理 學 碩 士 學 位 論 文

HFIP를 용매로 이용하여 나이트론을 만드는 옥사지리딘의 재배열 반응 개발

The Rearrangement of Oxaziridines to Nitrones

Using HFIP as Solvent

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指 導 敎 授 우 상 국

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2022年 2月

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金 蘭 喜의 理學碩士 學位論文을 認准함

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1. Abstract

We developed a reaction to generate nitrones from oxaziridines using 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) that possesses unique chemical properties. In this reaction, we developed the rearrangement of oxaziridines to nitrones at room temperature under mild conditions without any addtitives with various functional group tolarence in good yields.

2. Introduction

Nitrone is a functional group in organic chemistry consisting of an N-oxide of imine. Nitrones can react in cycloaddition, rearrangement reaction, addition, and substitution reactions with nucleophilic, electrophilic, and radical reagents because of their electronic nature.[1] Following their chemistry, nitrones are used to make diverse building blocks in various synthetic strategies. Especially, the 1,3-dipolar cycloaddition reactions of nitrones are the most useful aspect in organic chemistry. According to the 1,3-dipolar cycloaddition reactions, nitrones can generate isoxazolidines or 4-isoxazolines, and they are key intermediates that make useful biologically important nitrogen scaffolds via various functionalization reactions (**Scheme 1a**). Traditionally, nitrones could be prepared by the condensation reactions of N-monosubstituted hydroxylamines[2], oxidation reactions of N,N-disubstituted hydroxylamines[3], reactions of oximes with electrophiles[4], and other various methods.

Representative generation of nitrones from oxaziridines is thermal, photochemical rearrangement and Brønsted or Lewis acidic conditions involving cleavage of C-O bond (**Scheme 1b**). In thermal rearrangement reaction case, the oxaziridines can convert to nitrones by heating over 100 ℃ to break strong C-O bond[5]. Additionally, photoisomerization reactions of oxaziridines to form nitrones were discovered by photosensitized electron transfer[6]. Nitrones are mostly generated by acid-catalyzed rearrangement of oxaziridines. Both Brønsted-Lowry and Lewis acid can be used for the rearrangement of oxaziridines to the corresponding nitrones[7-9]. According to these methods, the rearrangement reaction conditions of oxaziridines require high thermal

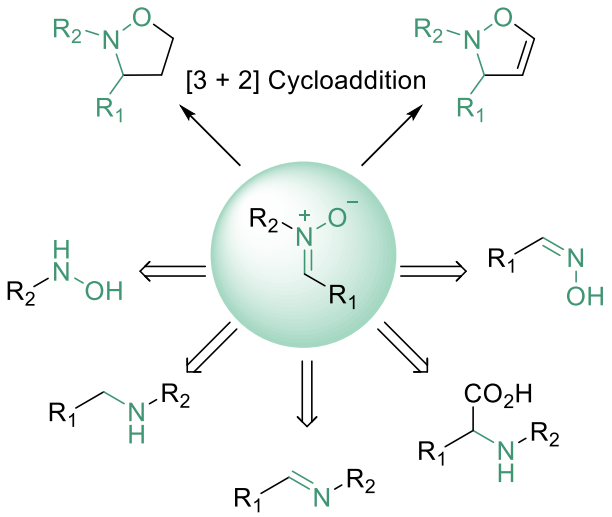
energy or using Brønsted-Lowry and metal Lewis acid reagents that could be harsh and toxic conditions. Also, the reactions have a disadvantage that the oxaziridines involving electron-deficient aryl group are hardly rearranged.

1,1,1,3,3,3-Hexafluoroisopropylalcohol (HFIP) has recently been found to be an unusually interesting and beneficial properties for diverse chemical reactions as solvent or additive in organic chemistry. Colomer (2017)[10] and Ramos-Villaseñor (2020)[11] reported the various properties and usage of HFIP in chemistry. Based on the previous reports, there are some key chemical effects of HFIP such as enhanced acidity, reduced nucleophilicity, hydrogen-bond donating ability, redox stability, and cation stabilization. Through these properties, HFIP could be applicated in the fields of organic, inorganic chemistry and electrochemistry. Particularly, we are focused on the strong hydrogen-bond donating ability of HFIP to lead oxaziridines' activation (**Scheme 1c**). In 2006, Maiti and co-workers observed that the C-H bond could affect to increase the hydrogen bonding interaction of O-H bond.[12] Following this report, they explained that the hydrogen bond donating strength of HFIP is increased by the negative hyperconjugation between the σ-bonding orbital of the O-H bond and the σ^*-bonding orbital of the C-H bond, which changes the bond length of C-H bond according to the observed $\mathbf{\nu}_{CH}$. Berkessel and co-workers discovered that the conformation of H-C-O-H bond in HFIP could effect the orbital energy and the dipole moment.[13] In this study, the result shows that σ^*_{OH}-orbital energy of the HFIP decreases and the dipole moment increases depending on the torsion angle of H-C-O-H bond from antiperiplanar to synperiplanar, and consequently, the HFIP molecule favored

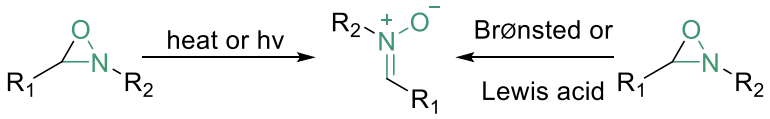
synclinal or even synperiplanar conformation than antiperiplanar. In addition, the aggregation of H-bonded HFIP molecules enhanced the hydrogen-bond donating ability of HFIP. The aggregated HFIP tended to decrease the LUMO (σ^*_{OH}-orbital ene) and increase the partial charge compared to monomer. Also, the limit molecule number of this effect is a trimer of HFIP monomers. So the hydrogen-bond donating parameter α value of HFIP (α = 1.96) is larger than any other protic solvent[14].

Herein, we present a rearrangement of oxaziridines to form nitrones without any acidic conditions at room temperature under mild condition (**Scheme 1d**). This reaction involves oxaziridines' activation via proton donation and hydrogen-bond donation of HFIP to stabilize intermediate.

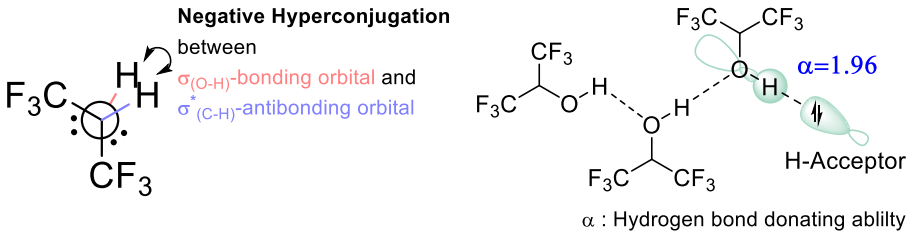
a) Importance of nitrone moiety and common method to generate nitrones



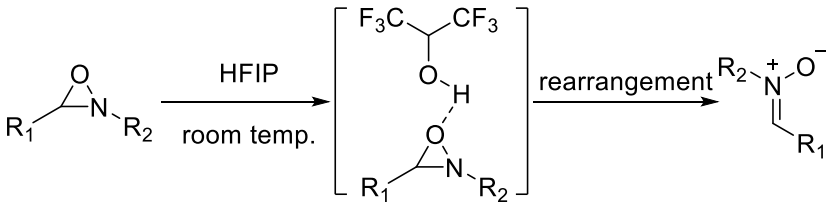
b) Rearrangement of oxaziridines to nitrones



c) Strong Hydrogen-bond donating ability of HFIP



d) This work

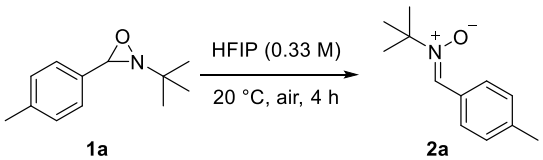


Scheme 1. Synthesis approach of nitrones and chemical properties of HFIP

3. Results and Discussion

a. Optimization of the Reaction Conditions

Table 1. Optimization of the Reaction Conditions



1a
(0.2 mmol)

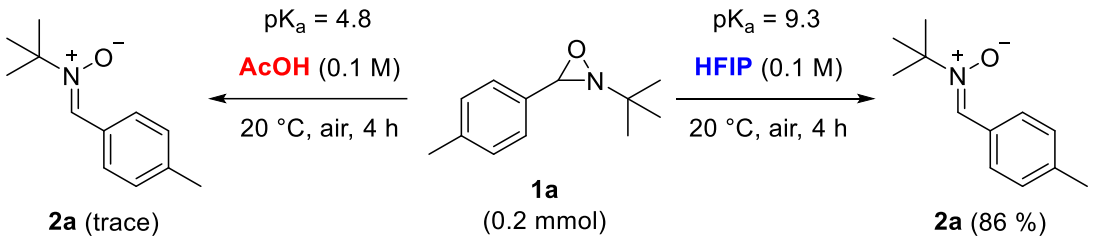
2a

entry	scale (mmol)	solvent	conc. (M)	temp. (°C)	time (h)	yield (%)[b]
1	0.2	MeOH	0.1	25	16	trace
2	0.2	EtOH	0.1	25	16	trace
3	0.2	i-PrOH	0.1	25	16	trace
4	0.2	DCM	0.1	25	16	trace
5	0.2	1,2-DCE	0.1	25	16	0
6	0.2	$CHCl_3$	0.1	25	16	trace
7	0.2	HFIP	0.1	25	16	88
8	0.2	HFIP	0.1	40	16	79
9	0.2	HFIP	0.1	50	16	82
10	0.2	HFIP	0.1	60	16	90
11	0.2	HFIP	0.1	25	4	88
12	0.2	HFIP	0.2	25	4	88
13	0.2	HFIP	0.3	25	4	89
14	0.4	HFIP	0.5	25	4	89
15	1	HFIP	1	25	4	87
16	1	HFIP	2	25	4	56
17	1	HFIP	3	25	4	32
18	2	HFIP	5	25	4	12

[a] Standard condition : 1a (1 mmol) in HFIP (1 ml, 1 M) at 25 °C under air atmosphere for 4 hours. [b] The yield was determined by HPLC (Internal standard=Mesitylene).

We initially examined the reaction of 2-(tert-butyl)-3-(p-tolyl)-1,2-oxaziridine **1a** (0.2 mmol) in some alcohol or halogenated solvents (0.1 M) under air atmosphere for 16 hours at 25 ℃ (**Table 1**. entries 1-7). The corresponding nitrone product **2a** was not formed in any alcohol and halogenated solvents (**Table 1**. 1-6 entries); especially, the

HFIP have been found to play a crucial role than any solvent in 88 % yield as determined in HPLC (**Table 1**. entry 7). The temperature of the reaction is also played an important role in the yield (**Table 1**. entries 8-10). The rearrangement reaction could be occured by thermal conditions, so the more temperature is applied, the better the reaction occurs at 90 °C in 90 % yield (**Table 1**. entry 10). When we proceeded reaction time oprimization, it took only 4 hours for the reaction to consume starting material and be completed (**Table 1**. entry 11). At the solvent concentration screen (**Table 1**. entries 12-18), the efficient of HFIP in the reaction was the best when the concentration was 1 M obtained the product **2a** in 87 % isolated yield (**Table 1**. entry 15) and it was an amount to 10 equivalents for the starting oxaziridine **1a**.



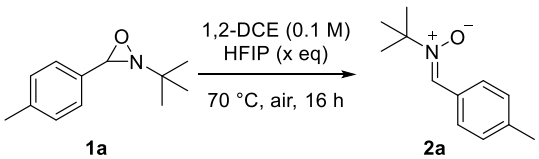
Scheme 2. Reaction with acetic acid for the reaction solvent instead of HFIP

HFIP is also a good Brønsted-Lowry acid, but it does not only act as a Brønsted-Lowry acid in this reaction. For example, when we used acetic acid (pK_a = 4.8) as the reaction solvent that has lower than 9.3, the pK_a value of HFIP, almost no corresponding product **2a** was produced (**Scheme 2**). It means that the stronger acid

than HFIP could not rearrange the oxaziridines to nitrones. With this result, we thought that HFIP could react as hydrogen-bond donor in this rearrangement reaction of the oxaziridines.

Since HFIP is a volatile, corrosive and toxic material, we confirmed whether the reaction is performed or not even when used as reagent amount of HFIP with other solvent condition despite some advantages in this reaction (**Table 2**). When we examined the equivalent of HFIP with 1,2-DCE as solvent, it was found that the reaction result was better as the amount of HFIP increased (**Table 2**. entry 3).

Table 2. Reaction Using HFIP as an equivalent



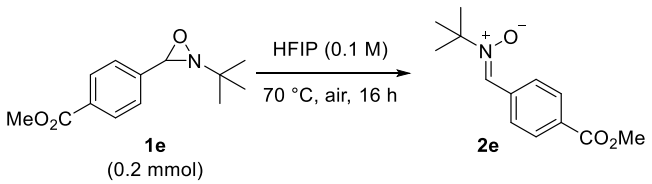
entry	solvent	conc. (M)	atmosphere	temp. (°C)	additive	time (h)	yield (%)[b]
1	1,2-DCE	0.1	air	70	HFIP (2 eq)	16	74
2	1,2-DCE	0.1	air	70	HFIP (5 eq)	16	82
3	1,2-DCE	0.1	air	70	HFIP (10 eq)	16	86

[a] Standard condition : 1a (0.2 mmol) in 1,2 DCE (0.1 M) at 70 °C with HFIP as equivqlent under air atmosphere for 16 h.
[b] The yield was isolated yield.

In previous work, it is not easy to form electron-withdrawing group substituted aryl nitrones than electron-donating group substituted aryl nitrones[15]. Compared with

electron-donating group, the electron-withdrawing group substituted aryl oxaziridines have stronger C-O bond and higher HOMO energy, so the LUMO of proton or Lewis acid could interact with electron-rich oxaziridines more favored. Because of this reason, the rearrangement of oxaziridine **1e** with electron withdrawing ester group in aryl ring to nitrone also difficult in our condition at room temperature (**Table 3**. entry 1). So we tried giving some thermal energy enough to break C-O bond of the oxaziridine **1e**. As a result, we could get 50 % yield for corresponding nitrone **2e** through the rearrangement of **1e** at 70 ℃ (**Table 3**. entry 3).

Table 3. Reacion with oxaziridine involving electron withdrawing group

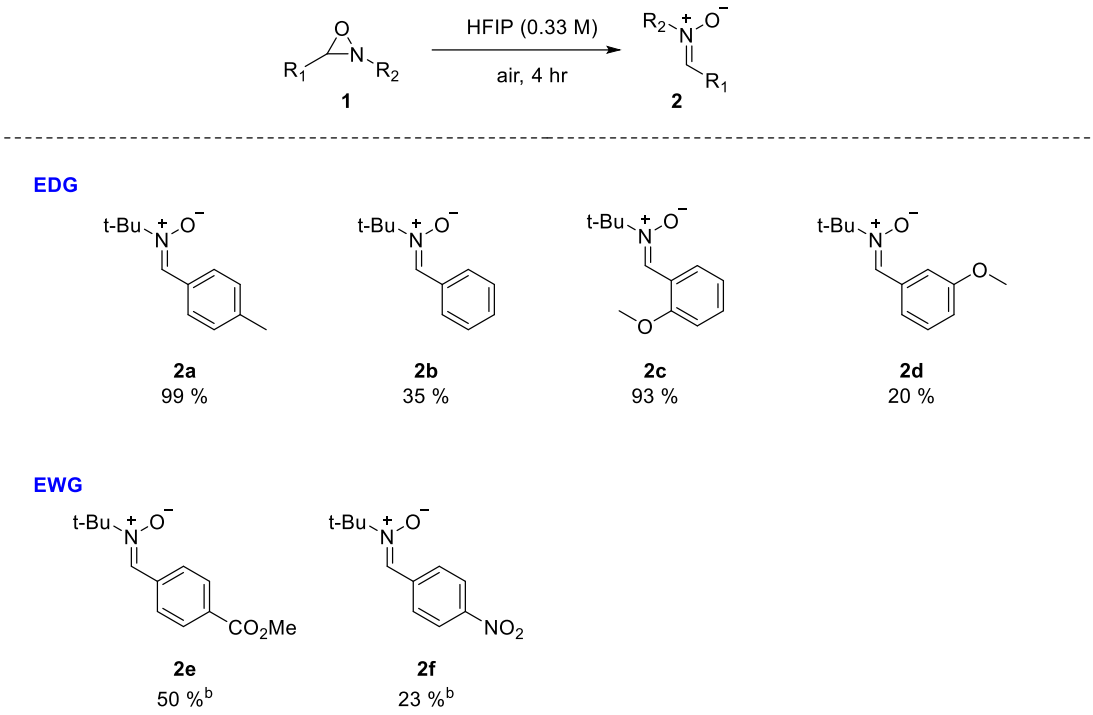


entry	solvent	conc. (M)	atmosphere	temp. (°C)	additive	time (h)	yield (%)[b]
1	HFIP	0.1	air	20	-	16	trace
2	HFIP	0.1	air	50	-	16	20
3	HFIP	0.1	air	70	-	16	50

[a] Standard condition : 1a (0.2 mmol) in HFIP (0.1 M) under air atmosphere for 16 h. [b] The yield was Isolated yield.

b. Substrate scope of Nitrones

Next, we explored the substrate scope of various oxaziridines with electron-donating or electron-withdrawing group to examine the electronic effect (see **Scheme 3**). Under optimized condition, oxaziridines **1a-1d** that involving electron-donating group could rearrange to form the corresponding nitrones at room temperature. However, an excellent yield could be obtained in the reaction only in oxaziridines that electron-donating group was substituted at the *para* or *ortho* position of the phenyl group (**2a**, **2c**). In the *meta* position case, even if the electron-donating group was substituted in oxaziridine, it could not have a significant effect compared to the *para* or *ortho* position (**2d**). At electron-withdrawing group substituted oxaziridine system, the activation barrier of the reaction is too high to rearrange for the formation of nitrones from oxaziridines at room temperature. So, we solved this problem by applying some heat. Although the reaction was not performed at room temperature, it was confirmed that a corresponding nitrone products were produced as a result of performing the reaction at 70 ℃ (**2e-2f**).

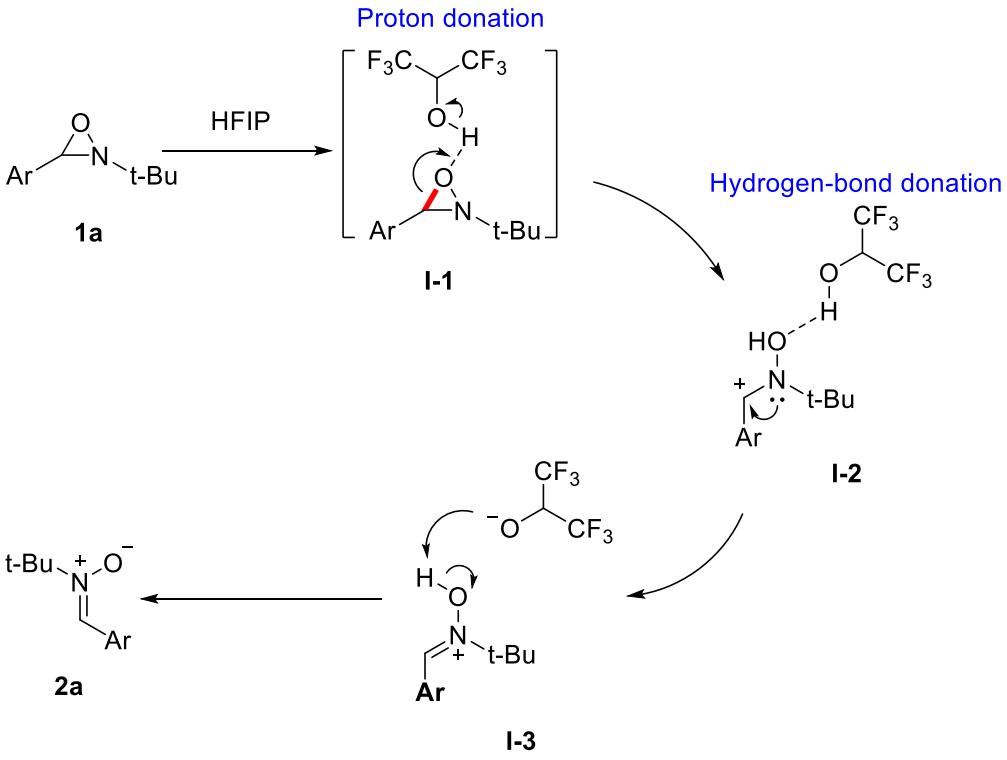


[a] Standard condition : 1 (0.2 mmol) in HFIP (0.33 M) at 20 °C under air atmosphere for 4 h, Isolated yield.
[b] 1 (0.2 mmol) in HFIP (0.33 M) at 70 °C under air for 16 h, isolated yield.

Scheme 3. Substrate scope of Nitrones

c. Plausible Mechanism

A plausible reaction mechanism was proposed as illustrated in **Scheme 4**. The activation of oxaziridine **1a** by proton donation with HFIP molecule produces intermediate **I-1**, which undergoes to **I-2** by breaking C-O bond of the oxaziridine **1a**. The intermediate **I-2** could be stabilized by hydrogen-bond donation of HFIP molecules. In this in-situ-generated carbocation intermediate **I-2**, nitrogen atom provides its lone pair electron to neighboring carbon to form the intermediate **I-3**. After deprotonation of intermediate **I-3**, the desired nitrone **2a** produces that has 1,3-dipole in the molecule.



Scheme 4. Proposed mechanism of rearrangement oxaziridine **1a** to nitrone **2a**

4. Conclusion

In conclusion, we found that oxaziridines could be rearranged into corresponding nitrones by HFIP effect. HFIP has useful chemical properties, and we proposed the reaction mechanism that involves hydrogen bond donation of HFIP for activation to cleavage of C-O bond in oxaziridines. In aryl oxaziridine system, the activation barrier of the rearrangement could be lowered when electron-donating group is substituted at the *ortho* or *para* position. Also, the reaction provides rearrangement of oxaziridines involving electron-withdrawing group to the corresponding nitrones in heating conditions.

5. Experiment Section

a. Reagent

All reactions were run under an atmosphere of air unless otherwise indicated.

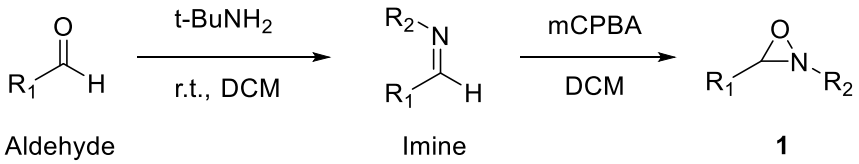
All commercial reagents were used directly without further purification. Pressure tubes (13x100 mm, PYREXPLUS) were dried in an oven for overnight and cooled under air prior to use. The progress of the reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized at 254 nm UV light. And the column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using Hexanes/EtOAc (v/v).

b. Instruments

Nuclear Magnetic Resonance spectra (^{1}H NMR, and ^{13}C NMR) were recorded woth a Bruker 300 MHz spectrometer. Chemical shift values were recorded as part per million relatives to tetramethylsilane (TMS) as an internal standard unless otherwise indicated and coupling constants in Hertz. The following abbreviations are used: m (multiplet), s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), etc.

c. Synthesis of Compound.

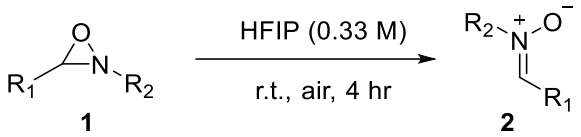
- General Procedure for synthesis of Oxaziridines



To round bottomed flask containing an equimolar amount of aldehyde (5.0 mmol, 1.0 equiv), tert-butyl amine (20 mmol, 4 equiv.) and a magnetic stir bar, this reaction mixture was added 15 ml of dry dichloromethane. The solution was stirred for 6 hours at room temperature. After reaction finished, the reaction mixture concentrated by rotary evaporator. This crude imine was dissolved in dry dichloromethane. After cooling to 0 ℃, mCPBA (7.5 mmol, 1.5 equiv.) in dry dichloromethane (25 ml, 0.5 M for aldehyde) was added to the solution. The solution was stirred at 0 ℃ until the imine was completely consumed by monitoring with TLC. The reaction mixture was quenched by H_2O and washed with Na_2SO_3, Na_2CO_3, and brine. The organic layer dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to furnish the corresponding oxaziridine **1**.

- General Procedures for synthesis of Nitrones by rearrangement of oxaziridines

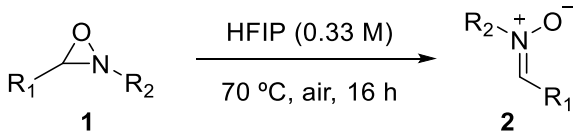
General procedure **A**



1 **2**

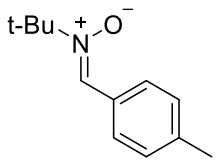
The oxaziridine **1** (1 mmol, 1.0 equiv.) and HFIP (1 ml, 1 M for **1**) was added to a pressure tube (13x100 mm) with a magnetic bar under air atmosphere. The reaction mixture was stirred for 4 hours at room temperature. After reaction finished, the crude of reaction mixture was concentrated by rotary evaporation to remove solvent, and the residue was purified by flash column chromatography on silica gel to afford the corresponding nitrone product **2**.

General procedure **B**



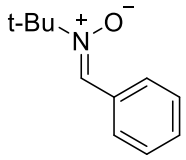
1 **2**

The oxaziridine **1** (1 mmol, 1.0 equiv.) and HFIP (1 ml, 1 M for **1**) was added to a pressure tube (13x100 mm) with a magnetic bar under air atmosphere. The reaction mixture was stirred for 16 hours at 70 ℃ in the oil bath. After reaction finished, the crude of reaction mixture was cooled, concentrated by rotary evaporation to remove solvent, and the residue was purified by flash column chromatography on silica gel to afford the corresponding nitrone product **2**.



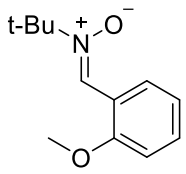
(Z)-N-tert-butyl-1-(p-tolyl)methanimine oxide (**2a**)

Following the general procedure A using 20 % ethyl acetate in hexanes as eluent, **2a** was obtained as a white solid (37.8 mg, 99 % yield); R_f = 0.30 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.64, 130.27, 129.16, 128.93, 128.28, 70.48, 28.33, 21.66.



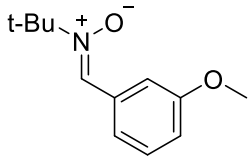
(Z)-N-tert-butyl-1-phenylmethanimine oxide (**2b**)

Following the general procedure A using 20 % ethyl acetate in hexanes as eluent, **2b** was obtained as a white solid (12.4 mg, 35 % yield); R_f = 0.30 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 8.25 (m, 2H), 7.56 (s, 1H), 7.48 – 7.35 (m, 3H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.94, 130.24, 128.88, 128.47, 70.84, 29.72, 28.35.



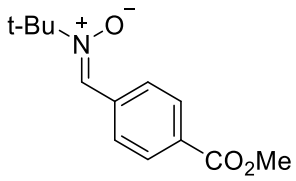
(Z)-N-tert-butyl-1-(2-methoxyphenyl)methanimine oxide (**2c**)

Following the general procedure A using 20 % ethyl acetate in hexanes as eluent, **2c** was obtained as a colorless liquid (38.6 mg, 93 % yield); R_f = 0.30 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.06 (s, 1H), 7.36 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.02 (ddd, *J* = 7.7, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.87 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.15, 131.25, 128.65, 124.61, 120.71, 119.98, 109.65, 70.94, 55.58, 28.36.



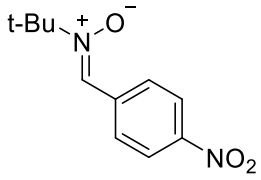
(Z)-N-tert-butyl-1-(3-methoxyphenyl)methanimine oxide (**2d**)

Following the general procedure A using 20 % ethyl acetate in hexanes as eluent, **2d** was obtained as a white solid (8.3 mg, 20 % yield); R_f = 0.30 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.2 Hz, 1H), 7.58 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.00 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.89 (s, 3H), 1.65 (s, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.56, 132.09, 129.22, 122.18, 117.67, 112.30, 70.99, 55.42, 29.72, 28.37.



(Z)-N-tert-butyl-1-(4-(methoxycarbonyl)phenyl)methanimine oxide (**2e**)

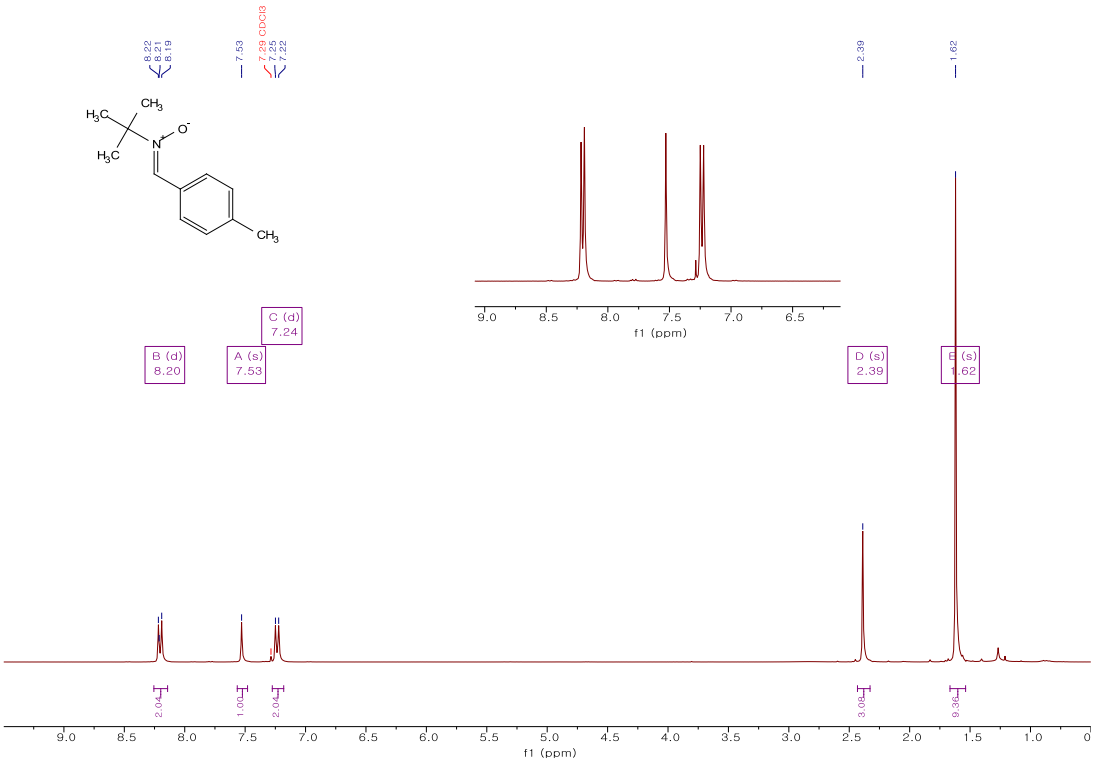
Following the general procedure B using 20 % ethyl acetate in hexanes as eluent, **2e** was obtained as a bright yellow solid (23.5 mg, 50 % yield); R_f = 0.50 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.31 (m, 2H), 8.15 – 8.03 (m, 3H), 7.64 (s, 1H), 3.93 (s, 4H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.51, 142.26, 134.95, 129.67, 128.38, 71.62, 52.22, 28.34.



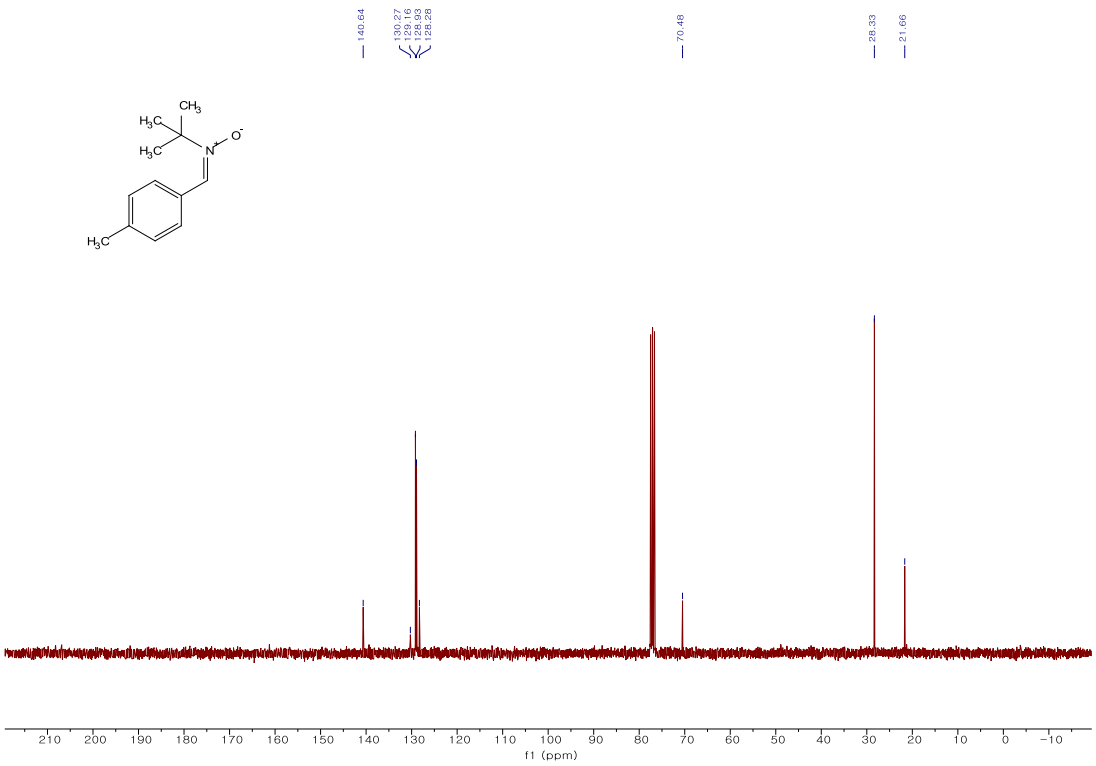
(Z)-N-tert-butyl-1-(4-nitrophenyl)methanimine oxide (**2f**)

Following the general procedure B using 20 % ethyl acetate in hexanes as eluent, **2f** was obtained as a brown solid (10.2 mg, 23 % yield); R_f = 0.50 (hexane:ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 – 8.41 (m, 2H), 8.34 – 8.22 (m, 3H), 7.72 (s, 1H), 1.66 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.72, 128.97, 124.54, 123.75, 72.38, 29.72, 28.35.

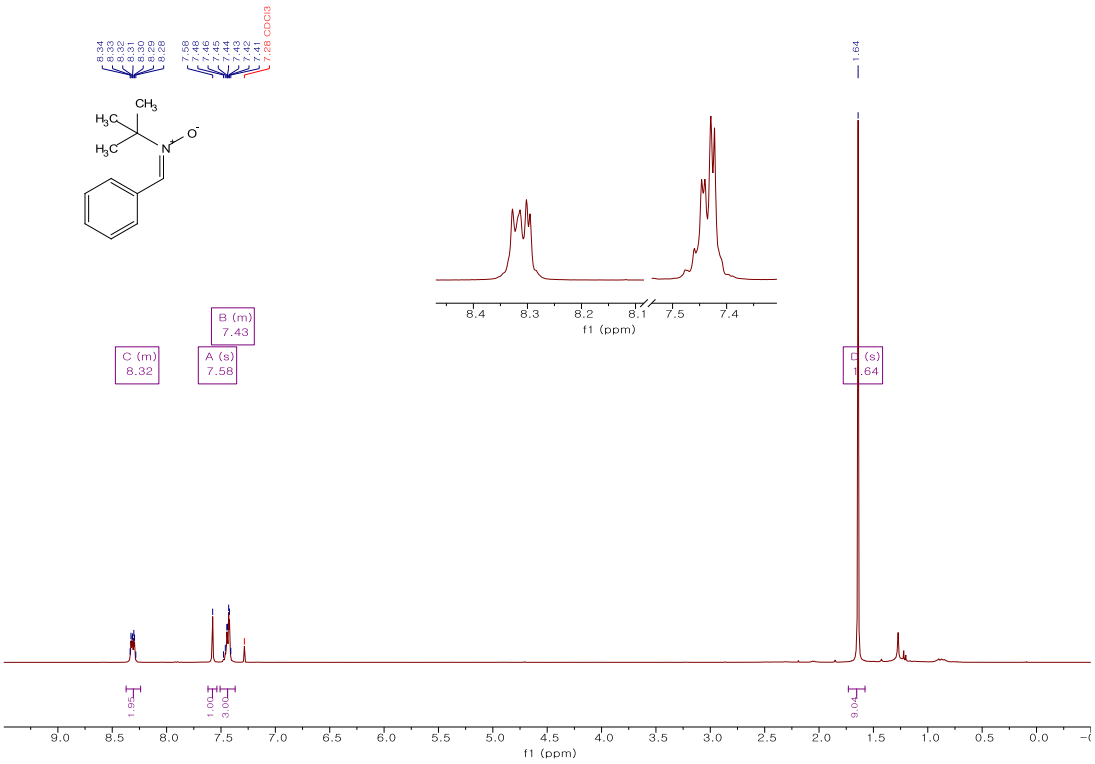
d. ^{1}H and ^{13}C NMR spectrum



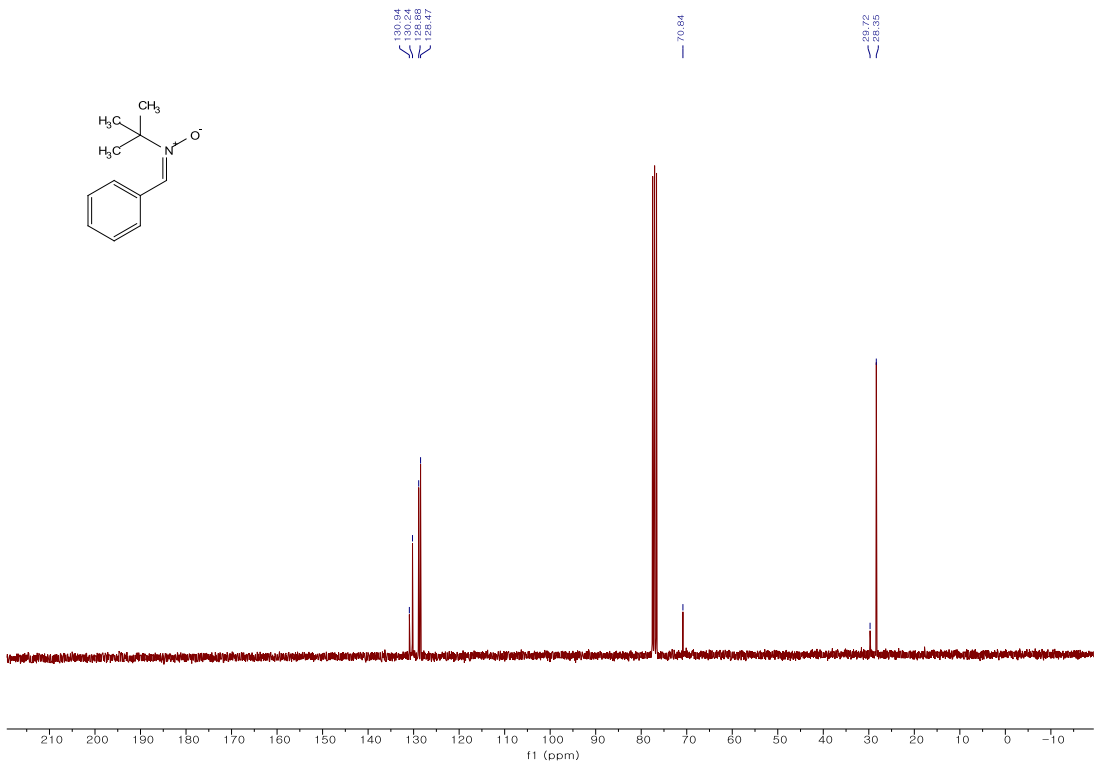
^{1}H NMR (300 MHz, $CDCl_3$) of **2a**



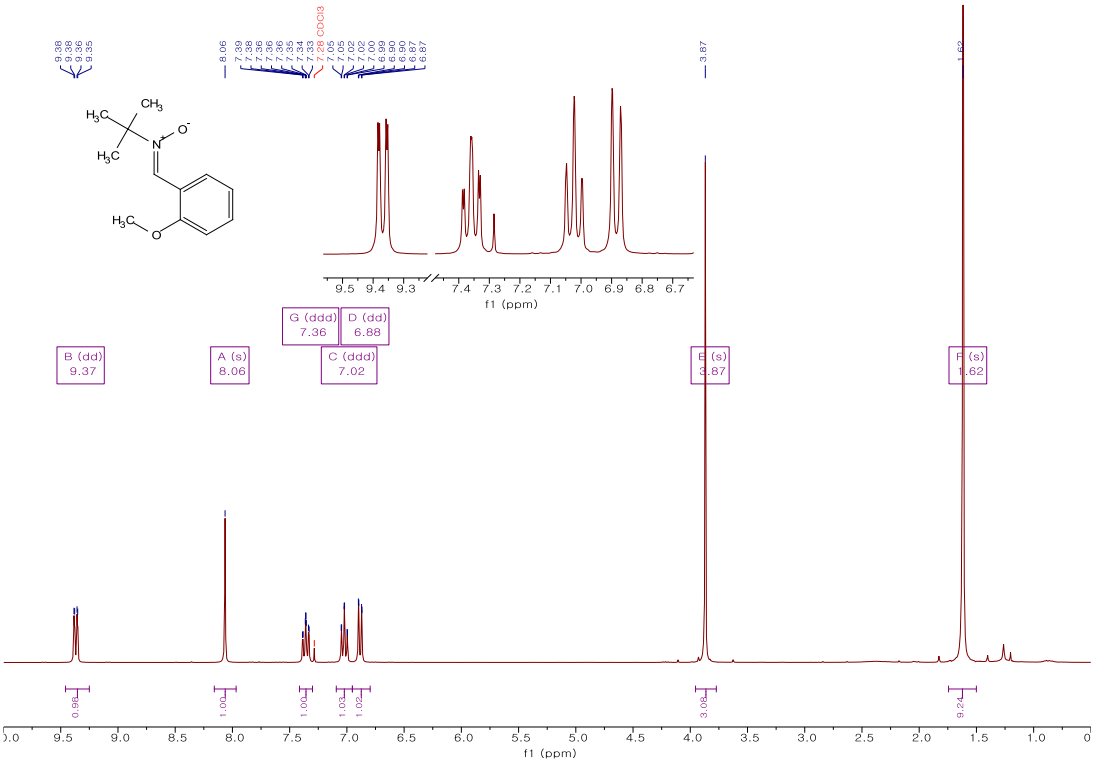
^{13}C NMR (75 MHz, $CDCl_3$) of **2a**



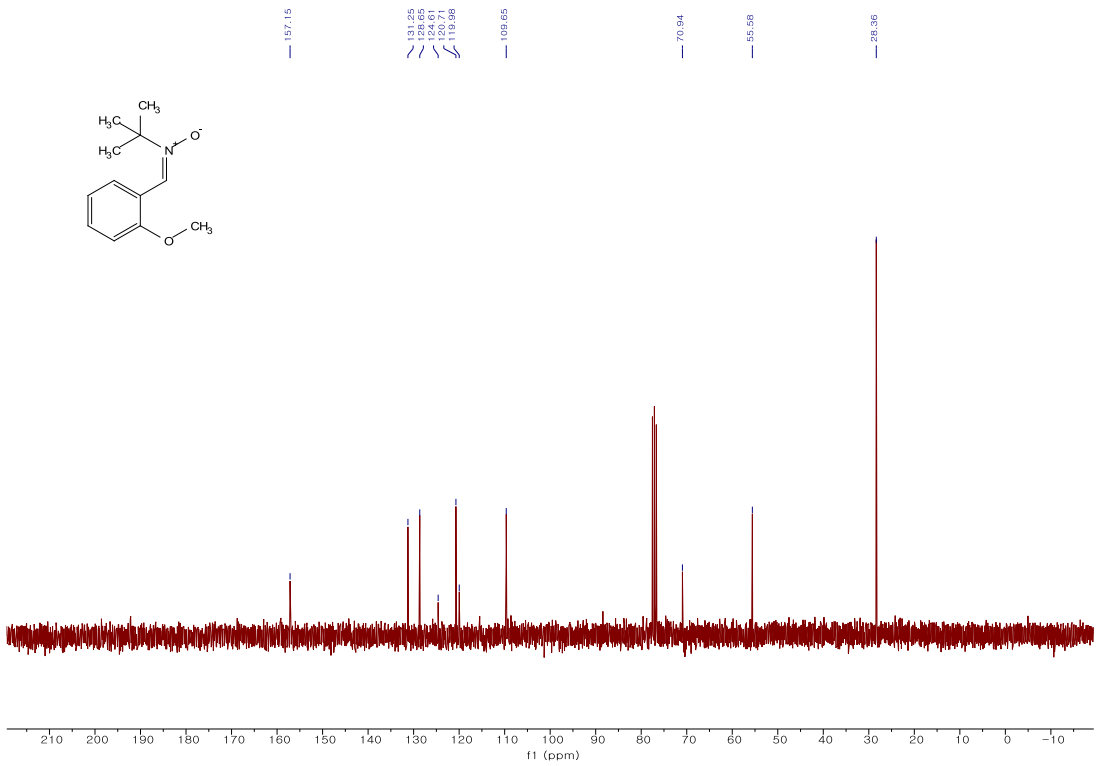
^{1}H NMR (300 MHz, $CDCl_3$) of **2b**



^{13}C NMR (75 MHz, $CDCl_3$) of **2b**

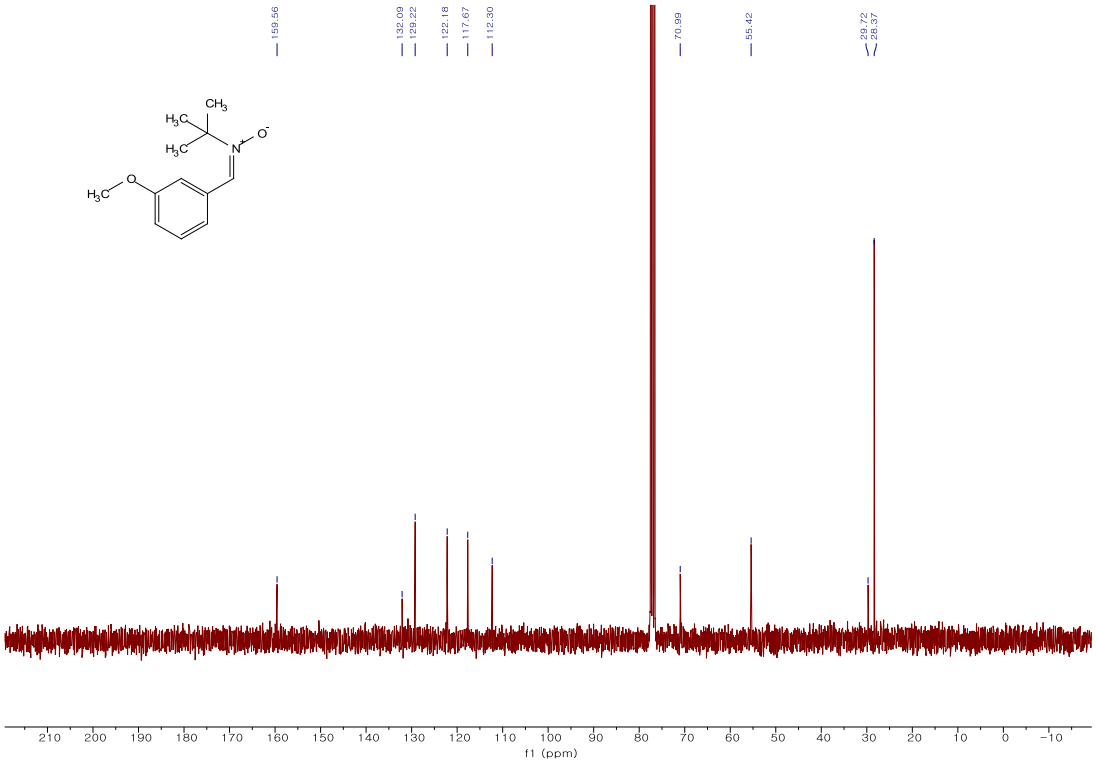


^{1}H NMR (300 MHz, $CDCl_3$) of **2c**

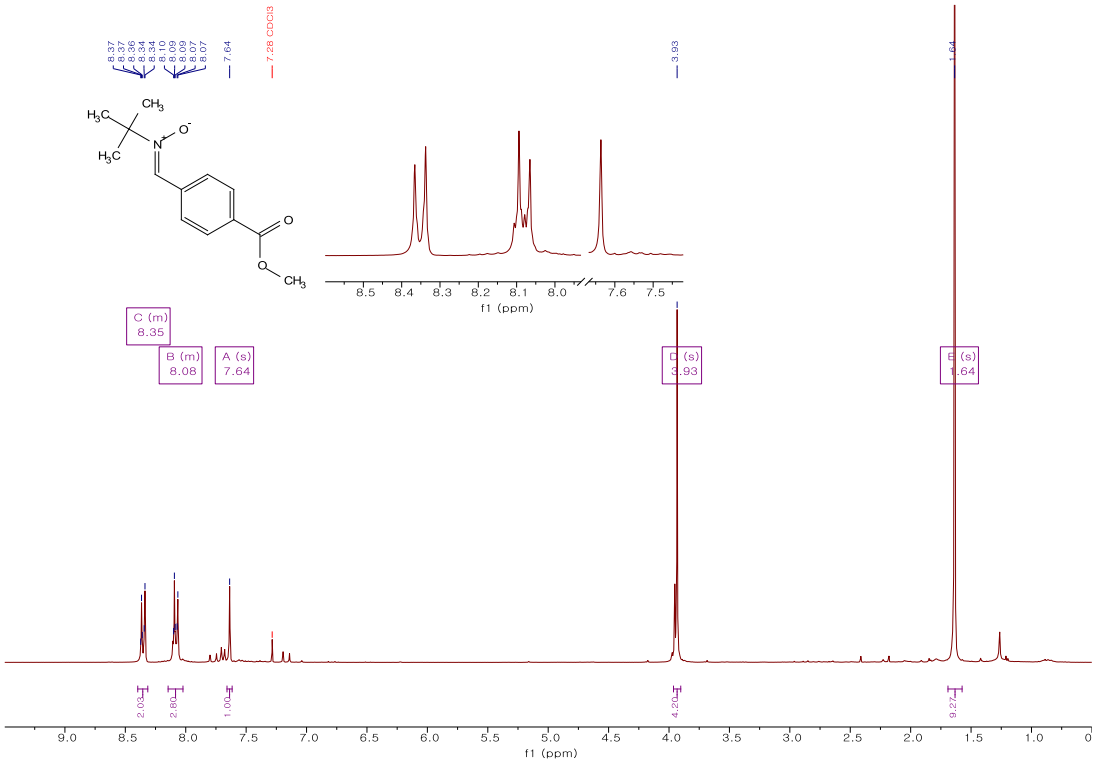


^{13}C NMR (75 MHz, $CDCl_3$) of **2c**

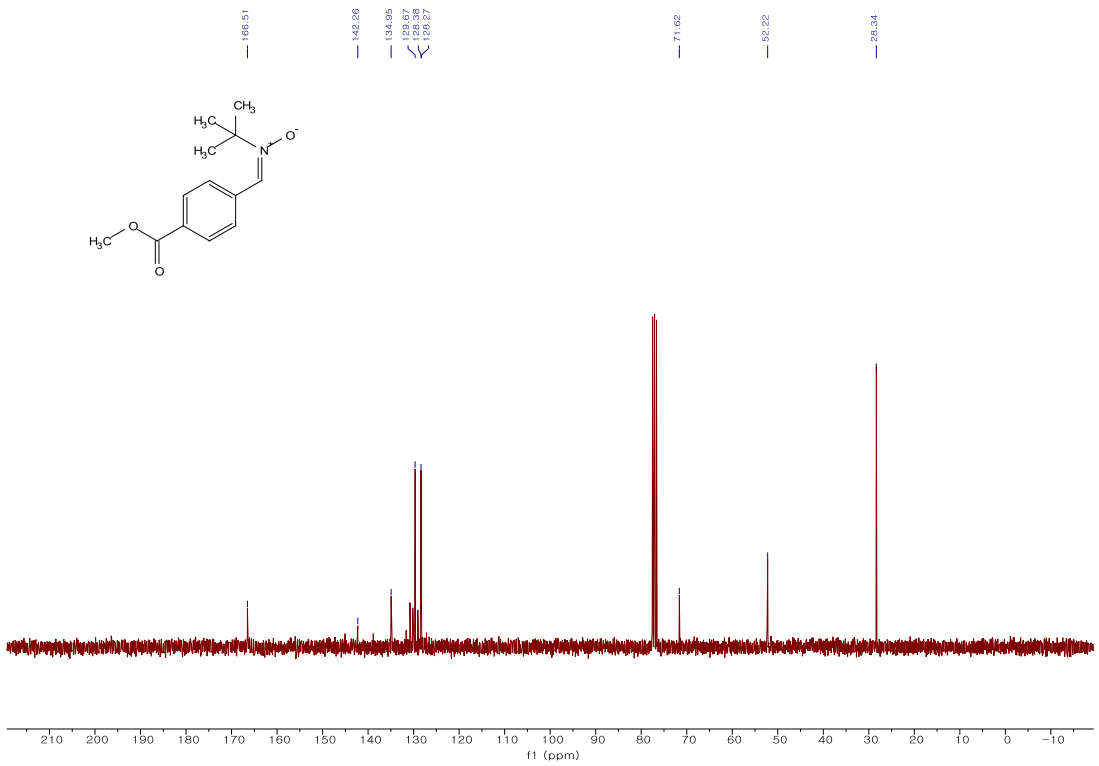
^{1}H NMR (300 MHz, $CDCl_3$) of **2d**



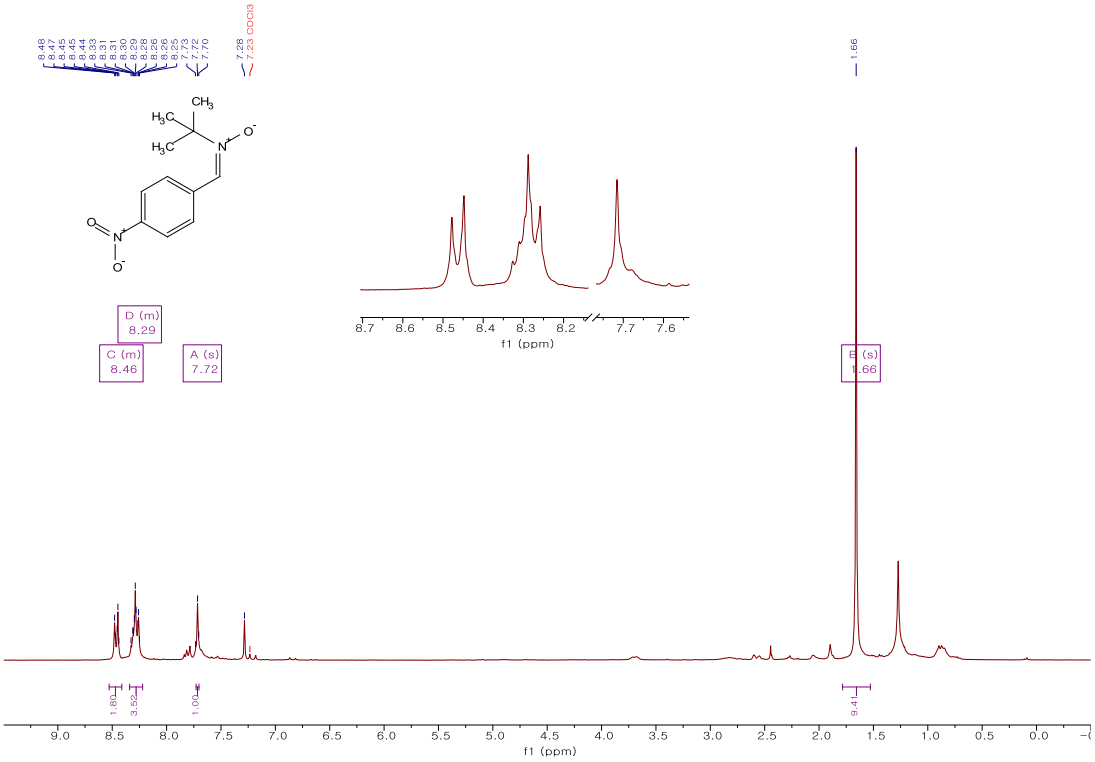
^{13}C NMR (75 MHz, $CDCl_3$) of **2d**



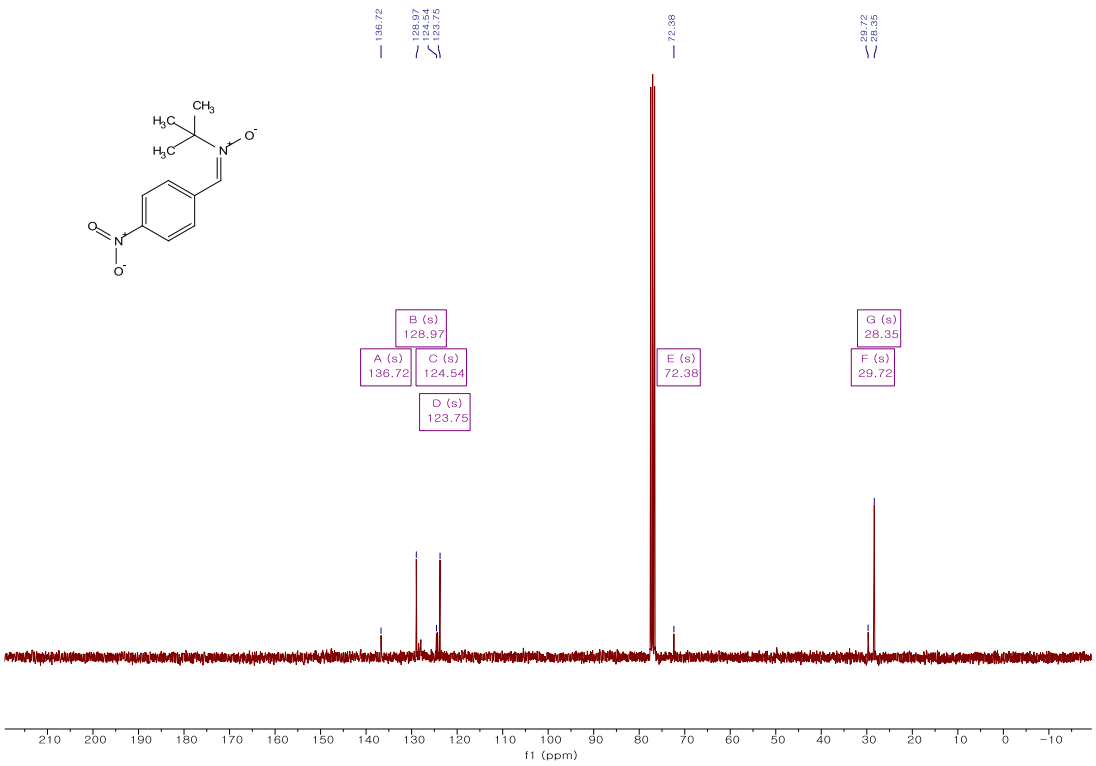
^{1}H NMR (300 MHz, $CDCl_3$) of **2e**



^{13}C NMR (75 MHz, $CDCl_3$) of **2e**



^{1}H NMR (300 MHz, $CDCl_3$) of **2f**



^{13}C NMR (75 MHz, $CDCl_3$) of **2f**

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