4.3.7 Reaction Between 1 and 2

Scheme 4.2



1 **2** **4**

The compound **1** (0.753 g, 1 mmol) and **2** (1.085 g, 4 mmol) were prepared in the same procedure with model reaction in various molar ratios of base (0.225 g, 4 mmol and 0.450 g, 8 mmol). The solvent was removed in vacuum to obtain the crude products. The crude products were dissolved in chloroform and washed several times with water and dried over sodium sulfate anhydrous followed by solvent removal to obtain crude products

In comparison, potassium hydroxide in dioxane was used to study the type of solvent which has similar point boiling with acetonitrile on the reaction. Because of studies of organic compounds, it was found that the nucleophilic substitute of thiols occurs in the presence of potassium carbonate in acetone at reflux temperature[10] so the other reaction was carried out by using potassium carbonate in acetone.

4.4 Result and Discussion

4.4.1 Characterization of ***1*** *and* ***2***

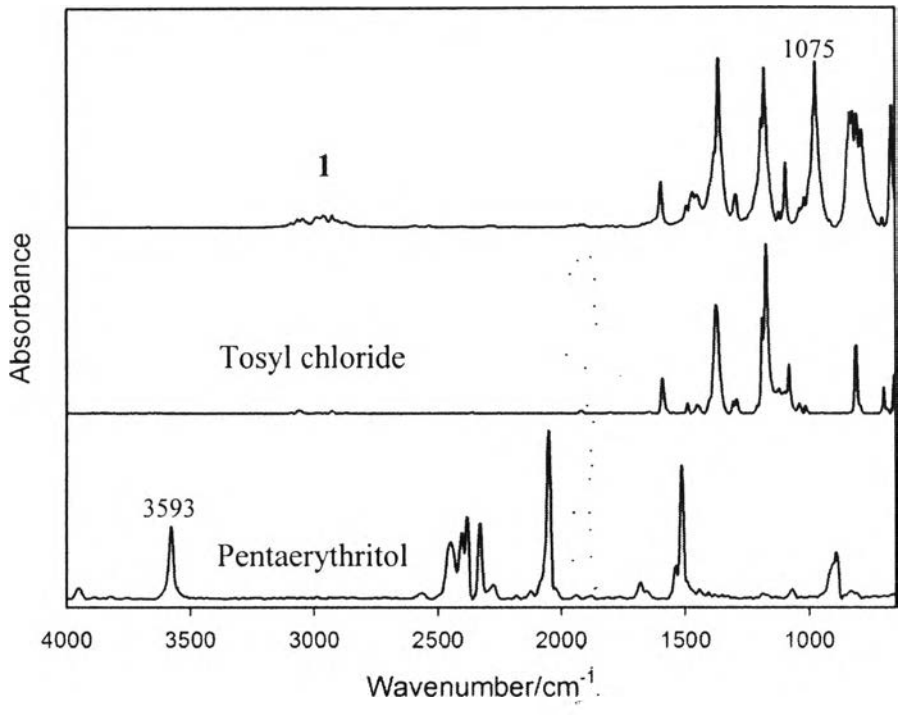


Figure 1. FTIR spectra of pentaerythritol, tosyl chloride, and **1**.

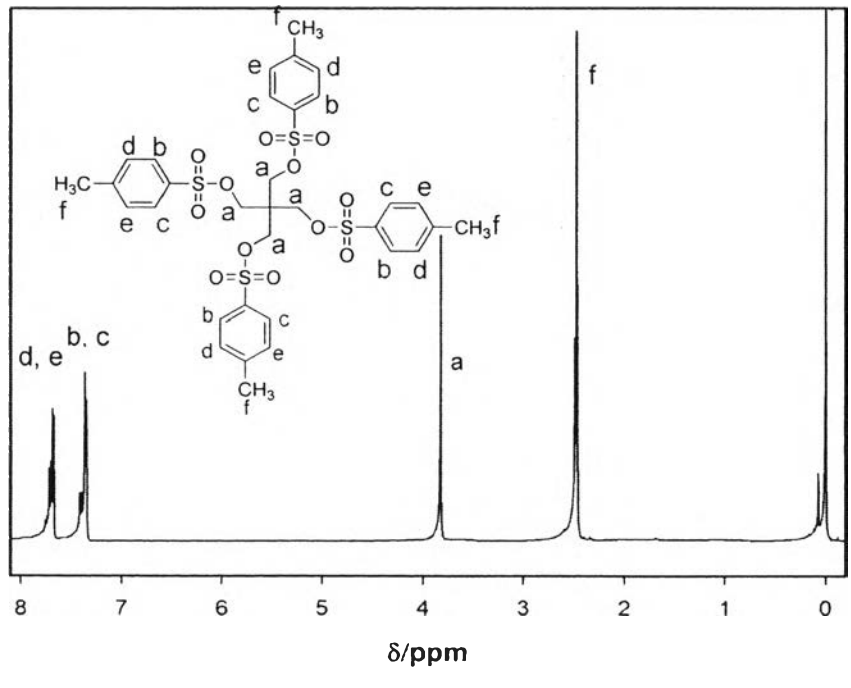


Figure 2. ^{1}H-NMR spectrum of **1** in $CDCl_3$.

FTIR spectrum in Figure 1 shows a new peak at 1075 cm^{-1} referring to sulfonyl groups. The peak at 3593 cm^{-1} due to the hydroxyl group of pentaerythritol disappeared confirming the success of tosylation. The important chemical shifts in ^{1}H-NMR spectrum are at δ_H=2.25 referred to four methyl groups and at δ_H=3.92 to four methylene groups as shown in Figure 2.

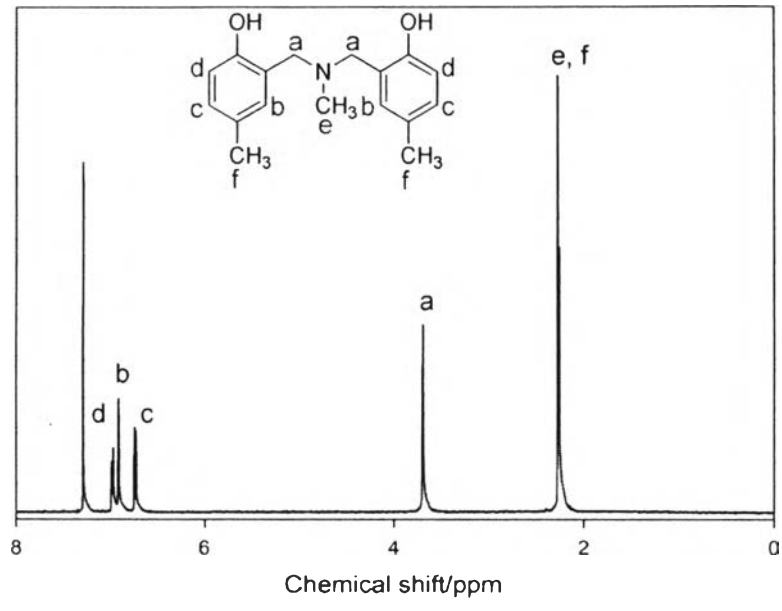


Figure 3. ^{1}H-NMR spectrum of **2** in $CDCl_3$.

The ring opening reaction of BZ-m with *p*-cresol was confirmed by FTIR which new broad peak of hydroxyl groups at 3338 $cm^{-1}$was observed. The disappearing of characteristic peak of oxazine ring at 917 cm^{-1} and 1225 cm^{-1} confirms the oxazine-ring-opening structure of **2**. ^{1}H-NMR spectrum shows new peak at δ_H=3.78 refer to four protons of mannich bridge as shown in Figure 3.

4.4.2 Model Reaction of 1 and p-Cresol

Firstly, the effect of base catalyst to the reaction was studied. The reaction of **1** and *p*-cresol was carried out with weak bases; triethylamine and sodium bicarbonate. This reaction could not be progressed as evidenced by TLC which the reactant spots still presented and there was no any new observed spot in three-day

reaction. For the reaction using stronger base, potassium hydroxide, the reactions were completed in one and a half days evidenced by totally disappearing of reactant TLC spots. The product obtained was confirmed the structure by FTIR which the characteristic peaks of both tosyl (1365 cm^{-1} and 1235 cm^{-1}) and phenol (1512 cm^{-1}) with new peaks at 1054-1020 cm^{-1} referring to ether linkage were observed. ESI-TOF MS (Figure 4) shows the peak of m/z = 663.15 which should be referred to the **1** with two-substituted *p*-cresol as possibly shown in either structure 3' or 3".

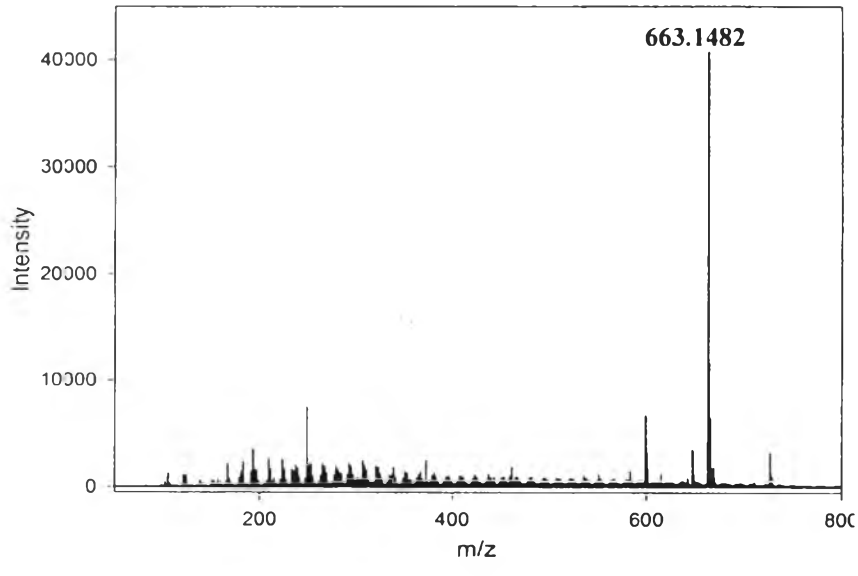
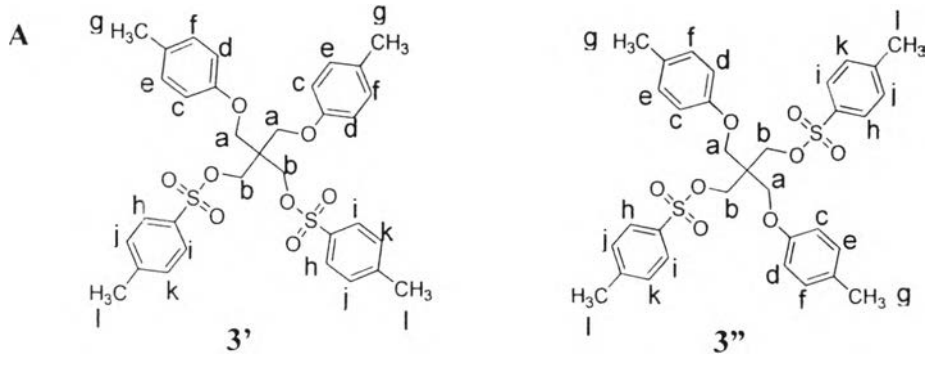


Figure 4. ESI-TOF MS spectrum of the product obtained by using potassium hydroxide as base catalyst.



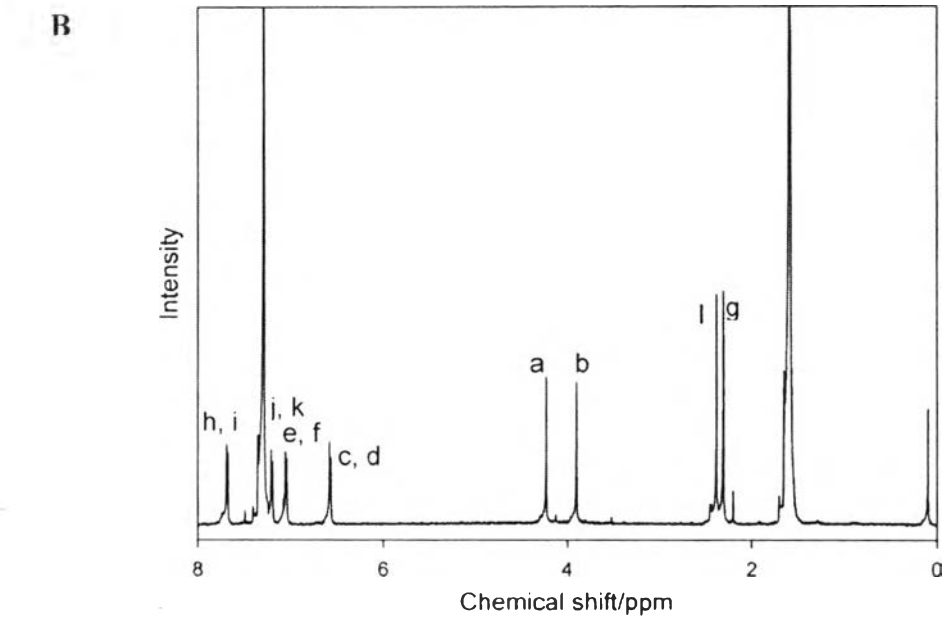


Figure 5. (A) Possible structures of the products obtained.

(B) ^{1}H-NMR spectrum of possible structures of the products obtained.

There are two possible structure for product obtained, 3' and 3", with the same m/z value as shown in Figure 5A. ^{1}H-NMR technique was used to clarify the structure of the crystal product after purification. Figure 5B shows the ^{1}H-NMR peaks at δ_H = 3.91 ppm and δ_H = 4.25 ppm referring to two species of methylene groups whereas the peaks at δ_H = 2.25 ppm and δ_H = 2.31 ppm also referring to two species of methyl groups.

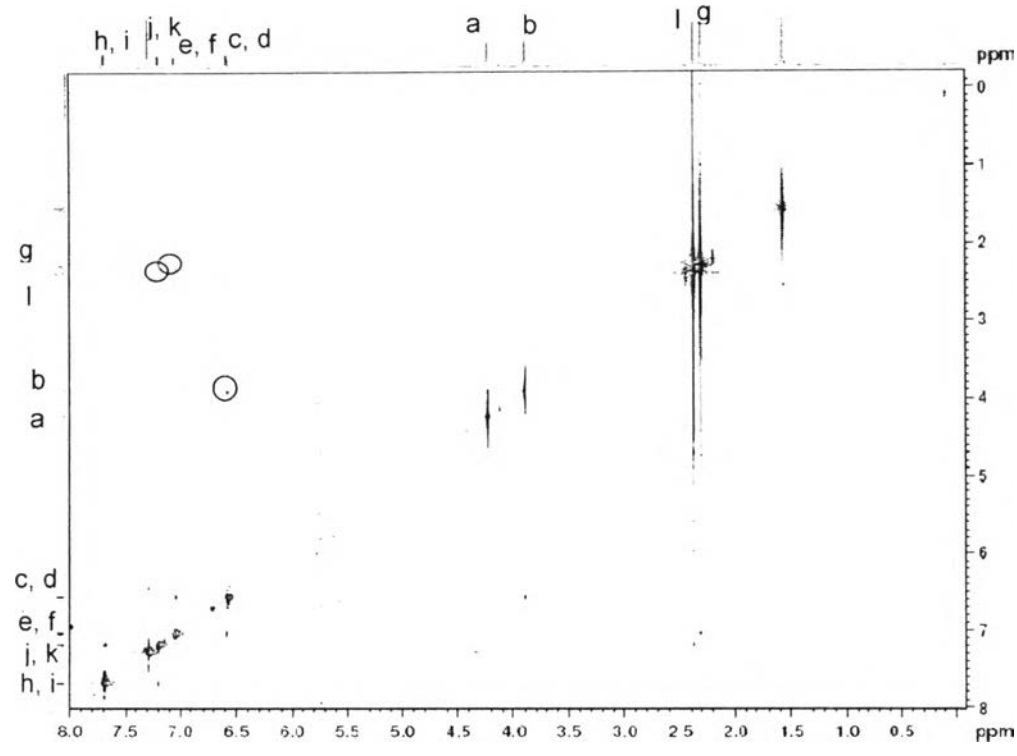


Figure 6. Nuclear overhauser effect spectroscopy (NOESY) contour plot of the product obtained.

To specify the product structure, NOESY technique was used. Figure 6 shows the NOESY contour plot of the product which three correlations between proton position g with e, f, l with j, k, and b with c, d (black circle) are observed. It indicates the structure of 3" which has two phenol groups connected at the opposite side. It is important to note that, instead of tetra-substituted structure, the reaction gives only a single species of di-substituted phenol structure. It might be due to the steric hindrance of di-substituted phenol structure.

In case of the strongest-base reaction, sodium hydroxide, ESI-TOF MS result (Figure 7) shows the major peak of m/z = 159.06 referred to fully-substituted phenol product, or pentaerythritol. Furthermore, two minor peaks of m/z = 249.11 and 625.19 are observed which should be referred to (i) compound consisting of one arm substituted with *p*-cresol and three arms substituted with hydroxyl groups (with Na^+), and (ii) m/z = 625.19 referred to two *p*-cresol (with Na^+), respectively. The reason why fully-substituted hydroxide product is favoured might be due to the basic strength of base catalyst that gives too high concentration of hydroxide ion. Thus,

that hydroxide ions, which have higher mobility than phenol, compete with *p*-cresol to react with **1** resulting in hydroxide-substituted product instead of phenol-substituted productd as majority. For that reason, potassium hydroxide was selected as base catalyst for further study.

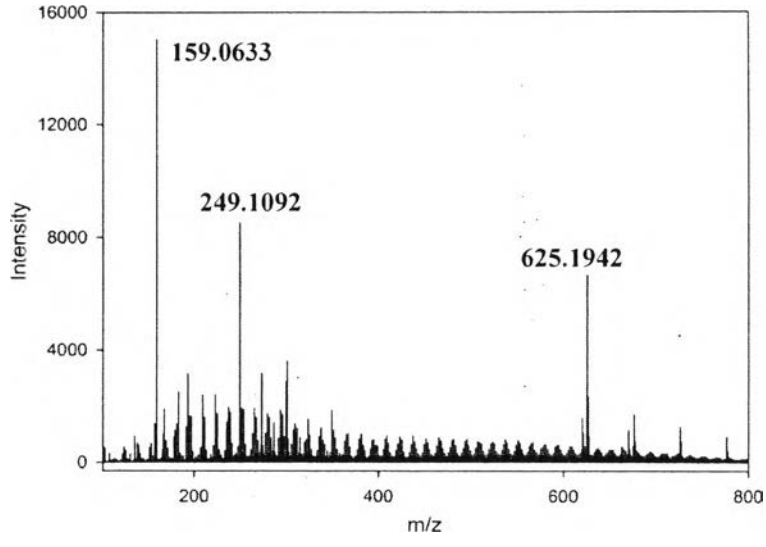


Figure 7. ESI-TOF spectrum of product obtained by using sodium hydroxide base as base catalyst.

In order to study the effect of refluxing temperature to the reaction, several polar aprotic solvents; tetrahydrofuran (THF), acetone and dimethyl formamide (DMF), were varied as reaction solvents. It should be noted that polar protic solvent, such as isopropanol, could not dissolve all catalyst bases, therefore only polar aprotic solvents were used. In case of THF and acetone, ESI-TOF MS results show the similar major peak of m/z = 775.10 referring to **1** (with Na^+) and the minor peaks of m/z = 711.14 referring to the compound consisting of one arm substituted with *p*-cresol and three arms with unreacted tosyl groups (with Na^+) (Figure 8). It might be due to the reflux temperatures which are not high enough to activate the reaction.

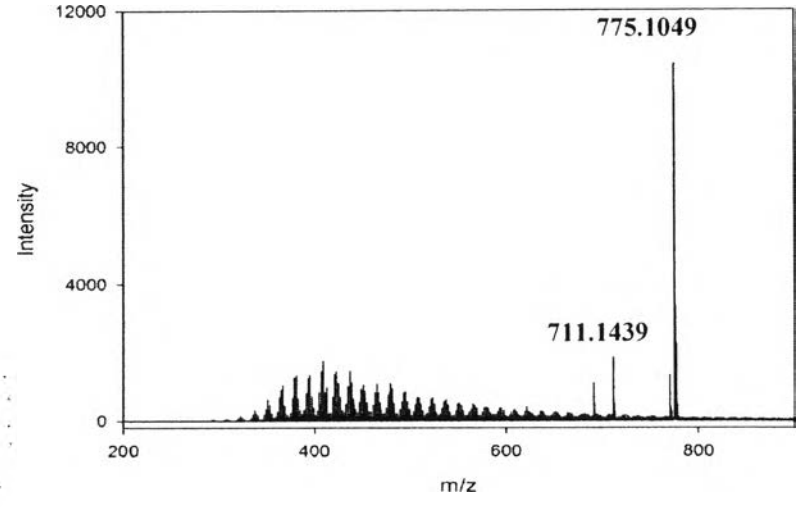


Figure 8. ESI-TOF spectrum of product obtained by using THF and acetone as reaction solvent.

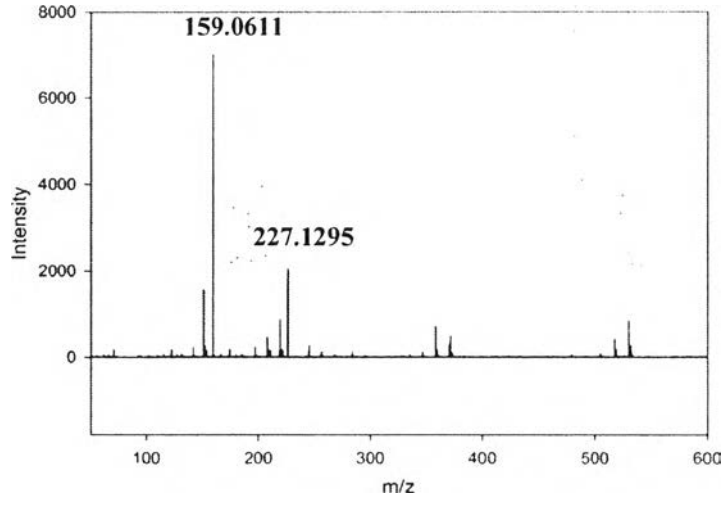
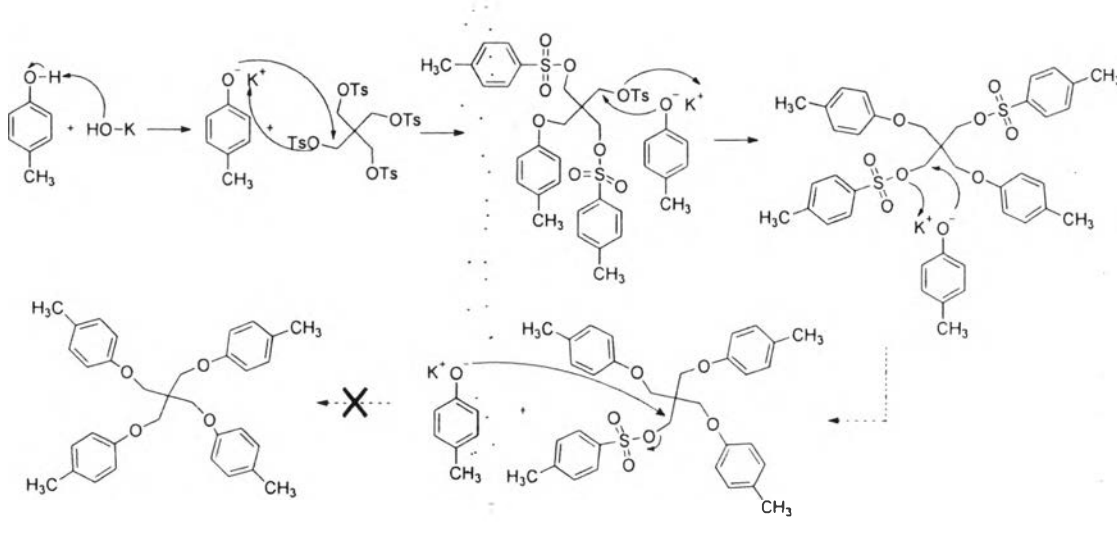


Figure 9. ESI-TOF MS spectrum of product obtained by using DMF as reaction solvent.

In case of DMF, ESI-TOF result shows two major peaks of m/z = 159.06 referred to pentaerythritol (with Na^+), and m/z = 227.13 referred to the product consisting of one arm substituted with *p*-cresol and three arms substituted with hydroxyl group (with H^+) (Figure 9). The reason why the reaction using DMF as solvent gives the phenol-substituted specie as major product might be because the reflux temperature of DMF, ~120°C, accelerates the reactivity between base and **1**

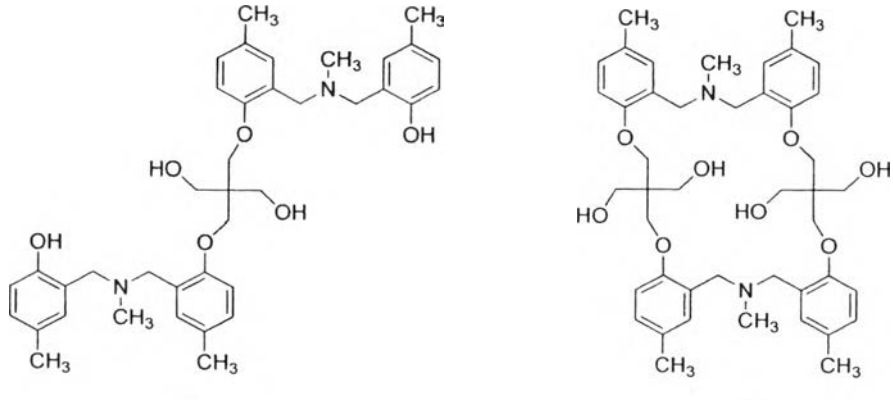
more effective than that of *p*-cresol and **1**. Base on the results, the mechanism of model reaction to obtain the two-arm phenol product can be proposed as shown in Scheme 4.3. It should be noted that the model reaction using potassium hydroxide in acetonitrile solvent cannot achieve the four-arm phenol product. However, this condition was used for star-shaped **2** synthesis in next step.

Scheme 4.3



4.4.3 Characterization of model reaction of 1 and 2

Scheme 4.4



4a **4b**

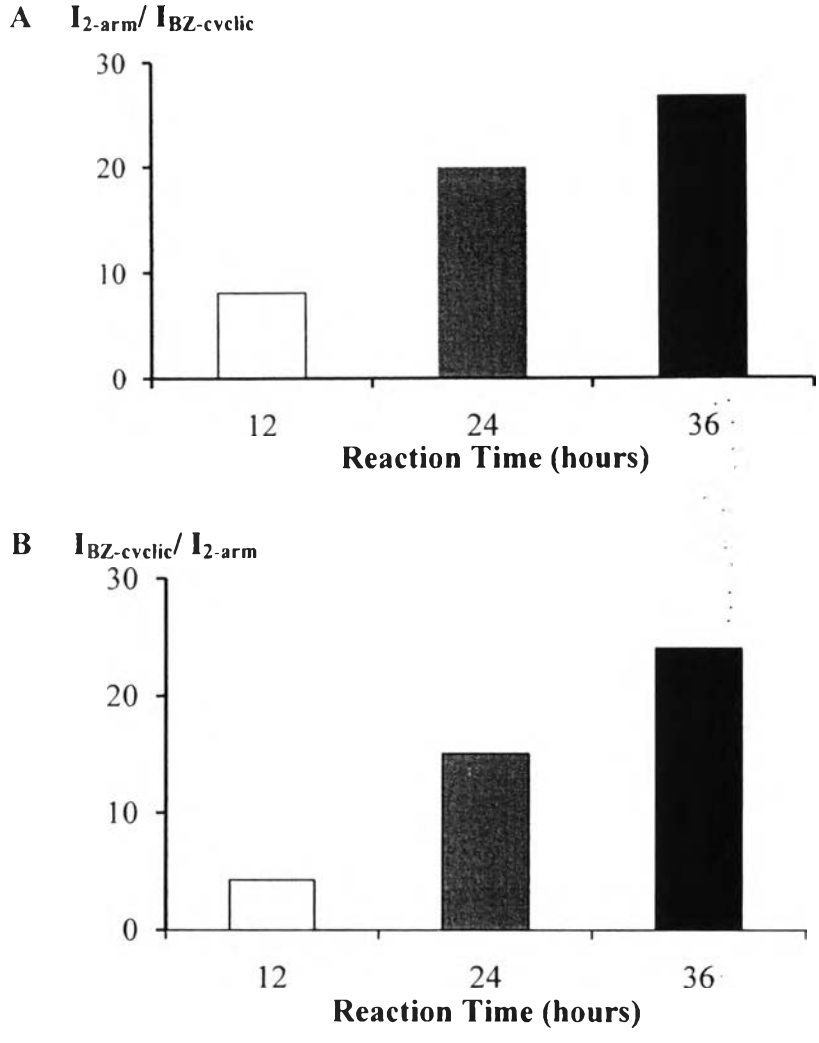
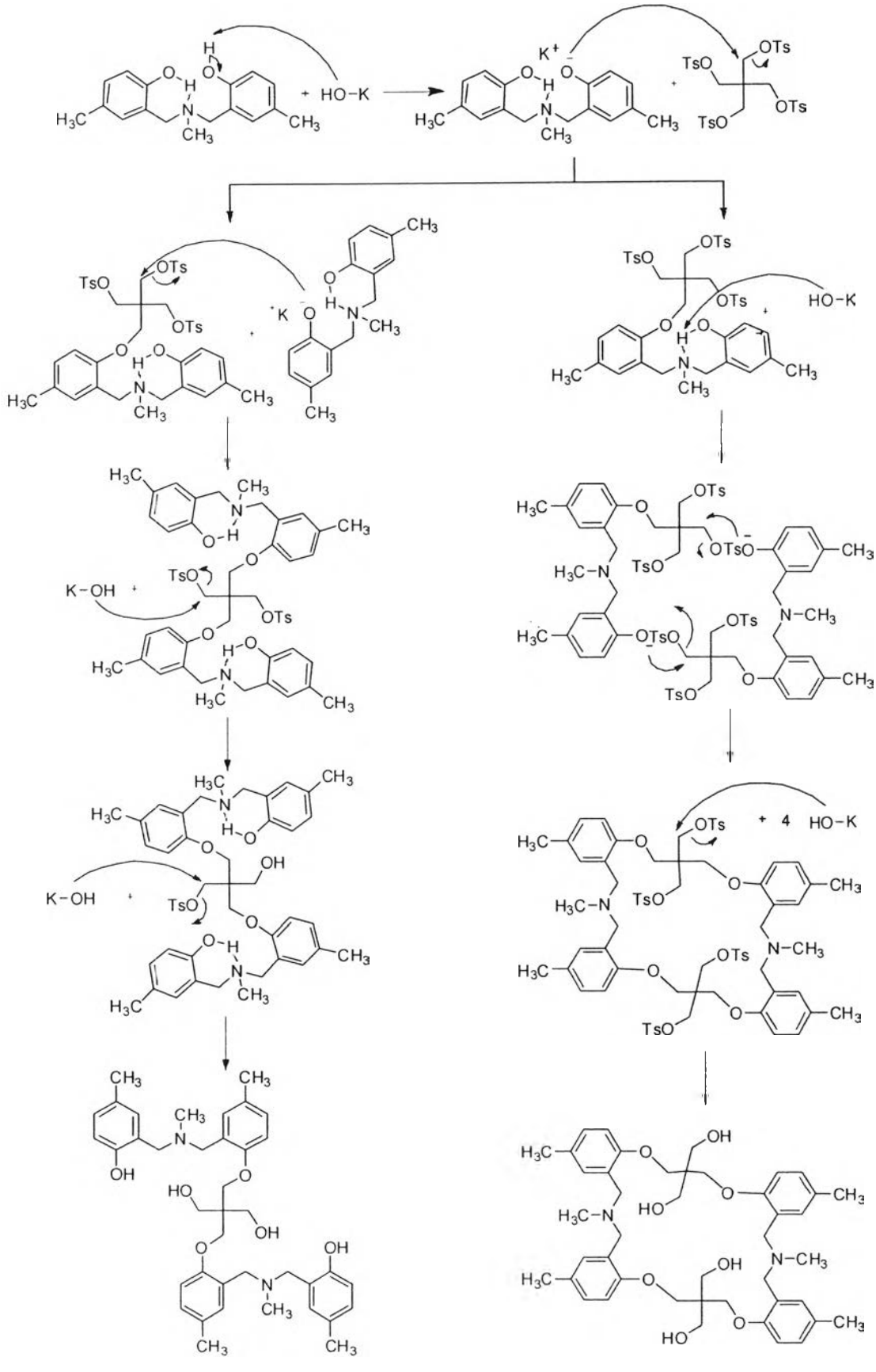


Figure 10. (A) Intensity ratios between two-arm benzoxazine dimer and cyclic benzoxazine dimer of 4 molar ratio of base.
(B) Intensity ratios between cyclic benzoxazine dimer and two-arm benzoxazine dimer of 8 molar ratio of base.

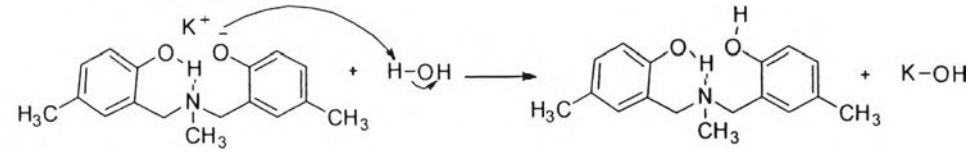
For the synthesis of star-shaped **2**, to understand the mechanism of this substituted reaction, ratio of base catalyst was varied; 1:4:4 and 1:4:8 mole ratio for **1**: **2**: potassium hydroxide. In case of 1:4:4 mole ratio, the ESI-TOF MS result shows the major peak of m/z = 680.23 referring to **1** substituted with two **2** (2-arm) (Scheme 4.4, 4.4a) (with K^+) and the small peak of cyclic **2** (BZ-cyclic) (Scheme 4.4, 4.4b) (with K^+) at m/z = 779.37. For the reaction of **1**: **2**: potassium hydroxide in molar ratio of 1:4:8, the ESI-TOF MS result shows the peak of BZ-cyclic at m/z =

779.37 as a major product and the minor peak of m/z = 680.23 referred to 2-arm product. To clarify this reaction in detail, the intensity ratio of 2-arm and BZ-cyclic obtained from ESI-TOF MS were evaluated as shown in Figure 10. In case of 1:4:4 molar ratio, the intensity of $\mathbf{I_{2\text{-}arm}/\ I_{BZ\text{-}cyclic}}$ increases as the reaction time increased (Figure 10A). Conversely, in case of 1:4:8 molar ratio, the intensity of $\mathbf{I_{BZ\text{-}cyclic}/\ I_{2\text{-}arm}}$ increases as reaction time increased (Figure 10B). It indicates that the 2-arm product is the major product in case of equivalent mole ratio of base catalyst and **2**. In contrast, BZ-cyclic is the major product in case of excess of base catalyst. However, it should be noted that the four-arm substituted product could not be achieved, even though the reaction conditions were changed, for example using toluene and dioxane as solvent, and potassium hydroxide as catalyst base. From that result, the mechanism of the reaction can be proposed as shows in Scheme 4.5.

Scheme 4.5



Additional information



4.5 Conclusion

The present work proposed a novel design and synthesis of star-shaped molecule through the chemistry of suprabenzoxazine. However, model reaction, reaction between **1** and phenol, and the reaction between **1** and **2** confirmed that, instead of tetra-substitutional four-armed star product, the di-substitutional two-armed star product was inevitably obtained. Furthermore, based on the systematic study, this work also proposed the mechanism of this phenomenon dealing with the steric hindrance of di-substituted phenol products and the strength of base catalyst.

4.6 Acknowledgements

This work was supported by The Thailand Research Fund (BRG5380010) and the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund). The author acknowledged the research facilities provided by the Petroleum and Petrochemical College, Chulalongkorn University, and the Center for Petroleum, Petrochemical, and Advanced Materials, Chulalongkorn University.

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