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Original Research

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Epoxide Ring Opening Under Mild Conditions Using Phenol, Amine, and Alcohols

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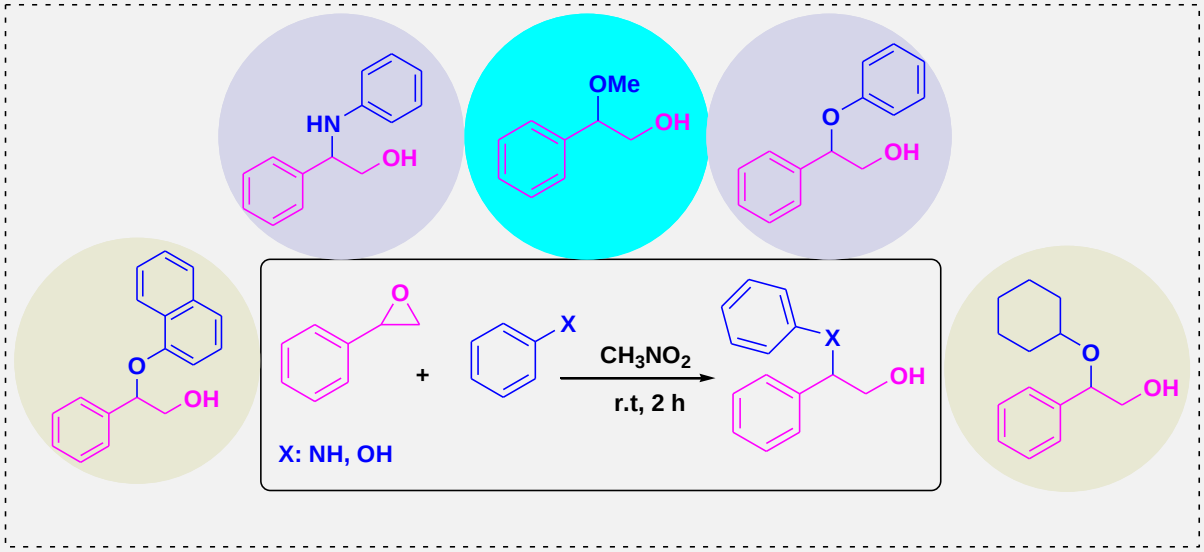
ABSTRACT: Epoxides are versatile and important intermediates in organic synthesis. The ring-opening reaction of epoxide associated with nucleophiles in organic is very important because this reaction can provide a suitable route to obtain various types of products. Therefore, how to develop a new synthesis method to improve the performance of the epoxide ring-opening reaction is of great importance. In this article, the comparison of ring opening of epoxides in acidic and basic environments was studied. For this purpose, amines, alcohols, and phenol were used to convert epoxides into 1,2-disubstituted compounds. Among the advantages of this method compared to the reported methods, he pointed out the reduction of reaction speed, easy separation of the product from the reaction mixture, and reaction using green solvents.



KEYWORDS: Epoxide, Ring-Opening, Nucleophiles, Intermediate.

Introduction

Three-membered cyclic molecules called epoxides are employed as organic syntheses' intermediates in numerous cases [1]. In organic chemistry, an ether group arranged in a ring with two carbon atoms and one oxygen atom is known as an epoxide [2]. With this arrangement, an equilateral triangle is formed. Compared to the typical ether structure, this structure is more reactive. Additionally, epoxy resins' primary component is this functional group [3]. Epoxides exhibit strong angular stretching, much like cyclopropanes. Compared to simple ethers, epoxides have a higher level of reactivity with nucleophilic

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reagents, which is their most significant chemical characteristic [4]. Epoxides react quickly with nucleophiles in an inert ether environment. When compared to the majority of other resins, epoxies are generally recognized for their exceptional mechanical qualities, adhesion, and resilience to chemicals and heat [5]. Epoxides, which include carbonyl compounds, alkyl halides, and alkyl sulfonates, are a significant source of electrophilic carbon [6]. Acidic media leads to the formation of similar products. Different products will arise in basic and acidic environments if the epoxide is asymmetric [7]. Chemists are currently concentrating on finding effective, fast-acting methods to study because of the significance of this reaction in both industrial and biological settings [8]. In organic chemistry, epoxide ring-opening reactions are helpful tools. The primary method of metabolism for the majority of naturally occurring epoxides in vivo is the catalytic addition of water to produce 1,2-diols [9].

Epoxide hydrolases are a family of enzymes that catalyze this process. The phenolic proton of a tyrosine moiety catalyzes epoxide ring opening in nature [10]. However, in a laboratory setting, the cleavage often takes place in non-aqueous conditions with the help of a Lewis acid catalyst, such as $MgCl_2$, $Zn(ClO_4)_2$–Al_2O_3. They are readily broken down by various nucleophiles to produce stereoselective and regioselective derivatives [11]. Recently, several techniques utilizing heterogeneous catalysts and metal triflates have been discovered. These do have certain drawbacks, though, including low yields and regioselectivity, the need for air, moisture-sensitive catalysts, stoichiometric quantities of catalyst, and issues with catalyst recovery [12]. Polymerization and the creation of a variety of regioisomers are seen in the majority of acidic epoxide ring-opening events [13]. Most of the reported methods suffer from disadvantages and limitations such as application of high temperature, long reaction time, low yield, use of toxic solvents, long steps of product extraction, a mixture of optical isomers, submission of reactants and products, multi-step reaction and lack of generalization of the method for different epoxides [14]. Therefore, the introduction and development of easy methods using inexpensive and accessible reagents, as well as magnetic catalysts with the ability to be easily separated and reused in the direct synthesis of esters from epoxides is of great importance [15]. Among the important advantages of one-pot synthesis, in which chemical changes and transformations take place simultaneously inside a container, we can mention the reduction of the extraction and purification steps of the products, as well as the increase of the reaction efficiency [16]. These methods are an effective step to reduce environmental pollutants to achieve the goals of green chemistry [17]. Ring opening of epoxides can be done in all three acidic, basic and neutral environments. Ring opening of epoxides is faster in the presence of acid. In this environment, protonated epoxides are attacked by nucleophiles [18]. In an acidic environment, the reaction mechanism is of the SN2 type, and normally the nucleophile attacks from the back, and the products 1 and 2 are substituted. The ring opening of asymmetric epoxides by nucleophiles is controlled by two factors, the structure of epoxides and the reaction conditions [19]. For monosubstituted epoxides, nucleophilic attack takes place in an acidic environment on carbon, which has a greater ability to accept a positive charge [20]. As shown in **Scheme 1**, it should be noted that if the R substituent is electron withdrawing, even in an acidic environment, the nucleophile attacks carbon with less steric hindrance [21].

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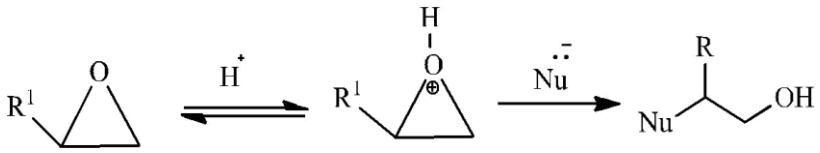
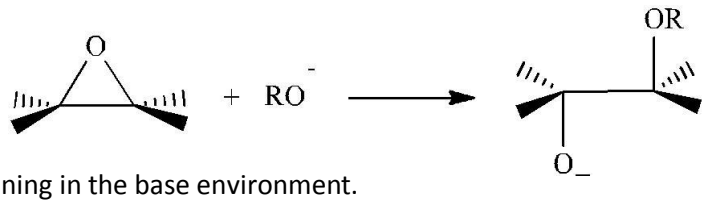


Scheme 1. Epoxide ring opening in acidic environment.

Unlike common ethers, epoxides are affected by bases and perform the ring opening reaction. In base and neutral environment, the reaction takes place through nucleophilic attack on neutral epoxide [22]. Therefore, epoxides are less active in the alkaline environment than in the acidic environment, and stronger nucleophiles such as alkoxy are needed to open them (**Scheme 2**) [23].



Scheme 2. Epoxy ring opening in the base environment.

The reaction mechanism of epoxides with nucleophiles in base or neutral environment proceeds through SN2 [24]. If the ring of epoxides is asymmetric, there is a possibility of nucleophile attack from both sides. But it usually attacks the carbon with less substitution which has less hindrance [25]. But it does not always follow this rule and the direction of nucleophilic attack is influenced by several factors such as solvent (protic or aprotic), temperature and substance concentration [26]. In this work, the ring opening of epoxides by amines, alcohols and phenol was investigated to convert epoxides into 1,2-disubstituted compounds in acidic and basic environments. Among the advantages of this method compared to the reported methods, he listed the reduction of the reaction speed, the easy separation of the product from the reaction mixture and the reaction using green solvents.

■ Results and Discussion

In order to identify the products, in addition to examining their physical properties, their IR and NMR spectra were also evaluated. In the IR spectrum of the obtained pure products, the broad peak corresponding to the stretching vibrations of the -OH group in the area of 3300-3500 cm^{-1} indicates the formation of the hydroxyl alcohol group. The peak related to the ether group can also be seen in the area of 1150-1200 cm^{-1} (**Figure 1**).

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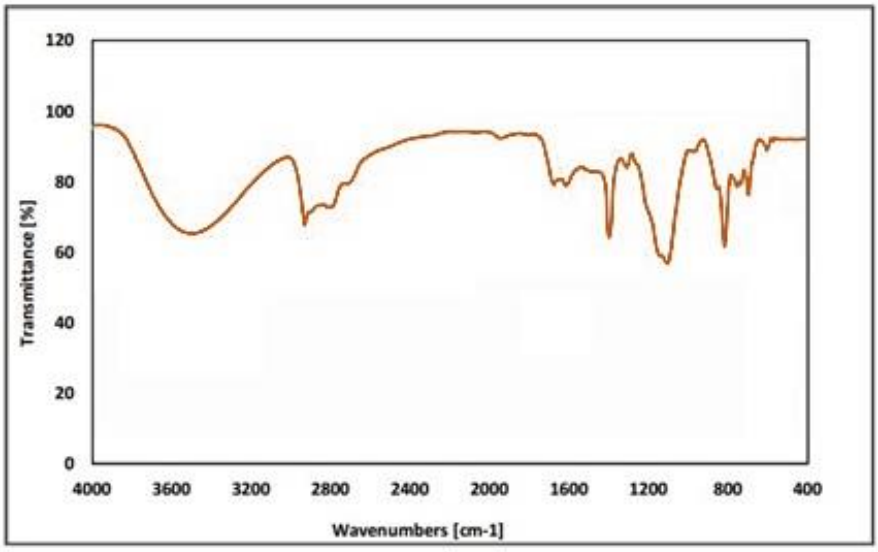
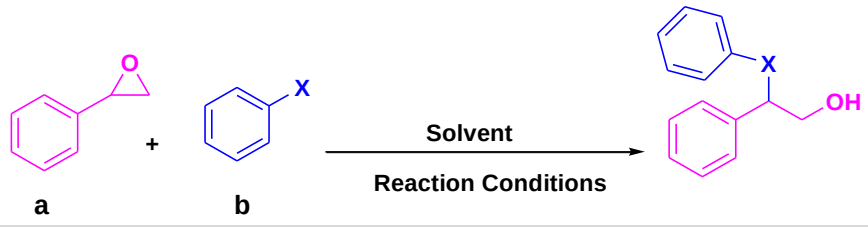


Figure 1. FT-IR spectra of products.

Table 1 shows the optimization of reaction conditions. First, different amounts of nucleophile (1, 2 and 3 mmol) were investigated. In the presence of 3 mmol, better results were obtained compared to 1 mmol. By increasing its amount to 4 mmol, there was no change in efficiency and reaction time. Then the amount of epoxide was checked. Amounts of 1, 2, and 3 mmol of epoxide were used and 1 mmol of it was selected as the optimal amount. By using 2 and 3 mmol of epoxide, the reaction time did not change and the efficiency did not increase significantly. In order to study the solvent effect, the ring opening reaction of the corresponding epoxide was investigated in different polar and non-polar solvents such as chloroform, ethanol and nitromethane. The results showed that the reaction does not take place in the presence of non-polar solvents. Polar solvents have the ability to promote the reaction, but compared to the solvent-free phase, they need more time to complete the reaction. The effect of temperature on the reaction was also investigated. The intended reaction was carried out at temperatures of 60 and 80 degrees Celsius in an oil bath. Applying high temperatures did not have much effect on the yield. The results showed that the reaction under room temperature needs less time than the oil bath with high temperature, therefore, this condition was chosen as the best option.

Table 1. Optimization parameters of epoxide ring opening reaction [a]



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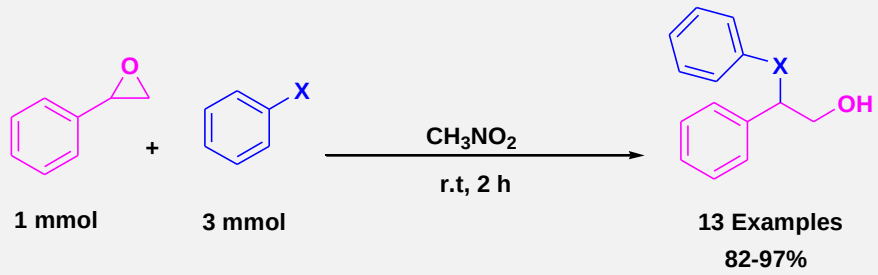
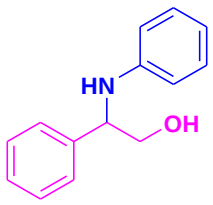
Entry	a (mmol)	b (mmol)	Solvent	Time (h)	Yield (%) [a]
1	1	1	CH_3NO_2	2	31
2	1	2	CH_3NO_2	2	51
3	**1**	**3**	**CH_3NO_2**	**2**	**97**
4	1	4	CH_3NO_2	2	97
5	2	3	$MeOH/H_2O$	2	80
6	3	3	THF	2	35
7	1	3	DMF	2	70
8	1	3	DMSO	2	58
9	1	3	EtOH	2	39
10	1	3	$CHCl_3$	2	21

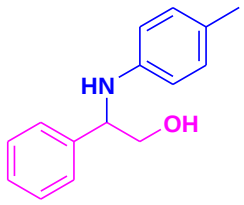
After optimizing the reaction conditions of different nucleophiles with electron-withdrawing or electron-donating substituent groups on the epoxide benzene ring, the ring opening reaction was successfully performed under optimal conditions, the results of which are presented in **Table 2**. The results showed that the reaction with electron-withdrawing groups has a higher efficiency.

Table 2. Scope of epoxide ring opening reaction [a]

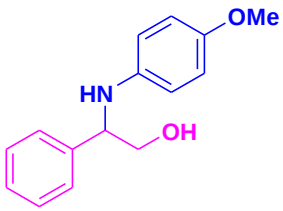




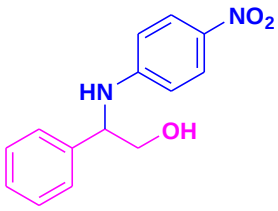
3a (97%)



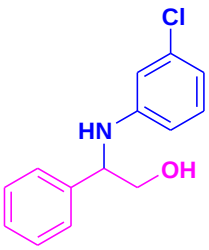
3b (89%)

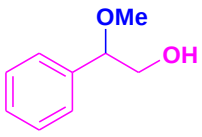


3c (88%)



3d (96%)





3f (94%)

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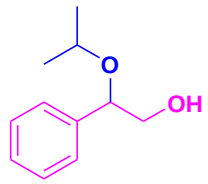
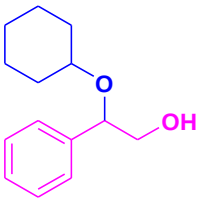
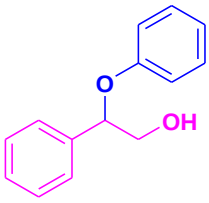
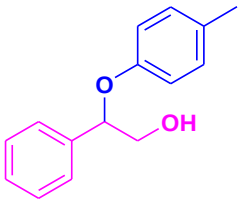
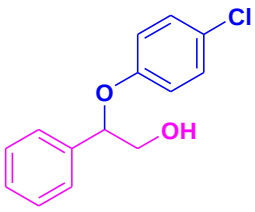
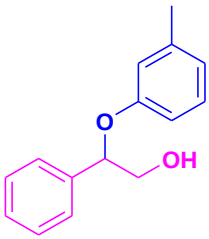
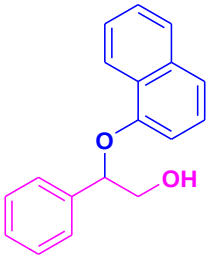
3e (93%)		
 **3g (93%)**	 **3h (91%)**	 **3i (90%)**
 **3j (87%)**	 **3k (94%)**	 **3l (86%)**
 **3m (82%)**		

Conclusion

In this research, the opening of epoxide ring by phenol, base and alcohol was investigated. Then the values of each were obtained in optimal conditions. The synthesized products were identified using different methods such as Fourier transform infrared spectroscopy (FT-IR) and NMR. Then different nucleophiles carrying electron donating and withdrawing groups were used with epoxide. This reaction had the best results in polar solutions. Polar solvent, no use of catalyst, application of mild conditions and low temperature, simplicity of the synthetic method, short reaction time, direction-selectivity, as well as high yield of products and easy separation of products from the reaction medium are the advantages of this green method.

Experimental

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All chemicals were utilized without being purified; they were bought from Fluka or Merck chemical businesses. Using Bruker Avance 300MHz equipment, the ^{1}HNMR (500 MHz) and the ^{13}CNMR (125 MHz) were recorded. As the internal standard, chemical changes are reported from TMS in parts per million downfield. Using a Bruker Model Tensor 27 spectrometer, IR spectra were captured; only the prominent peaks were reported. Thin-layer chromatography was used to track the reactions' development (TLC).

General procedure for ring opening of epoxide with amines, alcohols and phenol in nitromethane

For two hours at room temperature, a combination of styrene oxide (1 mg mol), nucleophile (3 mmol), and nitromethane (5 mmol) was agitated. TLC was used to track the reaction's development using n-hexane-EtOAc 70: 30. Following a water quench and dichloromethane extraction, the reaction mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography using n-hexane-Ethyl acetate for further purification. By comparing the IR ^{1}H and ^{13}C NMR with those of real materials, the structure was verified.

Supporting Information

2-(p-toluidino)-2-phenylethanol (3b) White solid. M.p.: 73–75 ℃. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.37–7.31 (m, 4H), 7.30–7.27 (m, 1H), 6.94 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 4.51 (dd, J = 4.0, 6.8 Hz, 1H), 3.95 (dd, J = 4.0, 10.8 Hz, 1H), 3.75 (dd, J = 7.2, 11.2 Hz, 1H), 2.25 (s, 3H), 1.86 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 144.2, 140.3, 129.7, 128.5, 127.8, 127.2, 126.3, 114.4, 67.2, 60.2, 20.4.

2-(4-chlorophenoxy)-2-phenylethanol (3k) ^{1}H NMR (500 MHz, $CDCl_3$, ppm, 20 ℃): δ 7.33–7.28 (m, 5H), 7.04 (d, J = 8.6 Hz, 2H), 6.48 (d, J = 8.8 Hz, 2H), 4.58 (br, 1H), 4.45 (dd, J = 4.0, 6.8 Hz, 1H), 3.95 (d, J = 10.8 Hz, 1H), 3.77– 3.72 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, 20 ℃): δ 145.6, 139.8, 129.7, 128.6, 127.4, 126.5, 122.0, 114.2, 67.8, 59.7.

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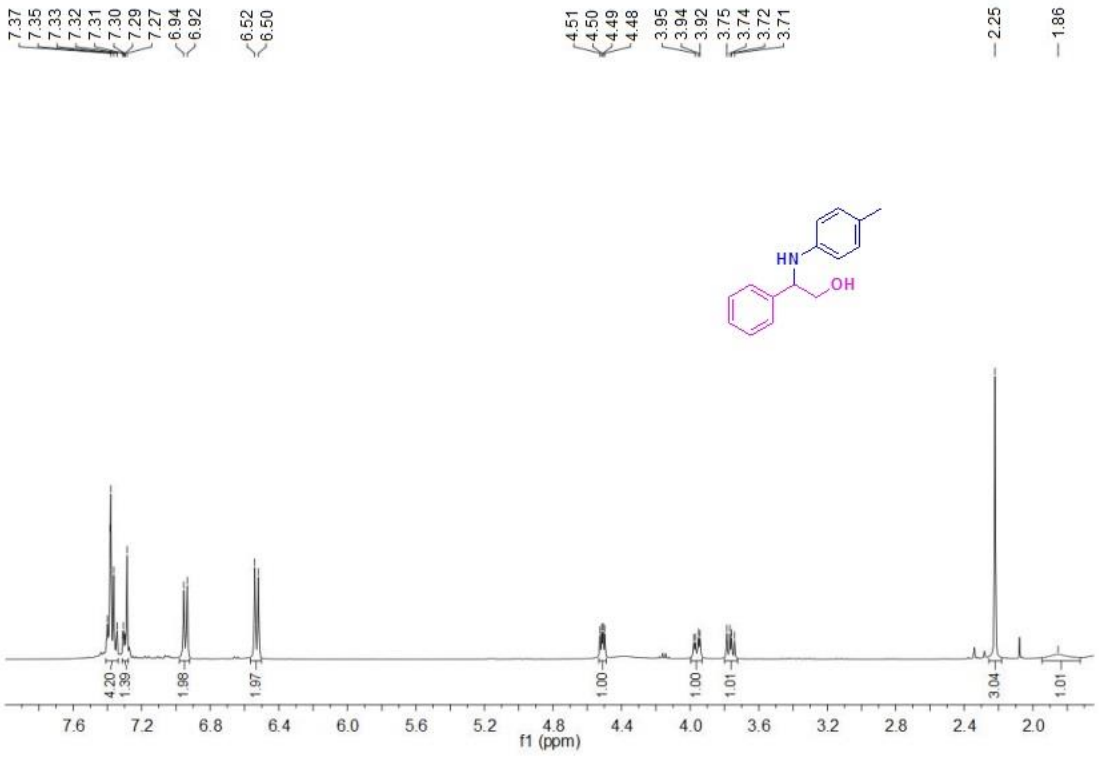
NMR



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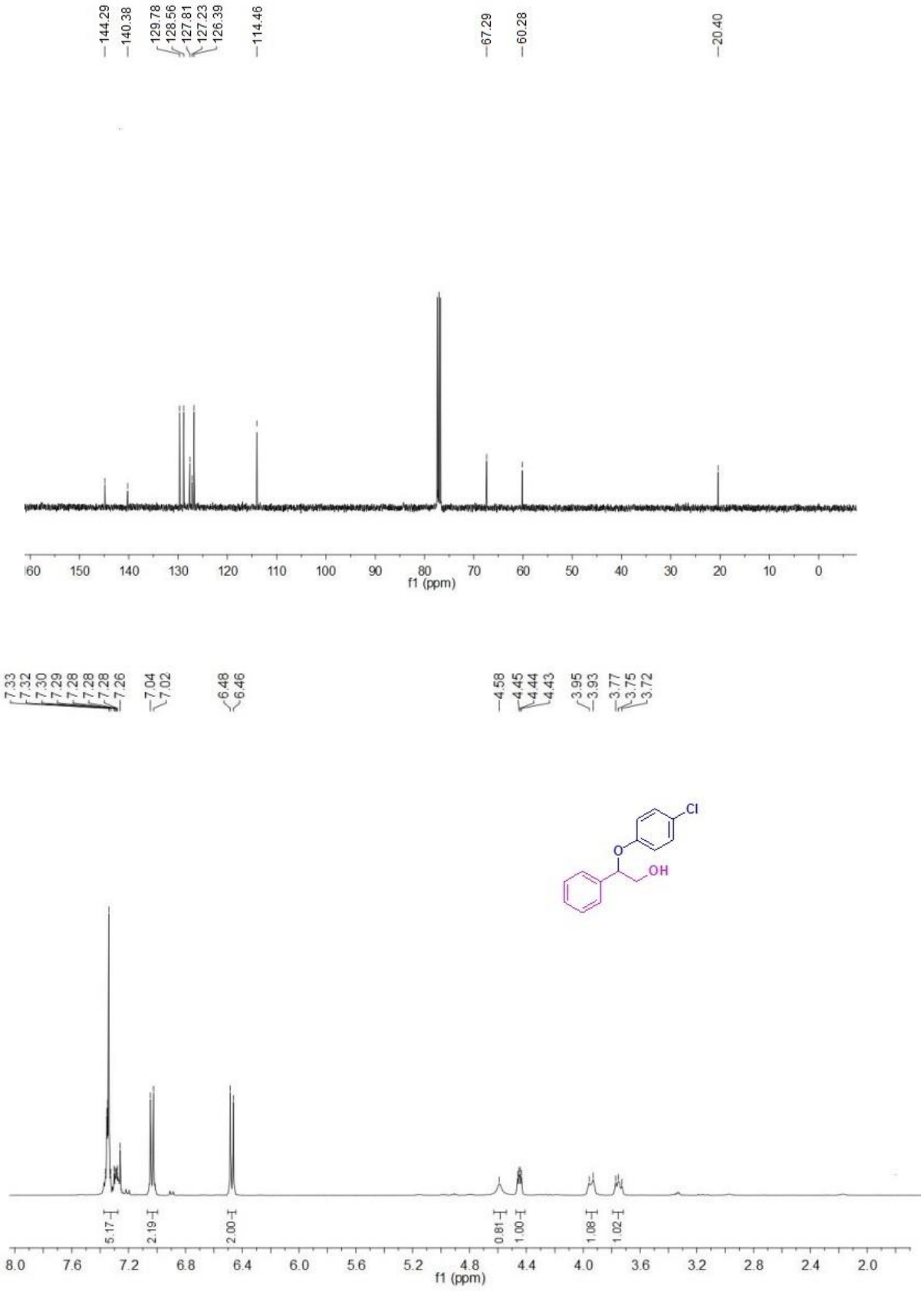

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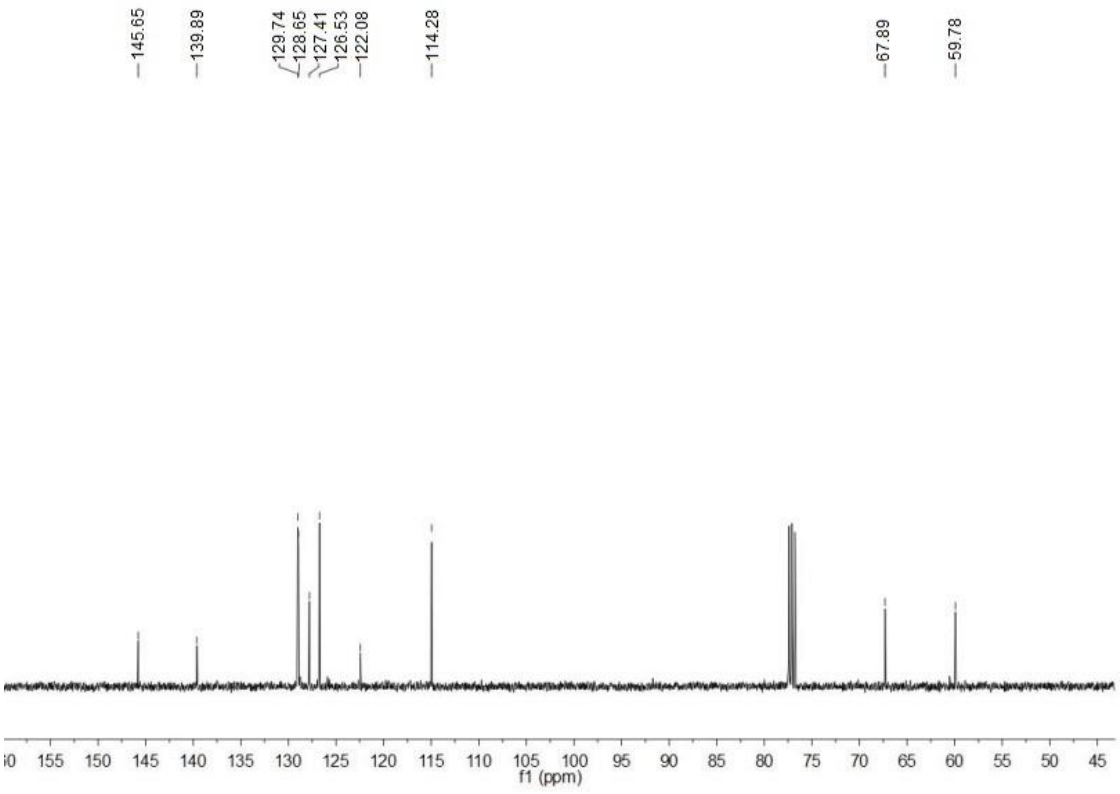

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