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PII: S0040-4020(14)00575-4

DOI: 10.1016/j.tet.2014.04.054

Reference: TET 25504

To appear in: *Tetrahedron*

Received Date: 16 January 2014

Revised Date: 9 April 2014

Accepted Date: 17 April 2014

Please cite this article as: Tang D, Li X-L, Guo X, Wu P, Li J-H, Wang K, Jing H-W, Chen B-H, Copper and Zinc co-Catalyzed Synthesis of Imidazoles via the Activation of sp3 C−H and N-H Bonds, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.04.054.

Graphical Abstract

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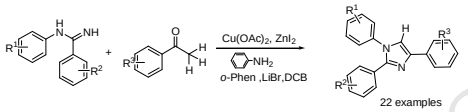

Tetrahedron
journal homepage: www.elsevier.com

Copper and Zinc co-Catalyzed Synthesis of Imidazoles via the Activation of sp3 C−H and N-H Bonds

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
imidazoles
amidines
cycloaddition reaction
oxidative coupling
C-N bond formation

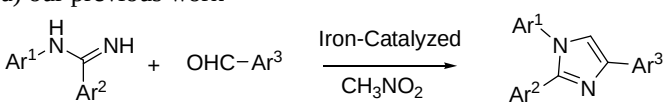
ABSTRACT

An efficient and facile approach to synthesize imidazoles from amidines and arylketone via oxidative coupling of sp^3 C−H bond and N-H bond is reported. This strategy exhibits high performance in terms of regionselectivity with moderate to high yields by using easily available materials, and provides an alternative method to synthesize multi-substituted imidazole skeletons.

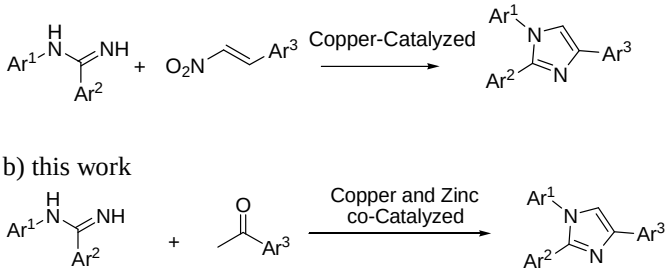
1. Introduction

The imidazole ring, as a privileged scaffold, represents an important class of heterocycle which has been frequently found in various natural products.[1] Moreover, imidazole derivatives possess many significant biological properties such as anti-plasmodium,[2] anti-inflammatory,[3] antifungal[4] and antibacteria.[5] Consequently, considerable efforts have been undertaken to develop efficient synthetic routes.[6] For example, Wolkenberg and co-workers introduced the construction of imidazoles from aldehydes and 1,2-diketones under microwave irradiation.[7] Xie *et al.* reported the synthesis of substituted imidazoles via intramolecular C-N bond-forming reactions.[8] In addition, α-bromoketones and N-arylbenzamidines were also employed to afford multisubstituted imidazoles.[9] In spite of many methodologies have been already described, most of them needed complex reagents or suffer from some other drawbacks. Thus, there is still an indispensable challenge to generate imidazoles from easily available starting materials.

a) our previous work [10]



b) this work



Scheme 1. Strategies for the Synthesis of imidazoles in our group.

In the past two years, we had reported copper-catalyzed [3 +2] cycloaddition reaction to synthesize multisubstituted imidazoles, and iron(III)-catalyzed synthesis of 1,2,4-trisubstituted imidazoles through the reactions of amidines and aldehydes, as shown in Scheme 1.[10] Recently, the Hajra group reported the synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines and ketones, respectively.[11] Encouraged by previous works, we aim to synthesize imidazoles by using easy-to-get reagents under mild conditions. Hence, we develop a copper and zinc co-catalyzed transformation for the synthesis of imidazoles, starting from amidines and arylketones.

2. Results and discussion

To evaluate the feasibility of our strategy, we initiated our studies by examining N-phenylbenzamidine (**1a**) and acetophenone (**2a**) as a model reaction, which was carried out in the presence of 1.10-phenanthroline (*o*-phen) over co-catalysts of

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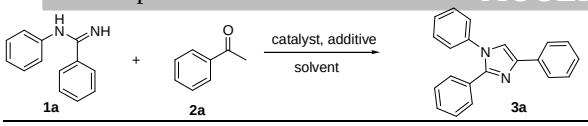
Table 1. Optimization of the Reaction conditions [a]



entry	catalyst	ligand	additive	solvent	yield (%) [b]
1	$Cu(OAc)_2$, ZnI_2	*o*-Phen		DCB	48
2	$CuCl_2$, ZnI_2	*o*-Phen		DCB	47
3	CuI, ZnI_2	*o*-Phen		DCB	47
4	CuBr, ZnI_2	*o*-Phen		DCB	44
5	$CuSO_4$, ZnI_2	*o*-Phen		DCB	43
6 [c]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr	DCB	59
7 [c, d]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	DCB	66
8 [c, d]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	DMSO	NR
9 [c, d]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	DMF	NR
10 [c, d]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	Dioxane	trace
11 [c, d]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	Toluene	20
12 [c, d, e]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	DCB	79
13 [c, d, e]	$Cu(OAc)_2$, ZnI_2		LiBr, aniline	DCB	52
14 [c, d, e]	$Cu(OAc)_2$	*o*-Phen	LiBr, aniline	DCB	trace
15 [c, e]	$Cu(OAc)_2$, ZnI_2		LiBr	DCB	44
16 [c, d, e]	ZnI_2	*o*-Phen	LiBr, aniline	DCB	trace
17 [c, d, e, f]	$Cu(OAc)_2$, ZnI_2	*o*-Phen	LiBr, aniline	DCB	trace
18 [c, d, e]	$Cu(OAc)_2$, $ZnBr_2$	*o*-Phen	LiBr, aniline	DCB	33
19 [c, d, e]	$Cu(OAc)_2$, TfOH	*o*-Phen	LiBr, aniline	DCB	NR

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (10 mol %), *o*-Phen (20 mol %), solvent (2 mL), 120 °C, 6 h under air.

[b] Isolated yield based on **2a**.

[c] LiBr (3 equiv).

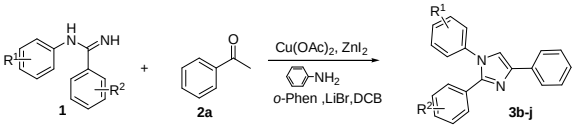
[d] aniline (5 mol %).

[e] The ratio of **1a** and **2a**: **1a** (0.24 mmol)/**2a** = 1.2:1.

[f] under the nitrogen atomosphere.

$Cu(OAc)_2$ and ZnI_2 in 1,2-dichlorobenzene (DCB) under air at 120 ^oC for 6 h, and the desired product was isolated in 48% yield (Table 1, entry 1). Various Cu sources, including $CuCl_2$, CuI, CuBr and $CuSO_4$, showed the similar catalytic activities (Table 1, entries 2-5). To our surprise, with 3 equiv of LiBr added, a 59% yield of product was obtained (Table 1, entry 6), which is probably serves as a desiccant due to its highly hygroscopic property. [12] In addition, when amidine **1a** with a trace amount of aniline impurity was employed, higher result was received, and further study indicated that a catalytic amount of aniline also played an important role in promoting this reaction (Table 1, entry 7), which is probably, as a ligand, assists some rearrangement processes in the reaction transformation. [13] The investigation of solvents effect suggested that DCB was superior to dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), dioxane or toluene (Table 1, entries 8-11). Moreover, raising the ratio of **1a**/**2a** to 1.2:1, the product was obtained in 79% yield (Table 1, entry 12). Furthermore, controlled experiments for this reaction confirmed that each of ZnI_2, $Cu(OAc)_2$, *o*-phen, oxygen and aniline was essentially needed for this transformation. (Table 1, entries 13-17). Otherwise, other Lewis and Bronsted acids, such as $ZnBr_2$ and trifluoromethanesulfonic acid (TfOH), were also tested, and no better results were observed (Table 1, entries 18-19).

Table 2. Reactions of Acetophenone (**2a**) with Various Substituted Amidines [a]



entry	R^1, R^2	product	yield (%) [b]
1	4-Me, H, **1b**	**3b**	81
2	4-Cl, H, **1c**	**3c**	77
3	2-ethyl, H, **1d**	**3d**	88
4	3-Cl,H, **1e**	**3e**	72
5	4-OMe, H, **1f**	**3f**	84
6	H , 2-Cl, **1g**	**3g**	86
7	H, 4-CF_3, **1h**	**3h**	67

8	4-Me, 4-OMe, **1i**	**3i**	83	12	**3v**	84

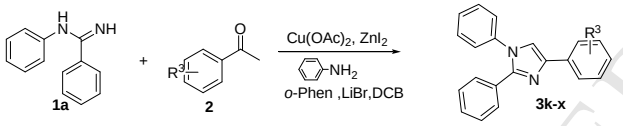
[a] Unless otherwise indicated, reactions were carried out with **1** (0.24 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), ZnI_2 (10 mol %), *o*-phen (20 mol %), aniline (5 mol %), LiBr (3 equiv), DCB (2 mL), the ratio of **1**:**2a**= 1.2:1, 120 °C, 6 h, under air.

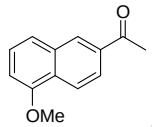
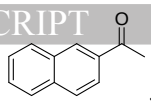
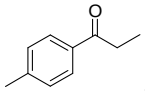
[b] Isolated yield based on **2a**.

With the optimized conditions in hand, various amidines **1** and acetophenone (**2a**) were examined to establish the scope and limitation of this reaction, and the results were presented in Table 2. The catalytic system was applicable for **1b**-**1j** providing the corresponding products **3b**-**3j** in 72-88% yields (Table 2, entries 1-9). However, the electron-deficient group trifluoromethyl reduced the yields apparently for 6 h (Table 2, entry 7).

To further investigate the reaction scope, a number of arylketone derivatives (**2b**-**2m**) were employed to react with N-phenylbenzamidine (**1a**), as shown in Table 3. To our delight, regardless of the electron-withdrawing or -donating groups in the aryl ring, the reactions of arylketones proceeded smoothly and provided moderate to good yields. Notably, the substrates with electron-withdrawing groups were utilized, and the corresponding products were obtained in good yields (Table 3, enties 9 and 10), and the ones with electron-donating groups in the *meta*-position could offer better results (Table 3, enties 5 and 7). Additionally, the substrates with bulky aromatic groups, such as 1-(5-methoxynaphthalen-2-yl)ethanone (**2l**) and1-(naphthalen-2-yl)ethanone (**2m**), were also tolerated and produced imidazoles **3u**, **3v** in 83% and 84% yield, respectively (Table 3, enties 11 and 12). Moreover, this strategy was performed well for the synthesis of tetrasubstituted imidazoles (Table 3, entry 13).

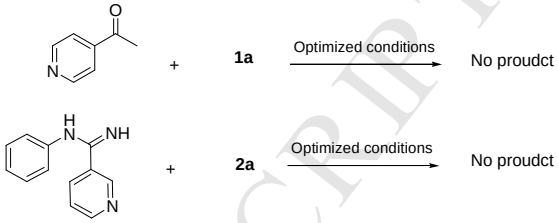
Table 3 Reactions of Acetophenone (**2a**) with Various Substituted Amidines [a]



entry	R^3	product	yield (%) [b]
1	4-F, **2b**	**3k**	72
2	2-F, **2c**	**3l**	68
3	3-CF_3, **2d**	**3m**	73
4	3,4,5-OMe, **2e**	**3n**	76
5	3-OMe, **2f**	**3o**	82
6	2-Me, **2g**	**3p**	77
7	3-Me, **2h**	**3q**	81
8	4-Me, **2i**	**3r**	70
9	4-Br, **2j**	**3s**	81
10	4-Cl, **2k**	**3t**	80
11	 , **2l**	**3u**	83
12	 , **2m**	**3v**	84
13	 ,**2p**	**3x**	39

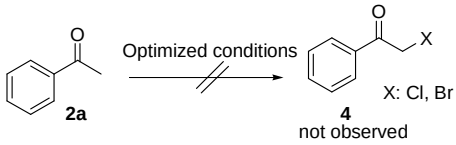
[a] Unless otherwise indicated, reactions were carried out with **1** (0.24 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), ZnI_2 (10 mol %), *o*-phen (20 mol %), aniline (5 mol %), LiBr (3 equiv), DCB (2 mL), the ratio of **1**:**2a**= 1.2:1, 120 °C, 6 h, under air.

[b] Isolated yield based on **2**



Scheme 2 The experiment of substrates with heteroaryl group.

Disappointingly, the desired products were not found when the substrates with substituents of amino and hydroxy such as 1-(4-amino-phenyl)ethanone and 1-(4-hydroxyphenyl)ethanone. In addition, alkylketones, such as cyclohexanone and butan-2-one, were not the suitable partners for the reaction. Moreover, the substrates with pyridine ring, such as 1-(pyridin-4-yl)ethanone and N-phenylnicotinamidine, could not be apply to this strategy (Scheme 2), which was probably due to the nitrogen on pyridine ring coordinating to the catalyst to effect formation of the intermediates.



Scheme 3 The control experiment of reaction intermediate.

To get further insight into our reaction, 1 equiv of a radical scavenger (TEMPO) was added to the catalyst system, and the yield did not reduce in our reaction system, which might rule out a radical process. In addition, when acetophenone conducted in absence of amidine under the optimized conditions, the α-halogenated product which maybe an important intermediate [9] was not observed, as shown in scheme 3. Recently, similar works had been reported to synthesize imidazoles through tandem imine formation-oxidative cyclization,[11, 14] hence, we supposed that the amidines in equilibrium with enamines reacted with arylketones following an analogous catalyst process based on those results. Further studies including the investigation of mechanism and related transformations are undertaken in our laboratory.

3. Conclusion

In summary, an efficient copper and zinc co-catalyzed method to synthesize multisubstituted imidazoles from amidines and arylketones was developed. In the synthetic protocol, easily available materials were employed to access a series of important imidazole skeletons in good yields with high regionselectivity. Moreover, the reaction, using air as oxidant, is economical, easy-to-operate and environmentally friendly.

4. Experimental section

*Typical Procedure for the Preparation of multi-substituted imidazoles **3**.* Synthesis of 1,2,4-triphenyl-1H-imidazole (**3a**): The reaction was carried out in a round-bottom sidearm flask (10 mL), **1a** (0.24 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), ZnI_2 (10 mol %), aniline (5 mol %), 1,10-phenanthroline (20 mol %), LiBr (3.0 equiv), and DCB (2 mL) were added to the flask with a magnetic stirring bar at 120 ^oC under air. After 6 h stirring at this temperature, the flask was took out and cooled to room temperature. The mixture was filtered with ethyl acetate (3 × 50mL), and the filtrate was concentrated under reduced pressure to distill ethyl acetate. Subsequently, the crude product with DCB was dried under heat gun, which was further purified by silica gel chromatography (petroleum/ethyl acetate = 10/1 as eluent) to obtain product **3a**. ^1H NMR and ^{13}C NMR spectra were determined on 300 MHz and 75 MHz in $CDCl_3$. unknown products were further characterized by HRMS (TOF-ESI), the melting points of solid products (**3u** and **3v**) were determined on a microscopic apparatus. The structures of the products (**3a**, **3b**, **3c**, **3f** and **3i**) were identified according to the literature.[15]

1,2,4-triphenyl-1H-imidazole 3a: 0.2 mmol, 47 mg, 79%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 790–7.80 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.45–7.42 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.39–7.37 (dd, *J* = 4.3, 3.2 Hz, 3H), 7.34 –7.30 (m, 3H), 7.25–7.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 141.5, 138.3, 133.7, 130.1, 129.3, 128.6, 128.4, 128.3, 128.3, 128.0, 128.0, 126.8, 125.6, 124.9, 118.4.

2,4-diphenyl-1-p-tolyl-1H-imidazole 3b: 0.2 mmol, 50 mg, 81%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93–7.84 (m, 2H), 7.50–7.41 (m, 2H), 7.40–7.30 (m, 3H), 7.26–7.15 (m, 4H), 7.14–7.06 (ddd, *J* = 9.6, 7.3, 0.8 Hz, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 141.4, 138.0, 135.8, 133.8, 130.3, 129.9, 128.6, 128.4, 128.2, 128.0, 126.8, 125.4, 124.9, 118.5, 21.0.

1-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole 3c: 0.2 mmol, 51 mg, 77%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.44–7.39(m, 2H), 7.37–7.30 (m, 4H), 7.29–7.19 (m, 5H), 7.13–7.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 141.8, 136.8, 133.8, 133.5, 129.9, 129.5, 128.7, 128.5, 128.2, 127.0, 126.9, 124.9, 118.1.

1-(2-ethylphenyl)-2,4-diphenyl-1H-imidazole 3d: 0.2 mmol, 57 mg, 88%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93–7.90 (dd, *J* = 5.2, 3.4 Hz, 2H), 7.49–7.45 (dd, *J* = 6.6, 3.3 Hz, 2H), 7.41–7.35 (dd, *J* = 10.3, 4.8 Hz, 3H), 7.34 – 7.29 (m, 2H), 7.28 – 7.22 (m, 3H), 7.22–7.16 (tt, *J* = 5.7, 2.6 Hz, 3H), 2.37–2.26 (ddd, *J* = 15.0, 12.1, 7.5 Hz, 2H), 0.99–0.94 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 141.3, 140.6, 137.1, 133.8, 130.3, 129.4, 129.3, 128.5, 128.2, 128.1, 127.7, 126.8, 124.7, 118.9, 23.6, 13.9.

1-(3-chlorophenyl)-2,4-diphenyl-1H-imidazole 3e: 0.2 mmol, 48 mg, 72%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.835 (m, 2H), 7.46–7.40 (m, 2H), 7.38–7.33 (dd, *J* = 9.2, 6.1 Hz, 3H), 7.31–7.21 (m, 7H), 7.05–7.01 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 141.7, 136.8, 133.8, 133.5, 129.7, 129.5, 128.7, 128.5, 128.2, 127.0, 126.9, 124.9, 118.1.

1-(4-methoxyphenyl)-2,4-diphenyl-1H-imidazole 3f: 0.2 mmol, 55 mg, 84%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.47–7.44 (m, 2H), 7.40–7.34 (dt, *J* = 7.8, 0.9 Hz, 3H), 7.26–7.19 (m, 4H), 7.13–7.08 (m, 2H), 6.87–6.83 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 146.9, 141.2, 133.8, 131.2, 130.2, 128.5, 128.4, 128.2, 128.0, 126.9, 126.8, 124.9, 118.8, 114.4, 55.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2O$ $(M + H)^+$ 327.1492, found 327.1490.

2-(2-chlorophenyl)-1,4-diphenyl-1H-imidazole 3g: 0.2 mmol, 57 mg, 86%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92–7.87 (m, 1H), 7.55–7.49 (m, 1H), 7.40–7.34 (t, *J* = 7.6 Hz, 1H), 7.30–7.20 (m, 3H), 7.16–7.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 137.6, 134.2, 133.6, 132.5, 130.5, 130.3, 129.5, 129.0, 128.4, 127.6, 126.9, 126.6, 124.9, 124.5, 124.4, 116.8.

1,4-diphenyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazole 3h: 0.2 mmol, 49 mg, 67%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90– 7.86 (d, *J* = 7.4 Hz, 2H), 7.58–7.54 (d, *J* = 8.4 Hz, 2H), 7.51–7.47 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.36 (m, 6H), 7.30 – 7.21 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 142.1, 138.0, 133.6, 133.5, 131.3, 129.7, 128.7, 128.6, 128.5, 127.2, 125.8, 125.1, 125.1, 125.0, 125.0, 119.9, 119.3; HRMS (ESI) calcd for $C_{22}H_{16}F_3N_2$ $(M + H)^+$ 365.1260, found 365.1263.

2-(4-methoxyphenyl)-4-phenyl-1-p-tolyl-1H-imidazole 3i: 0.2 mmol, 56 mg, 83%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.40–7.34 (ddd, *J* = 8.3, 5.2, 1.6 Hz, 5H), 7.25–7.15 (ddd, *J* = 7.1, 6.1, 1.2 Hz, 1H), 7.14–7.07 (dt, *J* = 8.3, 4.7 Hz, 4H), 6.80–6.724 (m, 2H), 3.71 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 146.8, 141.1, 137.9, 135.9, 133.9, 123.0, 129.9, 128.4, 126.7, 125.5, 124.8, 122.9, 118.1, 113.5, 55.0, 21.0.

1,4-diphenyl-2-p-tolyl-1H-imidazole 3j: 0.2 mmol, 48 mg, 77%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.00–6.85 (m, 8H), 6.83–6.73(m, 3H), 6.63–6.60 (d, *J* = 8.4 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 141.4, 138.4, 138.1, 133.8, 129.2, 128.7, 128.5, 128.4, 127.9, 127.3, 126.7, 125.6, 124.9, 118.2, 21.1.

4-(4-fluorophenyl)-1,2-diphenyl-1H-imidazole 3k: 0.2 mmol, 45 mg, 72%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.79 (m, 2H), 7.47–7.39 (m, 2H), 7.37–7.34 (dd, *J* = 5.1, 1.9 Hz, 4H), 7.27–7.17 (m, 5H), 7.10–7.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 160.3, 146.9, 140.7, 138.2, 130.1, 130.0, 130.0, 129.4, 128.6, 128.4, 128.1, 126.6, 126.5, 125.7, 118.1, 115.5, 115.2; HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $(M + H)^+$ 315.1292, found 315.1295.

4-(2-fluorophenyl)-1,2-diphenyl-1H-imidazole 3l: 0.2 mmol, 43 mg, 68%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39–8.33 (ddd, *J* = 7.7, 3.9, 2.5 Hz, 1H), 7.66–7.63 (d, *J* = 4.0 Hz, 1H), 7.50–7.43 (m, 2H), 7.40–7.33 (m, 3H), 7.29–7.20 (m, 7H), 7.13–7.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 146.9, 141.2, 133.8, 131.2, 130.2, 128.5, 128.4, 128.2, 128.0, 126.9, 126.8, 124.9, 118.8, 114.4, 55.3; HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $(M + H)^+$ 315.1292, found 315.1294.

1,2-diphenyl-4-(3-(trifluoromethyl)phenyl)-1H-imidazole 3m: 0.2 mmol, 53 mg, 73%; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.09 – 8.02(m, 1H), 7.52–7.42 (m, 5H), 7.42–7.34 (m, 3H), 7.29–7.21 (ddd, *J* = 9.7, 3.9, 2.5 Hz, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3,

140.3, 138.2, 134.7, 130.0, 129.5, 129.0, 128.8, 128.6, 128.3, 128.2, 128.0, 125.7, 123.42, 123.37, 121.9, 121.7, 121.6, 119.1; HRMS (ESI) calcd for $C_{22}H_{16}F_3N_2$ $(M + H)^+$ 365.1260, found 365.1263.

1,2-diphenyl-4-(3,4,5-trimethoxyphenyl)-1H-imidazole 3n: 0.2 mmol, 59 mg, 76%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.41 (m, 3H), 7.41–7.36 (dt, *J* = 4.1, 2.2 Hz, 3H), 7.29–7.22 (m, 5H), 7.14 (s, 2H), 3.93 (s, 6H), 3.88(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 146.7, 141.4, 138.2, 137.2, 123.0, 129.5, 129.3, 128.7, 128.4, 128.1, 125.6, 118.2, 102.1, 60.8, 56.0; HRMS (ESI) calcd for $C_{24}H_{23}N_2O_3$ $(M + H)^+$ 387.1703, found 387.1705.

4-(3-methoxyphenyl)-1,2-diphenyl-1H-imidazole 3o: 0.2 mmol, 53 mg, 82%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.50 (m, 1H), 7.47–7.41 (ddd, *J* = 4.1, 2.0, 0.9 Hz, 3H), 7.41–7.39 (d, *J* = 1.0 Hz, 1H), 7.37–7.31 (m, 3H), 7.31 – 7.26 (m, 1H), 7.26–7.18 (m, 5H), 6.85–6.78 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 146.7, 141.4, 138.2, 135.2, 130.1, 129.4, 129.3, 128.6, 128.3, 128.0, 125.6, 118.6, 117.4, 113.0, 110.0, 55.1; HRMS (ESI) calcd for $C_{22}H_{19}N_2O$ $(M + H)^+$ 327.1492, found 327.1490.

1,2-diphenyl-4-o-tolyl-1H-imidazole 3p: 0.2 mmol, 48 mg, 77%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–7.98 (d, *J* = 7.8 Hz, 1H), 7.50–7.44 (m, 2H), 7.40–7.35 (dd, *J* = 6.9, 2.5 Hz, 3H), 7.30– 7.17 (m, 9H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 141.0, 138.4, 134.9, 133.1, 130.7, 130.2, 129.4, 128.7, 128.6, 128.3, 128.1, 128.0, 126.9, 125.9, 125.8, 120.9, 21.8; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $(M + H)^+$ 311.1543, found 311.1541.

1,2-diphenyl-4-m-tolyl-1H-imidazole 3q: 0.2 mmol, 50 mg, 81%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.67–7.63 (d, *J* = 7.7 Hz, 1H), 7.46–7.42 (dd, *J* = 6.8, 2.8 Hz, 2H), 7.39 (s, 1H), 7.38–7.30 (m, 3H), 7.30–7.16 (m, 6H), 7.09–7.04 (d, *J* = 7.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 141.7, 138.3, 138.0, 133.6, 130.2, 129.3, 128.7, 128.3, 128.26, 128.0, 127.97, 127.7, 122.0, 118.5, 118.4, 21.4; HRMS (ESI) calcd for $C_{22}H_{19}N_2$ $(M + H)^+$ 311.1543, found 311.1539.

1,2-diphenyl-4-p-tolyl-1H-imidazole 3r: 0.2 mmol, 43 mg, 70%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.76 (d, *J* = 8.1 Hz, 2H), 7.47–7.41 (m, 2H), 7.38–7.32 (m, 4H), 7.25–7.17 (m, 7H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 141.7, 138.4, 136.5, 131.0, 130.3, 129.3, 129.2, 128.7, 128.3, 128.1, 128.0, 125.7, 124.9, 118.0, 21.2.

4-(4-bromophenyl)-1,2-diphenyl-1H-imidazole 3s: 0.2 mmol, 61 mg, 81%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.70 (m, 2H), 7.50–7.44 (m, 2H), 7.44–7.39 (m, 2H), 7.39–7.31 (m, 4H), 7.25–7.16 (ddt, *J* = 6.0, 2.5, 2.1 Hz, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 140.4, 138.1, 132.8, 131.5, 129.9, 129.4, 128.6, 128.4, 128.1, 128.1, 126.4, 125.6, 120.4, 118.6.

4-(4-chlorophenyl)-1,2-diphenyl-1H-imidazole 3t: 0.2 mmol, 53 mg, 80%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.76 (m, 2H), 7.45–7.40 (m, 2H), 7.38–7.28 (m, 6H), 7.26–7.17 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 140.5, 138.1, 132.3, 130.0, 129.4, 128.6, 128.4, 128.1, 128.1, 126.1, 125.6, 118.5.

4-(5-methoxynaphthalen-2-yl)-1,2-diphenyl-1H-imidazole 3u: 0.2 mmol, 62 mg, 83%; yellow solid; mp 188–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.94–7.88 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.81–7.72 (dd, *J* = 13.0, 8.6 Hz, 2H), 7.52–7.44 (m, 3H), 7.40–7.35 (m, 3H), 7.30–7.21 (dtd, *J* = 6.2, 3.3, 1.2 Hz, 5H), 7.16–7.11 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 147.0, 141.7, 138.4, 133.7, 130.2, 129.6, 129.4, 129.2, 129.1, 128.8, 128.4, 128.1, 128.1, 126.9, 125.7, 124.2, 123.1, 118.8, 118.4, 105.8, 55.2; HRMS (ESI) calcd for $C_{26}H_{21}N_2O$ $(M + H)^+$ 377.1648, found 377.1651.

4-(naphthalen-2-yl)-1,2-diphenyl-1H-imidazole 3v: 0.2 mmol, 58 mg, 84%; yellow solid; mp 202–203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.93–7.81 (m, 3H), 7.54 (s, 1H), 7.51–7.34 (m, 7H), 7.31–7.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 141.6, 138.4, 133.8, 132.7, 131.1, 130.2, 129.4, 129.0, 128.8, 128.5, 128.2, 128.1, 127.6, 126.1, 126.0, 125.8, 125.4, 123.6, 123.2, 119.0; HRMS (ESI) calcd for $C_{25}H_{19}N_2$ $(M + H)^+$ 347.1543, found 347.1545.

5-methyl-1,2-diphenyl-4-p-tolyl-1H-imidazole 3x: 0.2mmol, 25mg, 39%; white solid, mp 188–194 °C; 1H NMR (300 MHz, $CDCl_3$) δ 7.7–7.65 (d, J = 8.1 Hz, 2H), 7.47–7.43 (dt, J = 5.8, 2.9 Hz, 3H), 7.41 – 7.36 (m, 2H), 7.27 – 7.17(m, 7H), 2.39 (s, 3H), 2.25 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 145.9, 137.4, 136.0, 132.1, 130.6, 129.5, 129.0, 128.6, 128.3, 128.0, 127.9, 127.8, 127.1, 125.8, 120.1, 21.2, 11.1; HRMS (ESI) calcd for $C_{23}H_{21}N_2$ $(M + H)^+$ 325.1699, found 325.1696.

5. Acknowledgements

We are grateful to the project sponsored by the National Natural Science Foundation of P. R. China (No. 21372102 and 21173106), the Project of National Science Foundation of Gansu Province P.R. China (No. 1208RJZA266).

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7. Supplementary Material

^{1}H NMR and ^{13}C NMR spectra of products associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tet.xxxxxx..

Supporting Information

Copper and Zinc co-Catalyzed Synthesis of Imidazoles via the Activation of sp3 C−H and N-H Bonds

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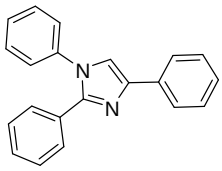

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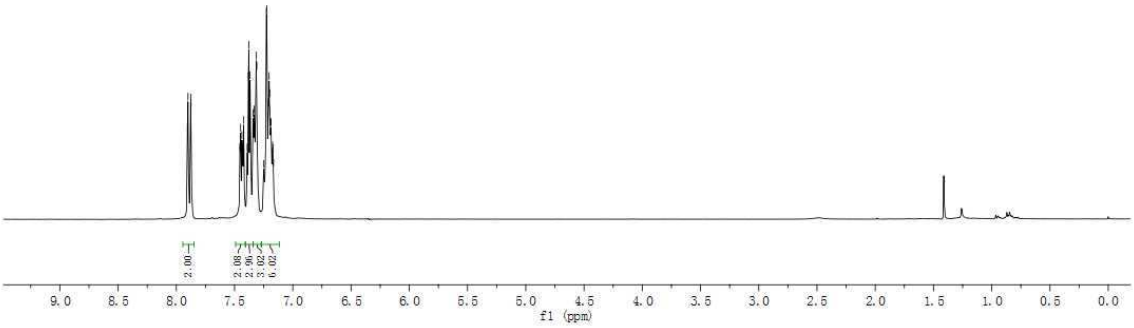
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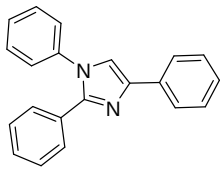

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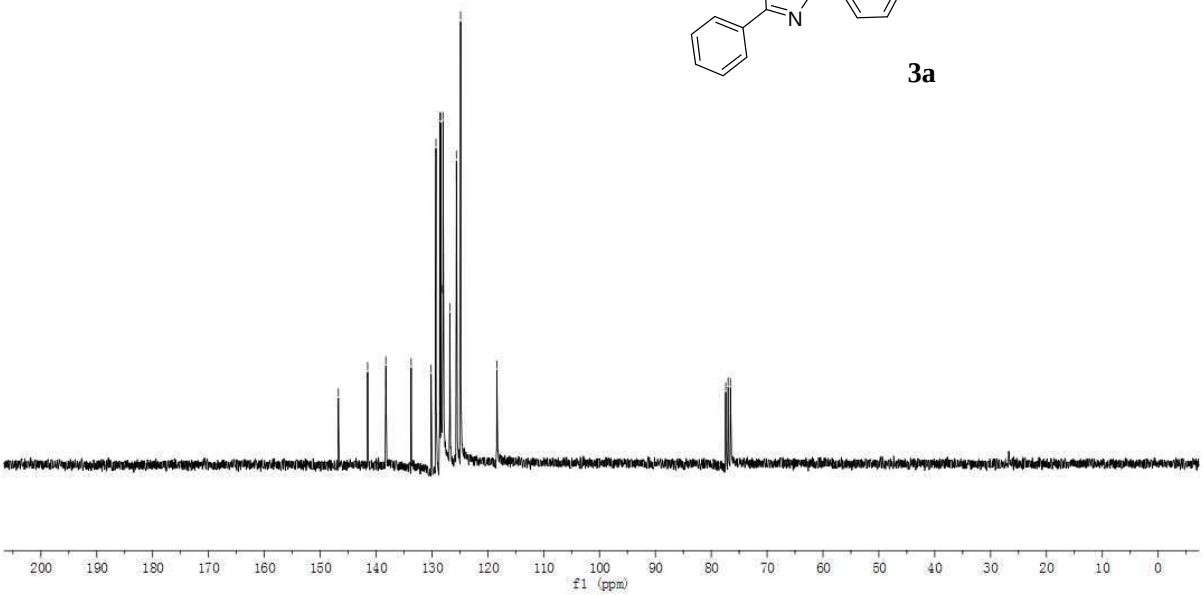
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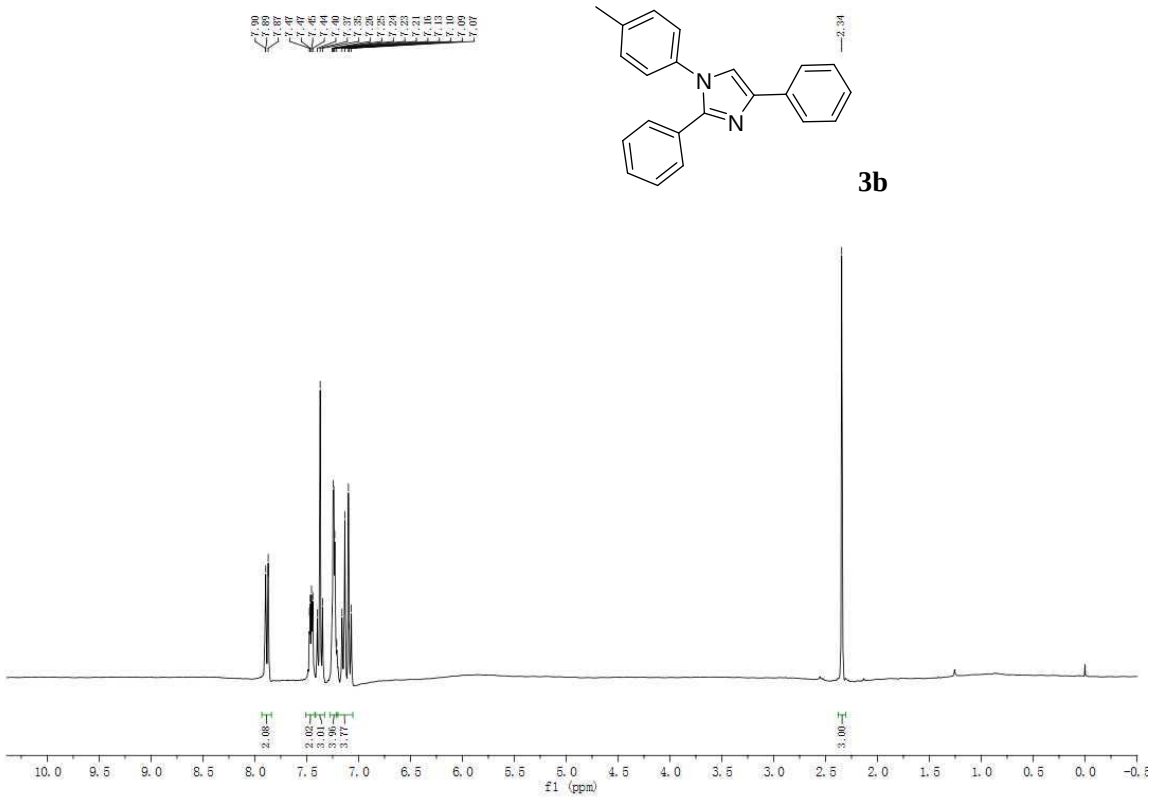
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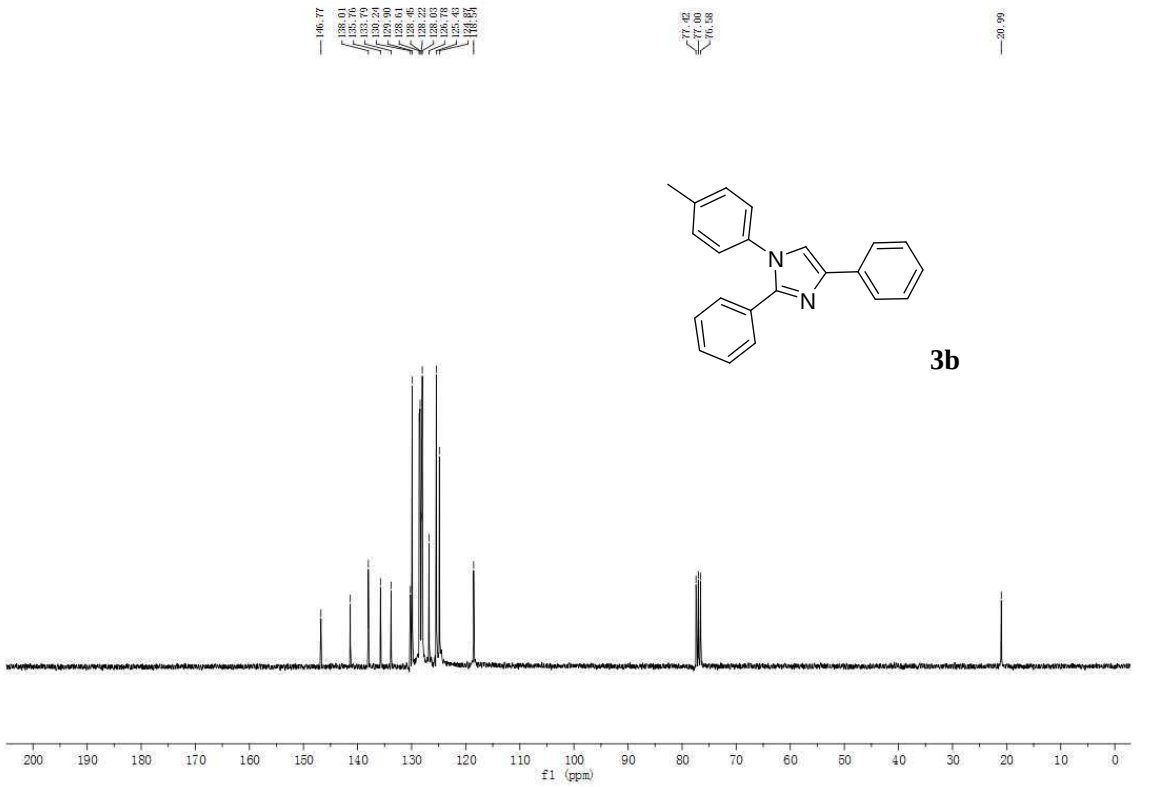
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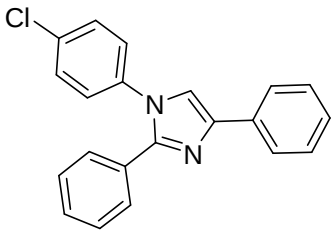
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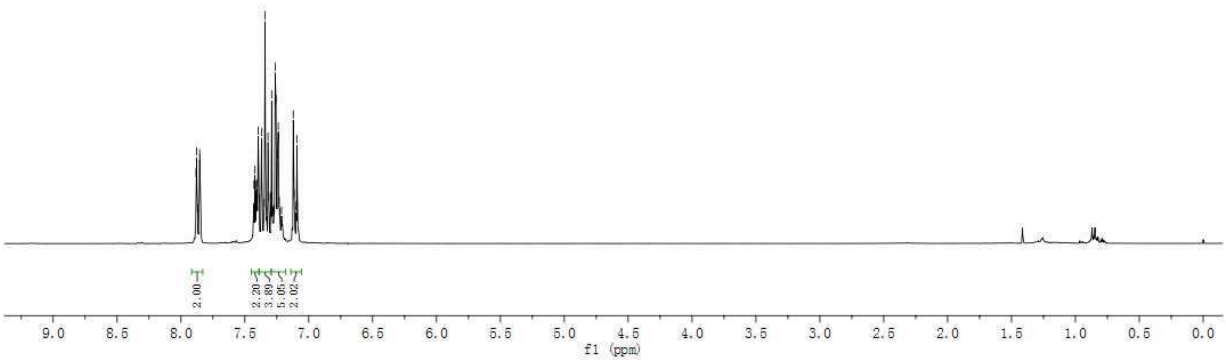
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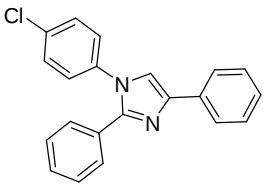
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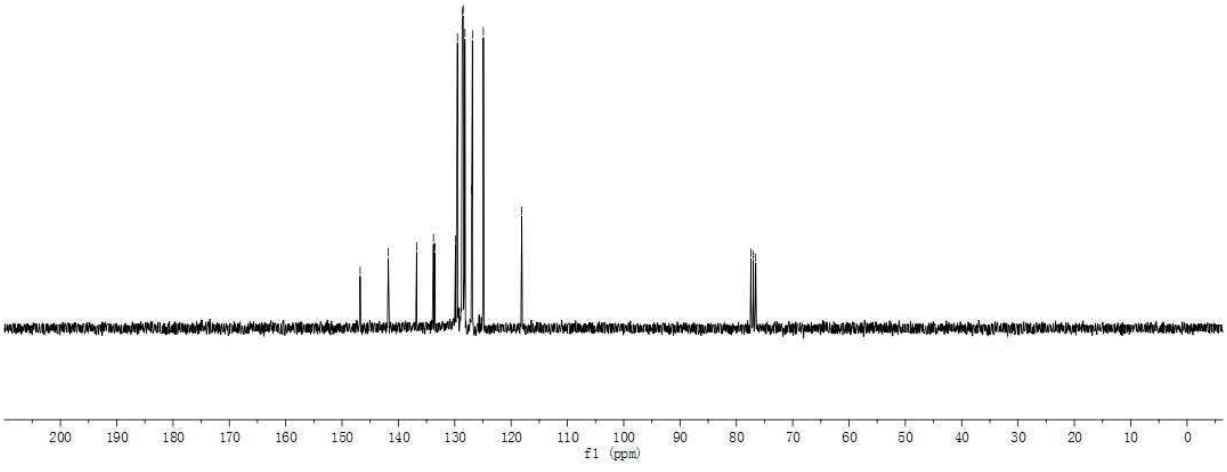
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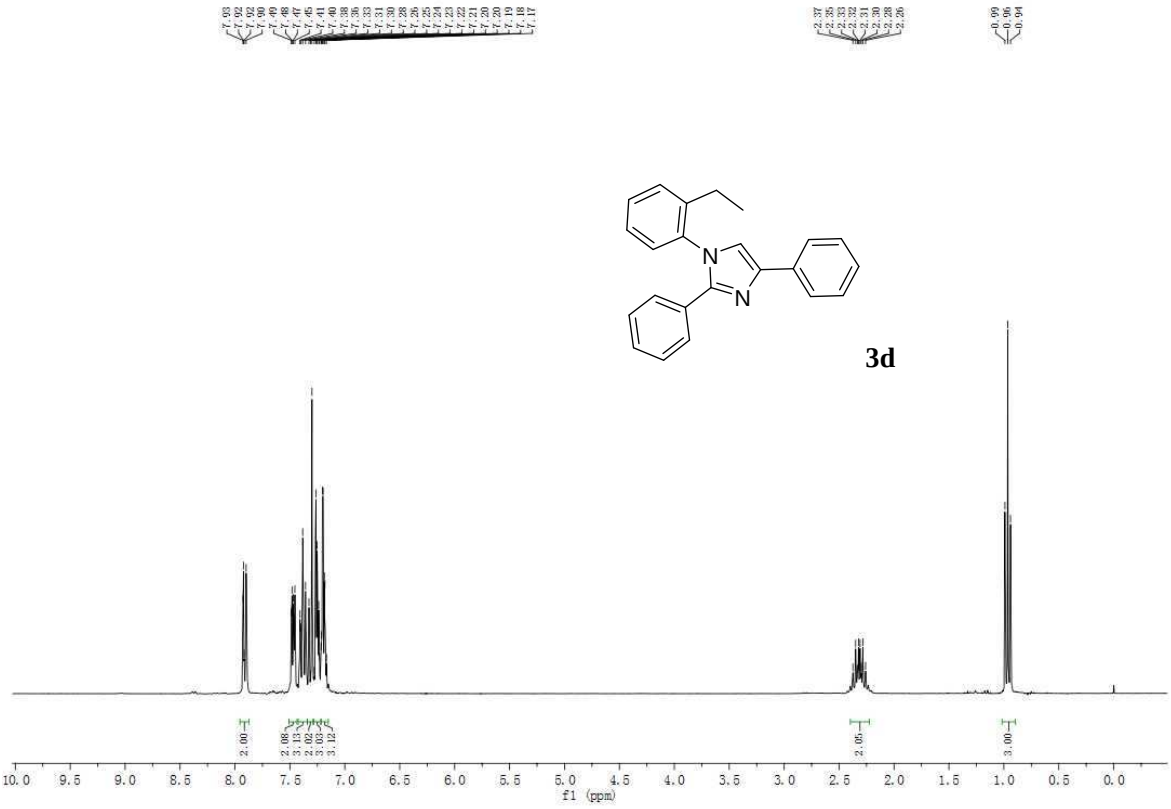
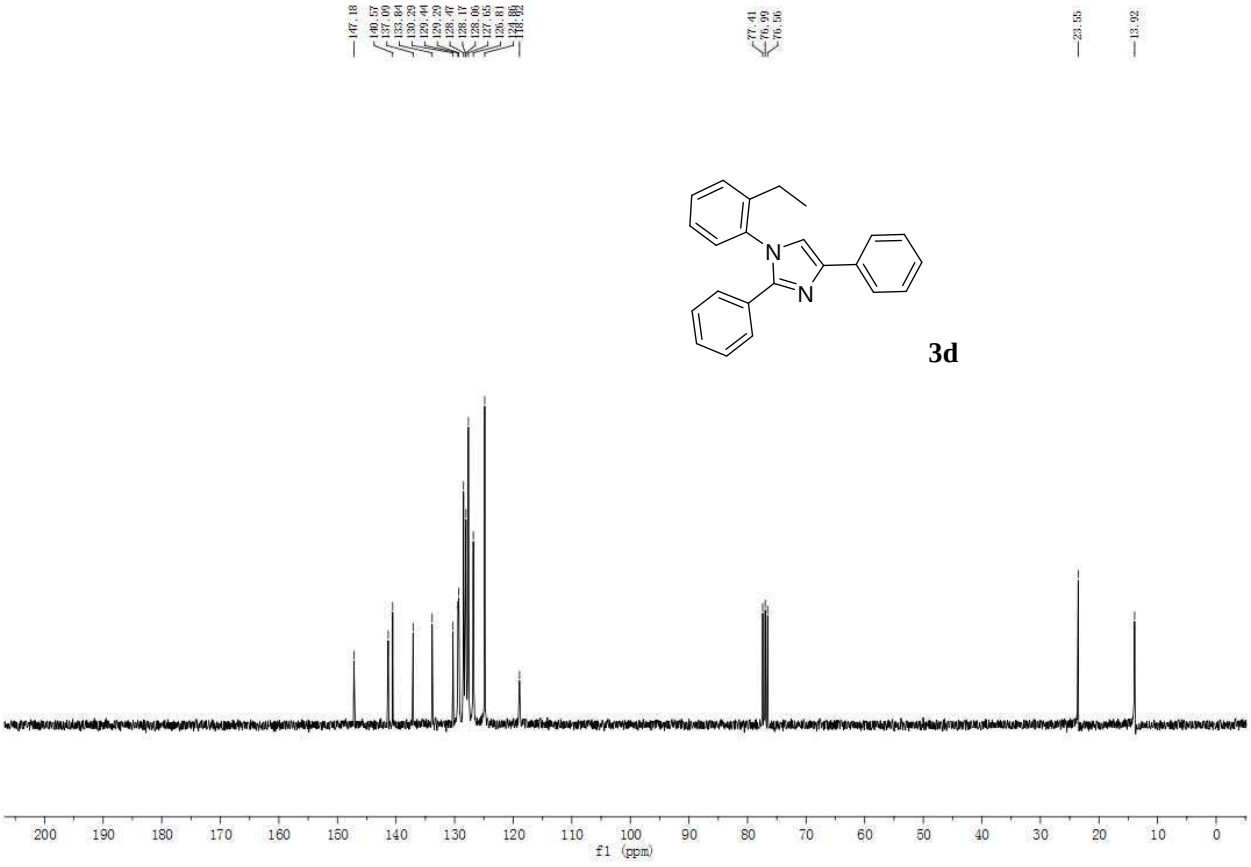
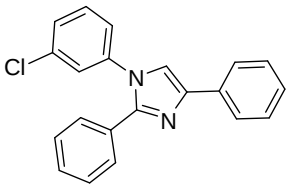
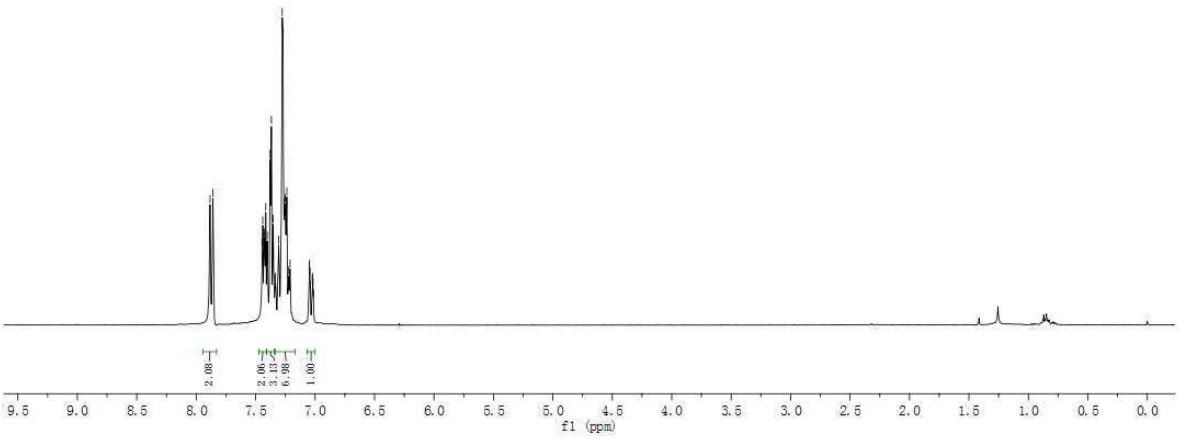
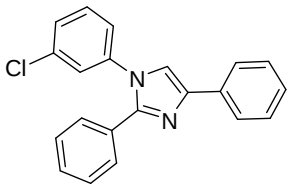

3d
f1 (ppm)


3d
f1 (ppm)



3e





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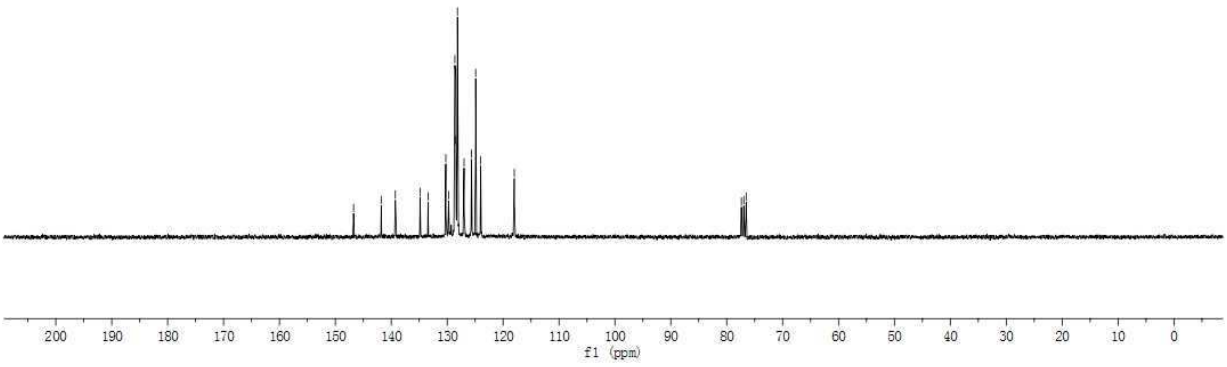

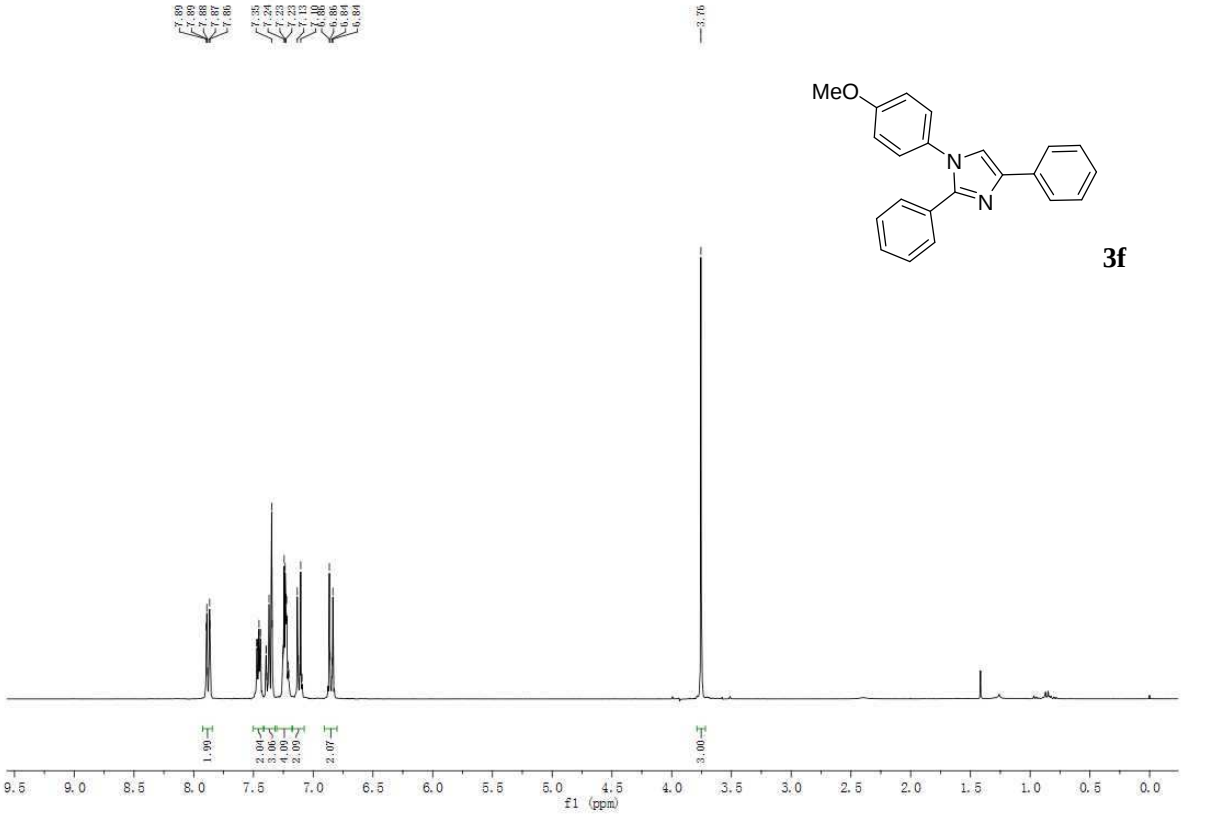
7.89
7.89
7.88
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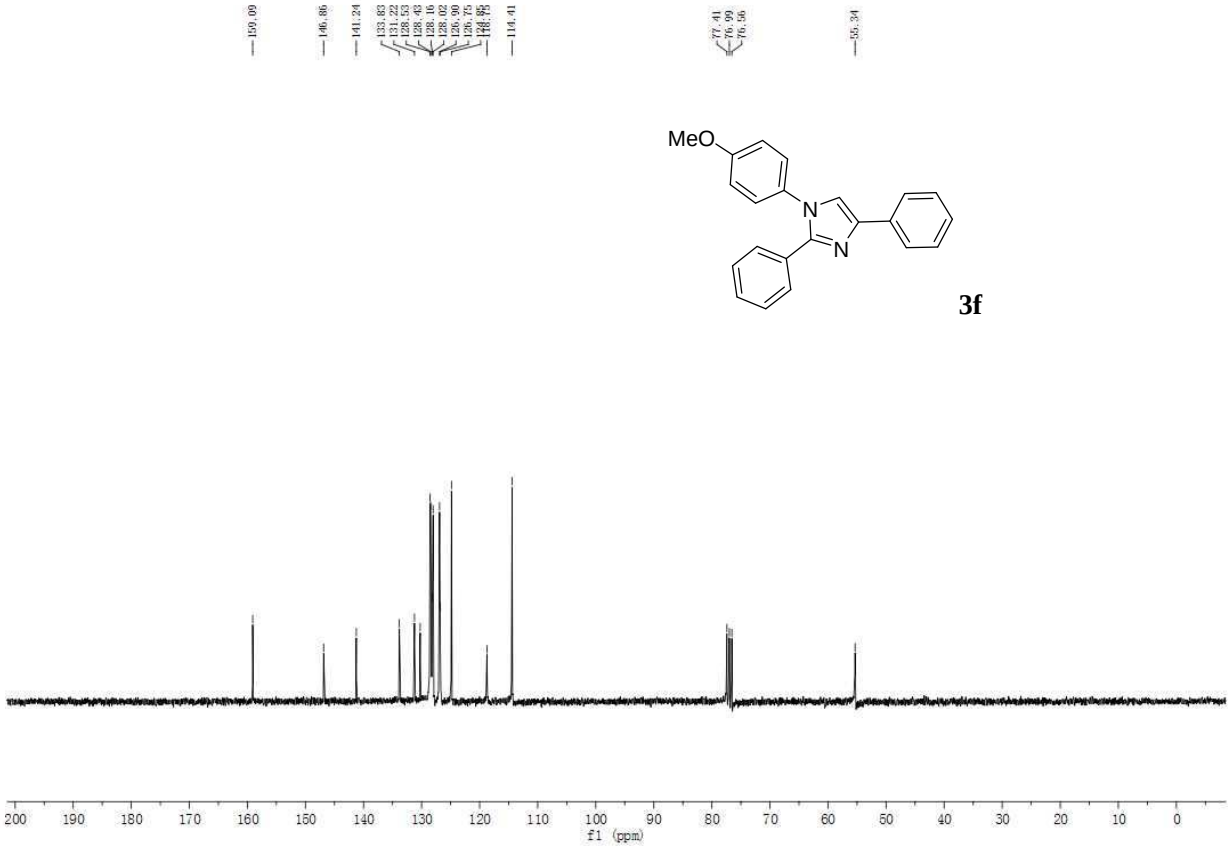
7.35
7.24
7.23
7.23
7.13
7.10
6.88
6.86
6.84
6.84
3.76
MeO
N
N
1.99
2.04
3.06
4.09
2.09
2.07
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

3f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146.86
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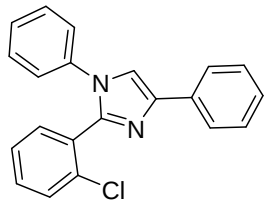
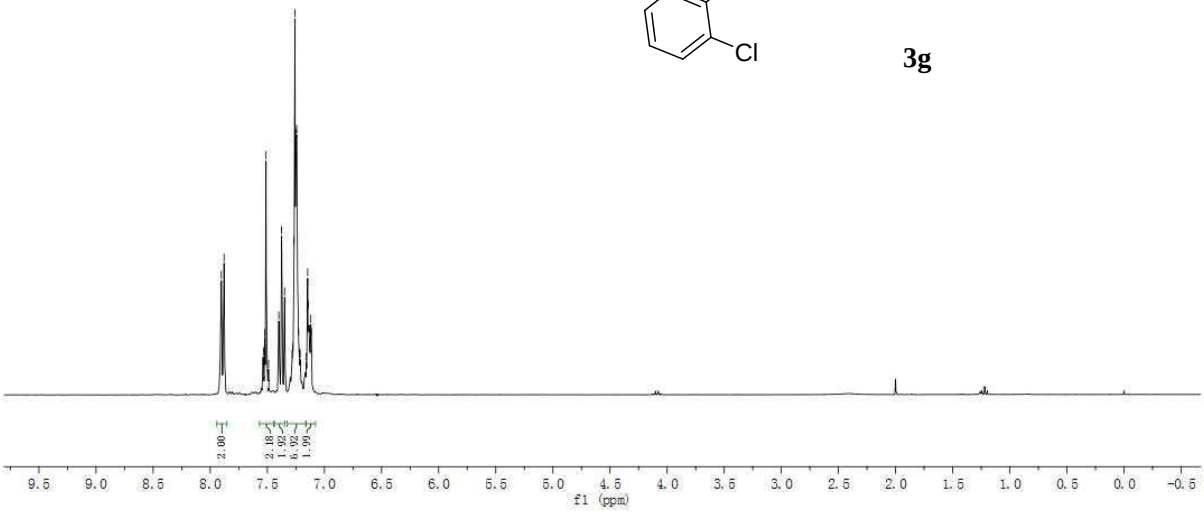
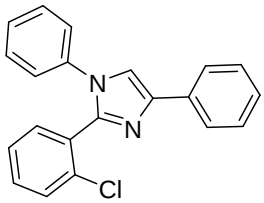
133.83
131.22
128.53
128.43
128.16
128.02
126.90
126.75
124.85
114.41
77.41
76.99
76.56
55.34
MeO
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3f

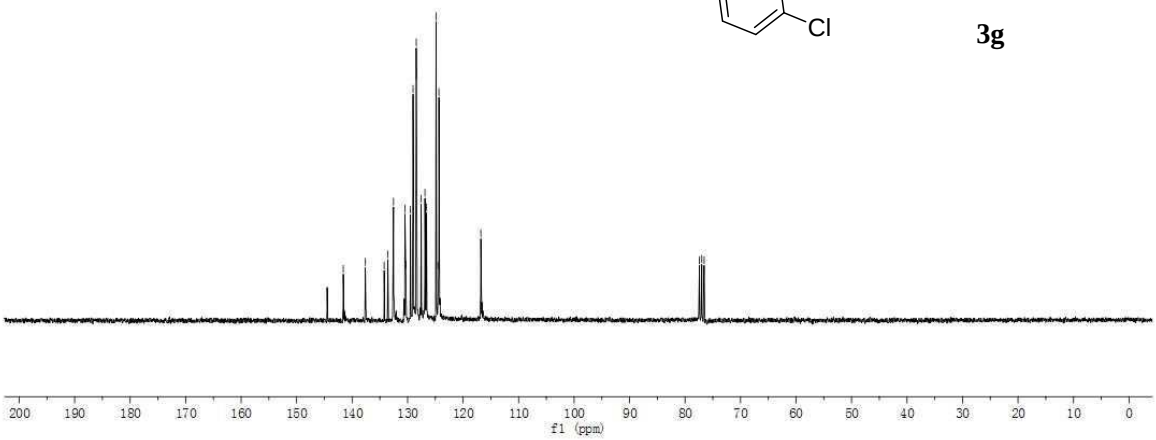


3g

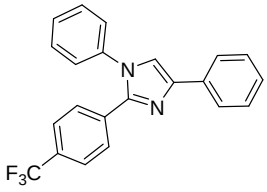




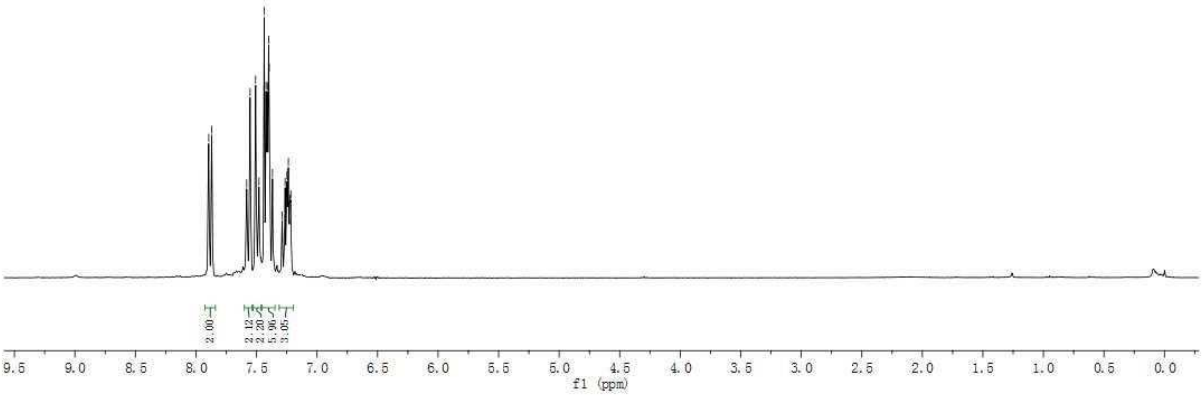
3g




7.89
7.87
7.55
7.51
7.48
7.44
7.42
7.41
7.40
7.39
7.37
7.29
7.26
7.25
7.24
7.23
7.22
7.22


N
N
F3C

3h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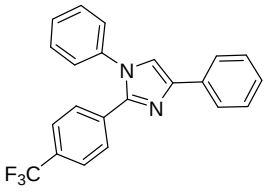
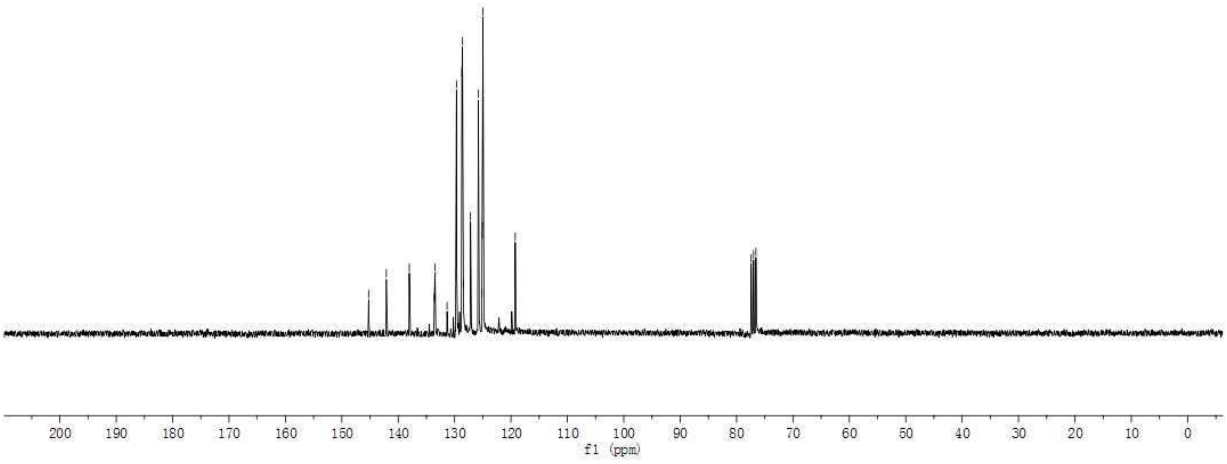
2.12
2.20
5.96
3.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

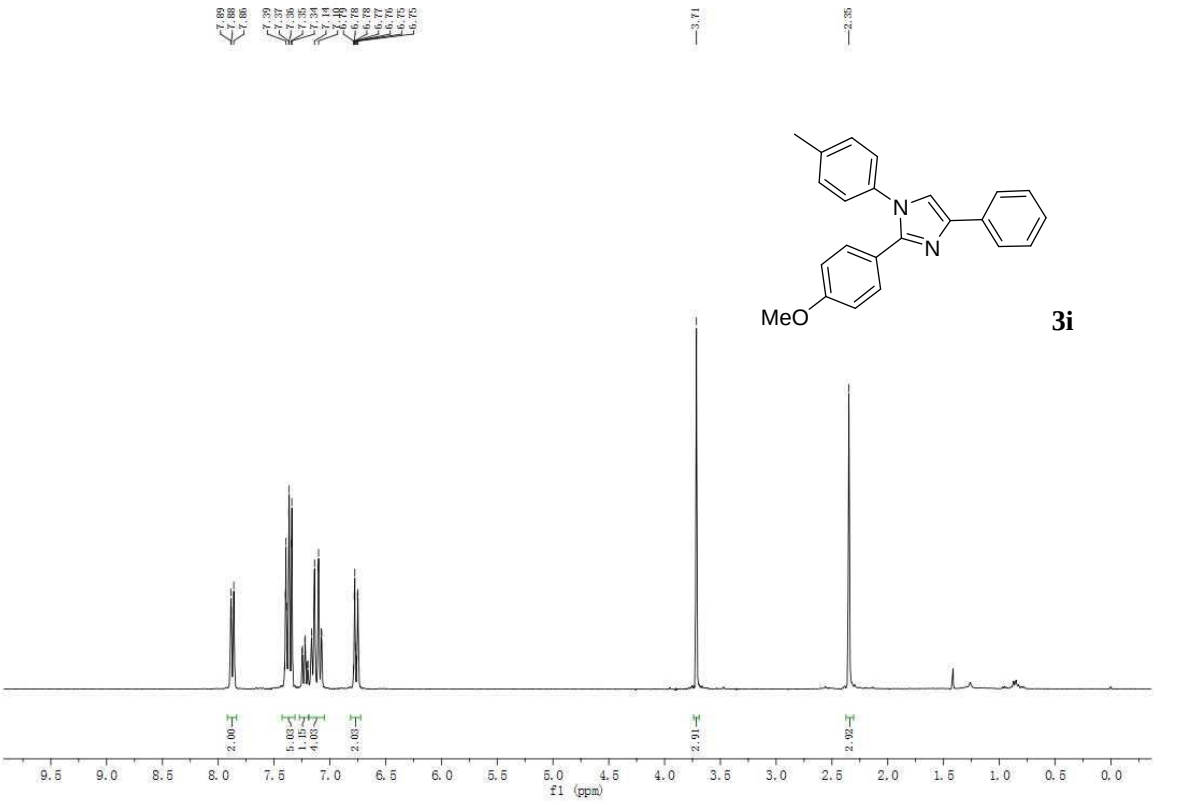

145.24
142.11
138.03
129.66
128.71
128.60
127.17
125.79
125.09
125.04
120.88
119.28

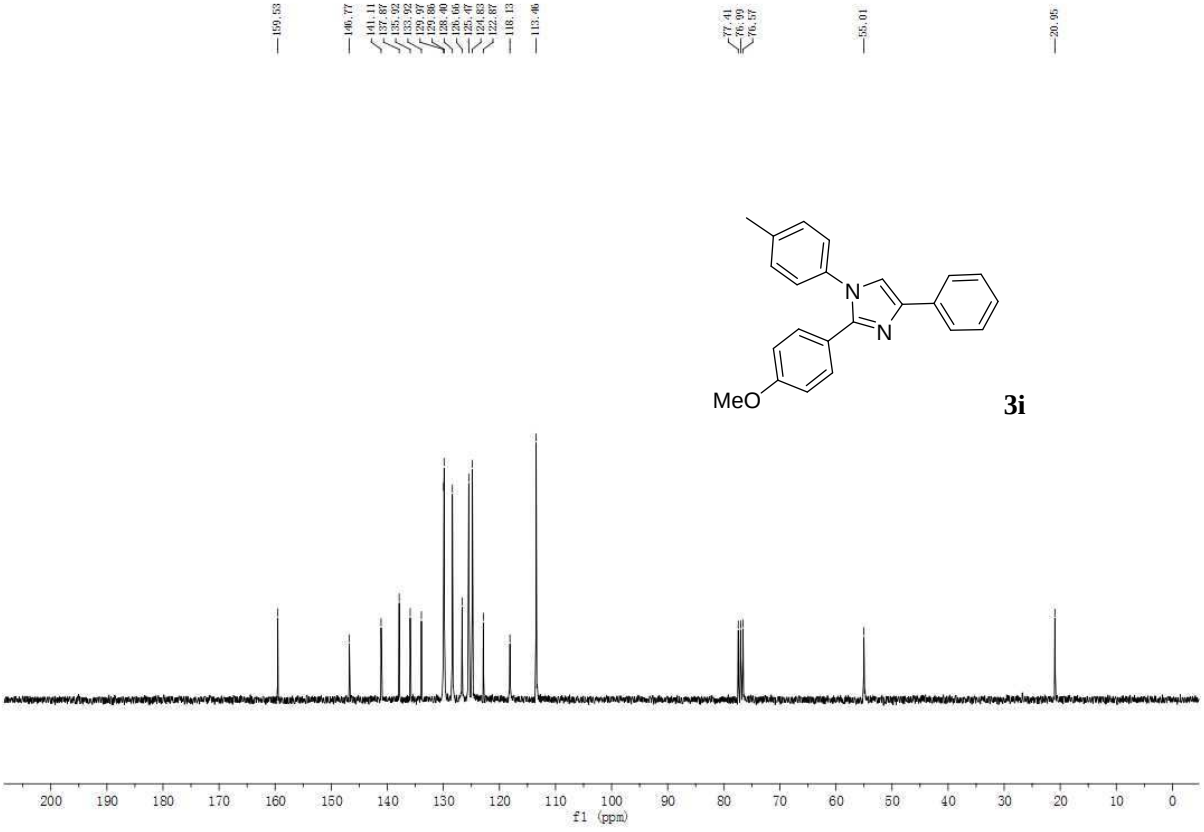

77.41
76.99
76.56


N
N
F3C

3h


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.89
7.88
7.86
7.39
7.37
7.36
7.35
7.34
7.14
7.10
6.79
6.78
6.77
6.76
6.75
6.75
3.71
2.35
MeO
3i
2.00
5.03
1.19
4.03
2.03
2.91
2.92
f1 (ppm)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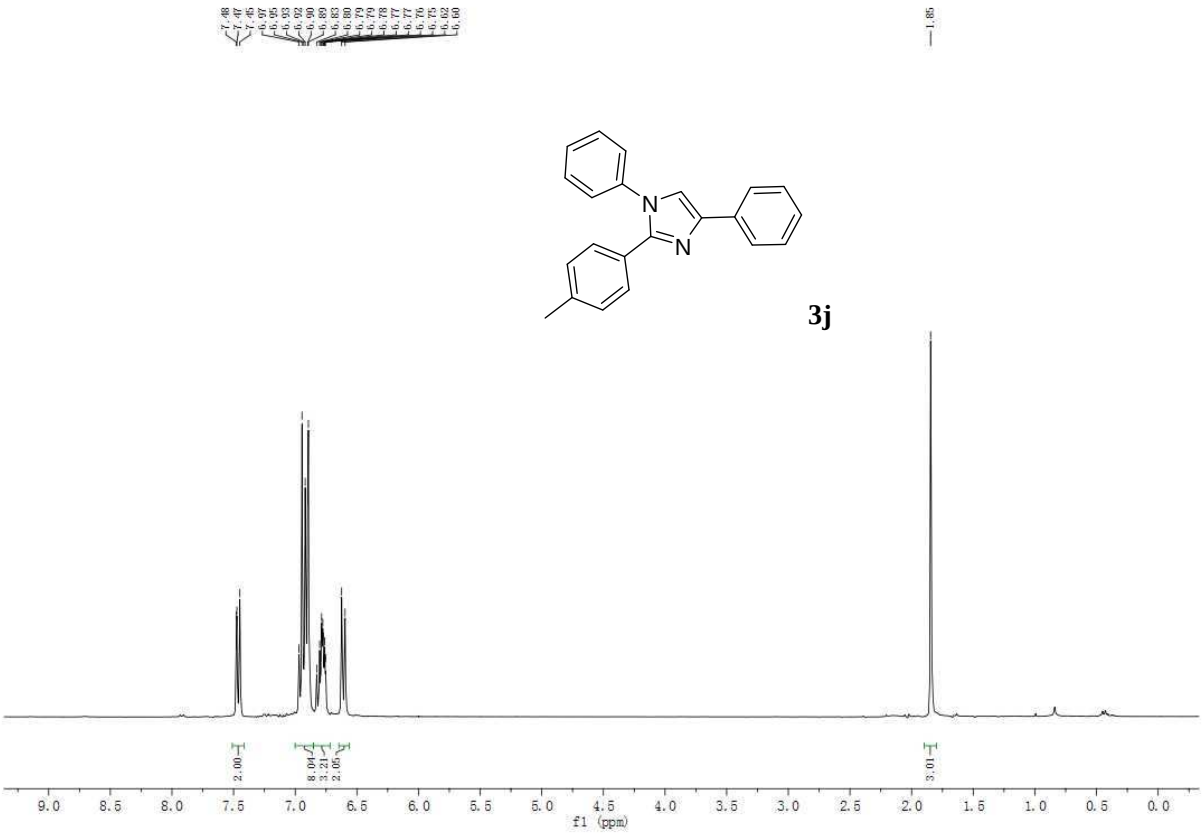
133.92
129.97
129.86
128.40
126.06
125.47
124.65
122.87
118.13
113.46
77.41
76.99
76.57
55.01
20.95
MeO
3i
f1 (ppm)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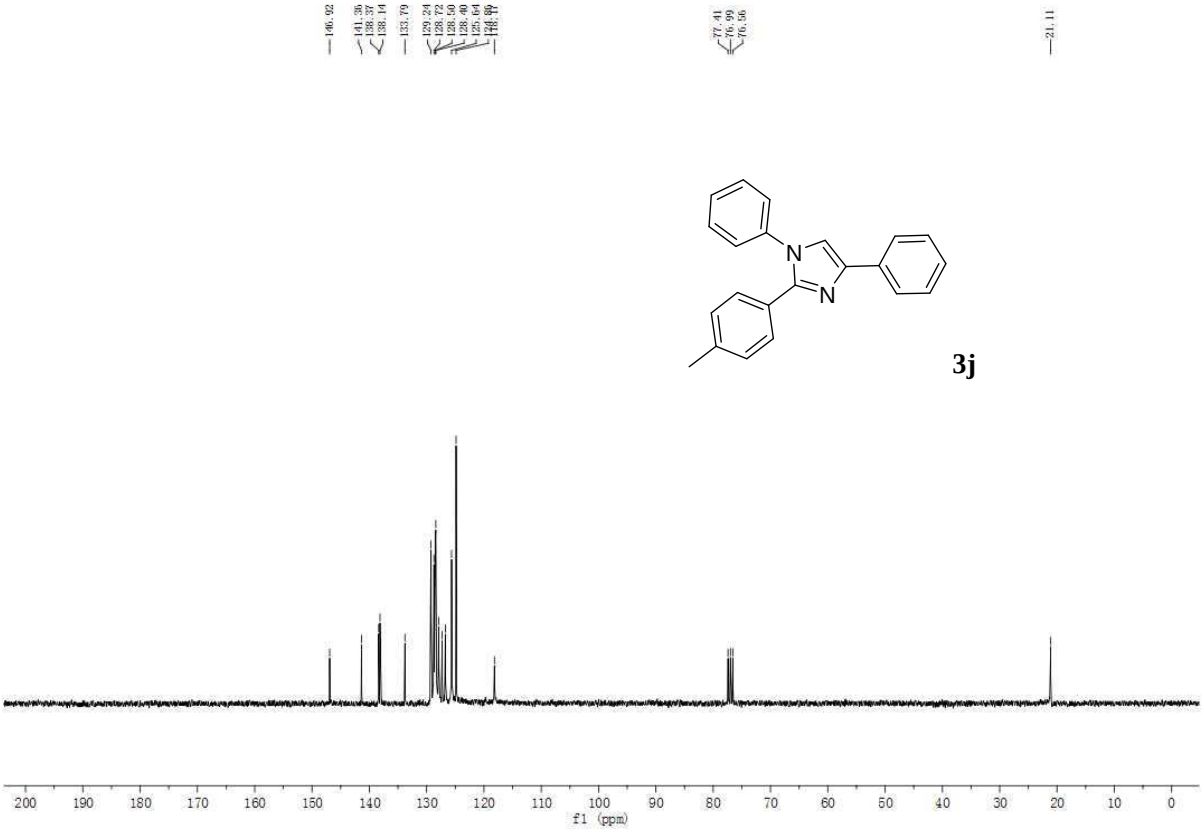
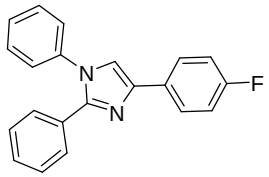
6.95
6.93
6.92
6.90
6.89
6.83
6.80
6.79
6.78
6.77
5.77
5.76
5.75
5.62
5.60
1.85
N
N
2.00
8.04
3.21
2.05
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

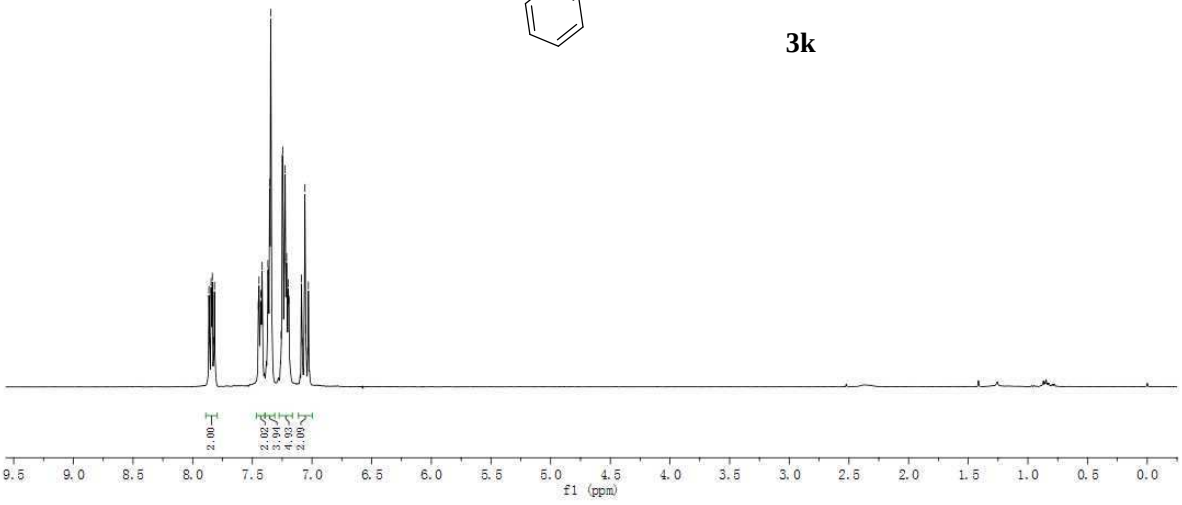
3j

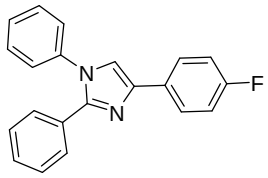

146.92
141.36
138.37
138.14
133.79
129.24
128.72
128.59
128.40
125.64
77.41
76.99
76.56
21.11
N
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3j



3k





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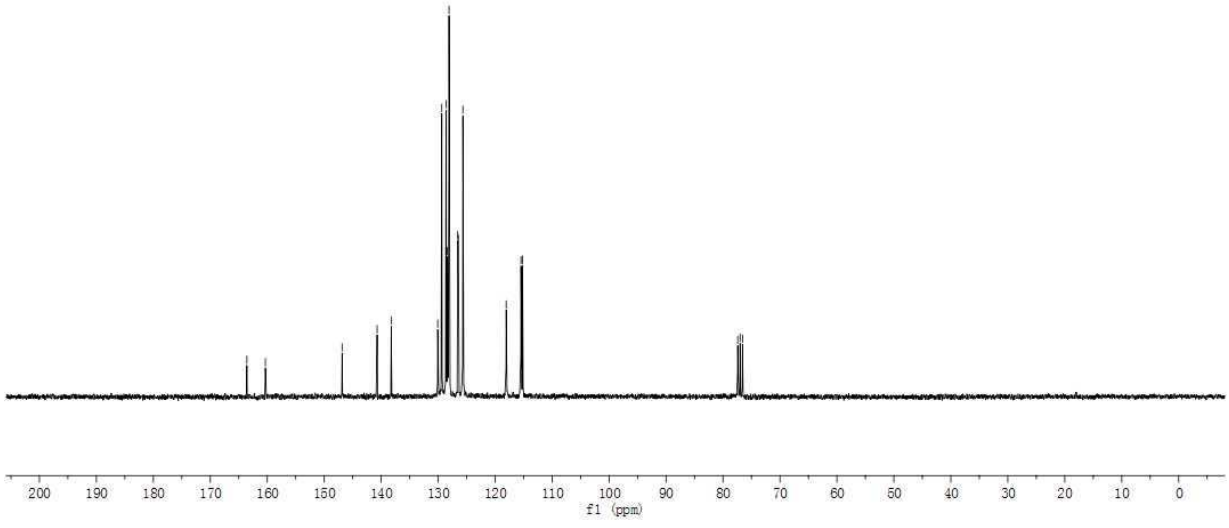
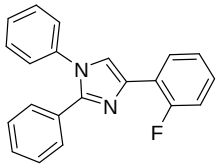
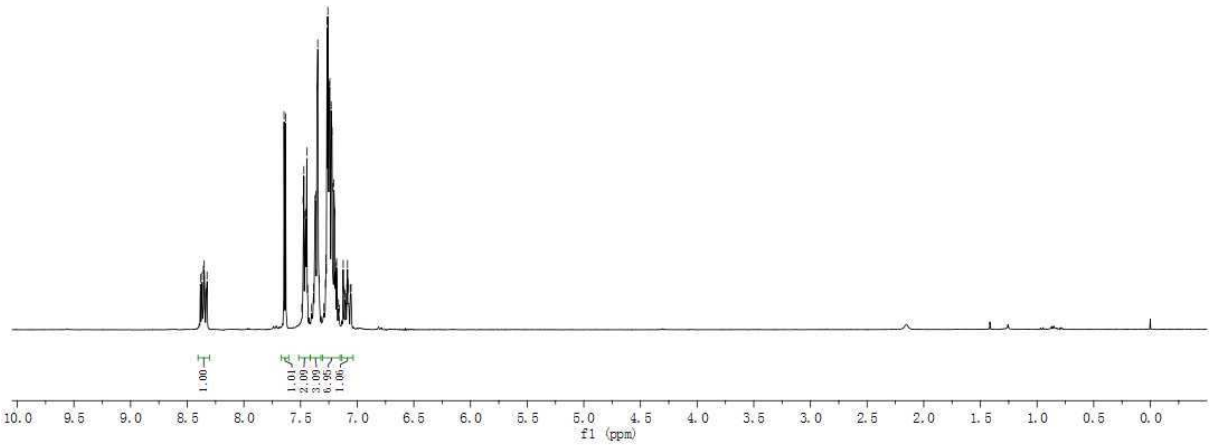
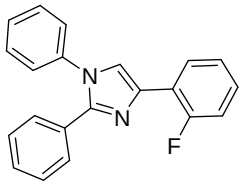


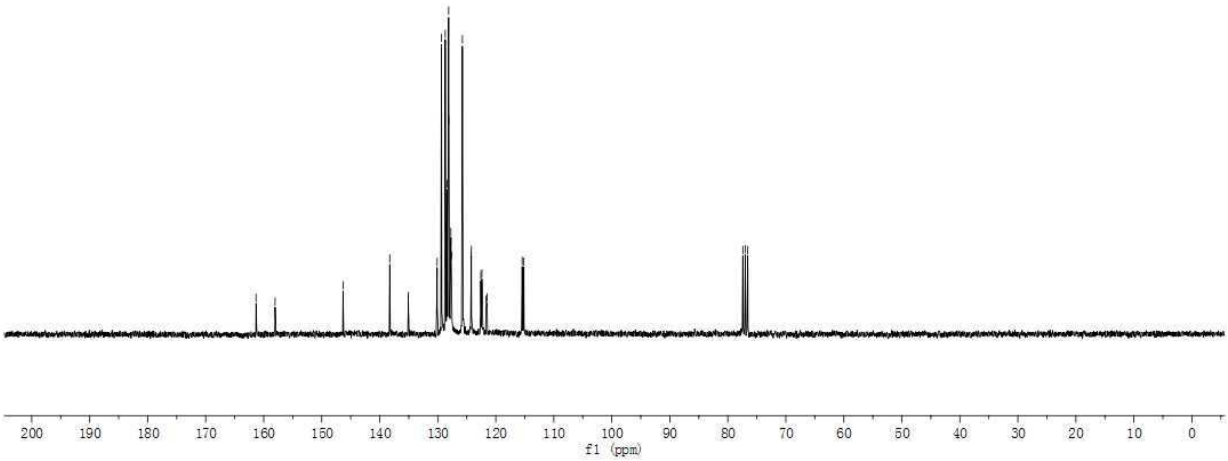


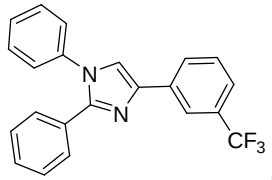
3l



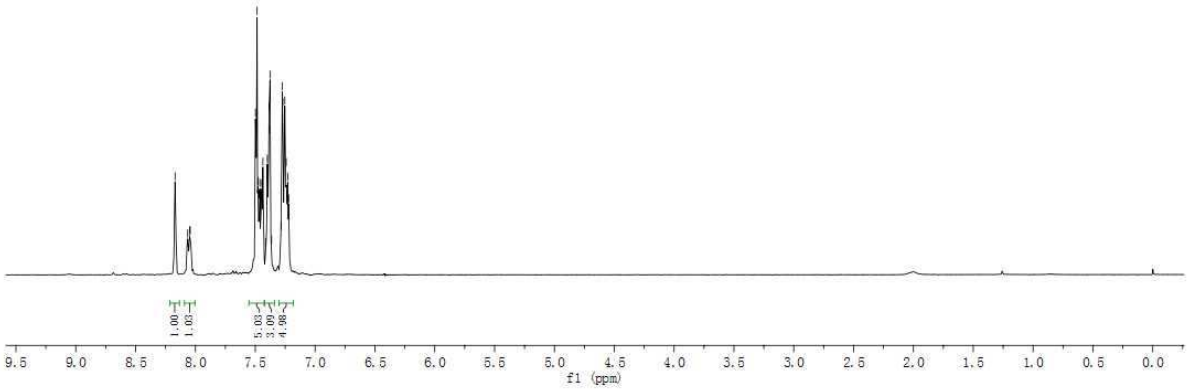


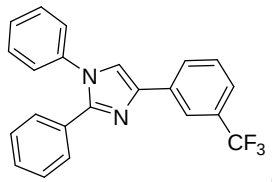
3l



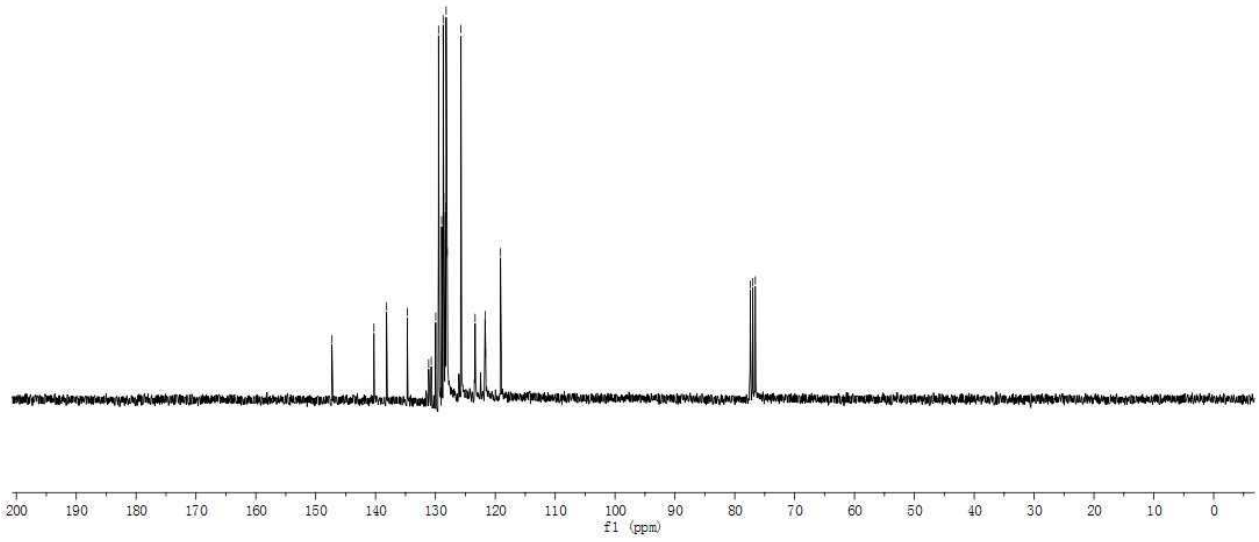

N
N
CF3

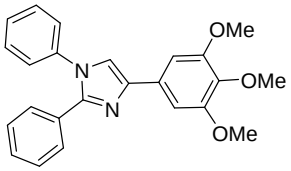
3m


1.00
1.03
5.03
3.09
4.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

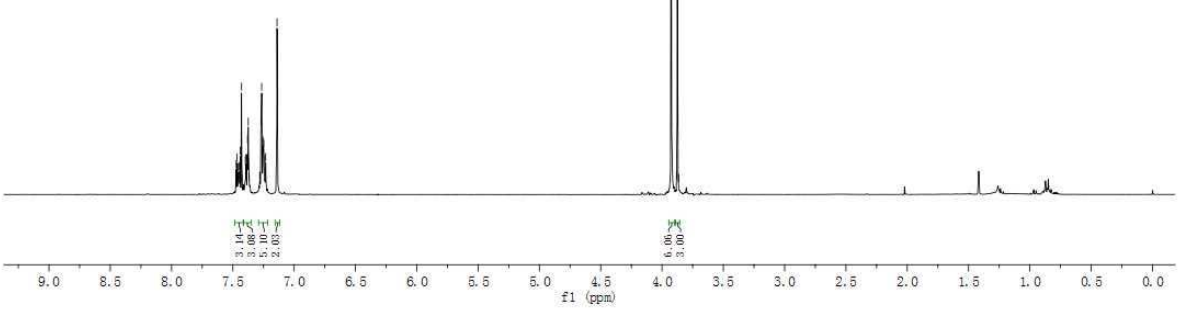

N
N
CF3

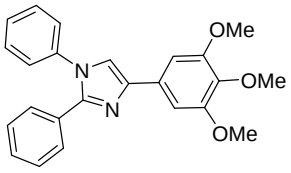
3m


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

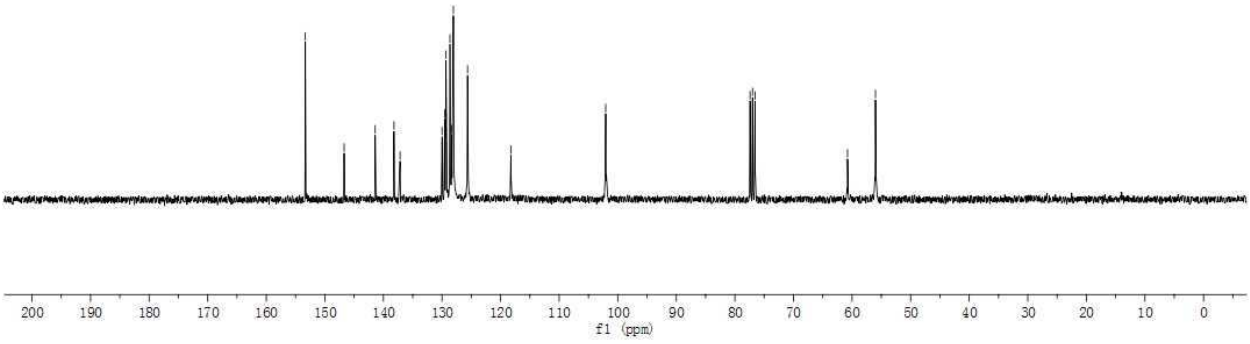

OMe
OMe
OMe
N
N

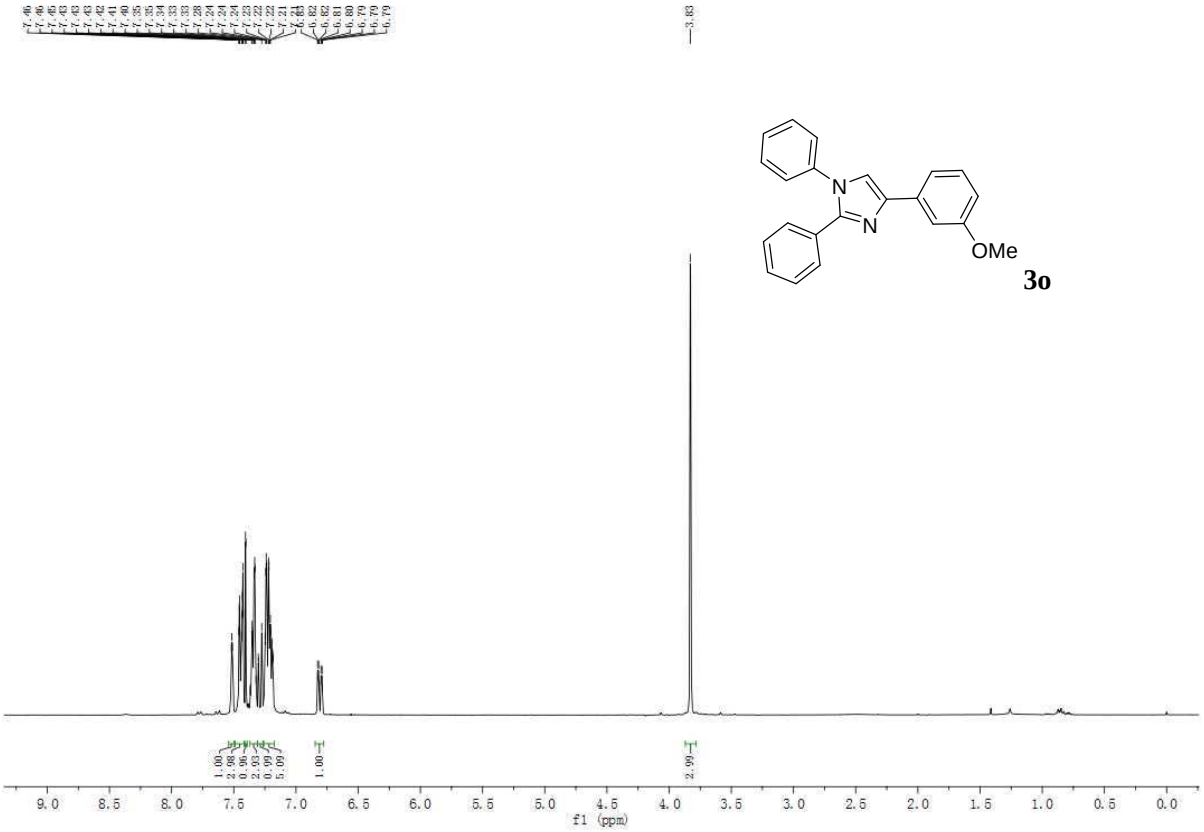
3n

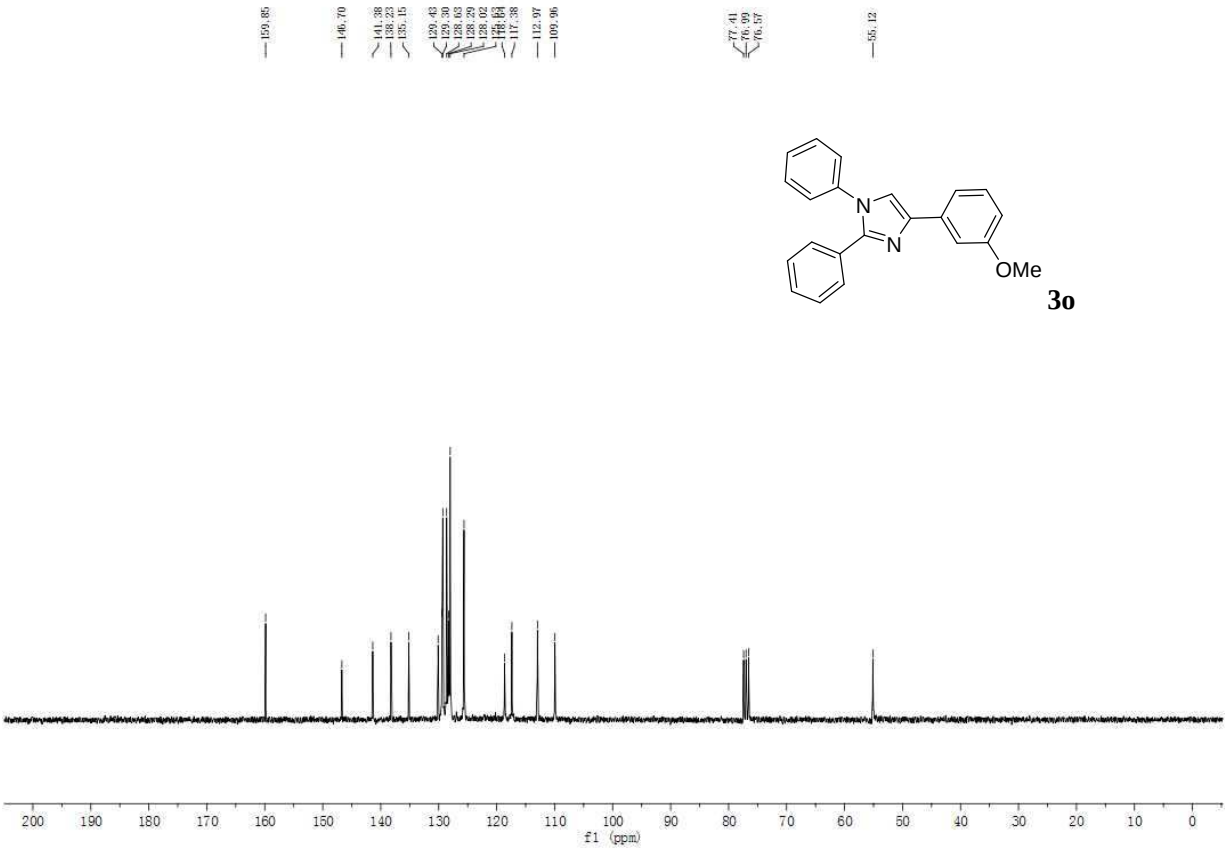

3.14
3.08
5.10
2.03
6.06
3.00
f1 (ppm)

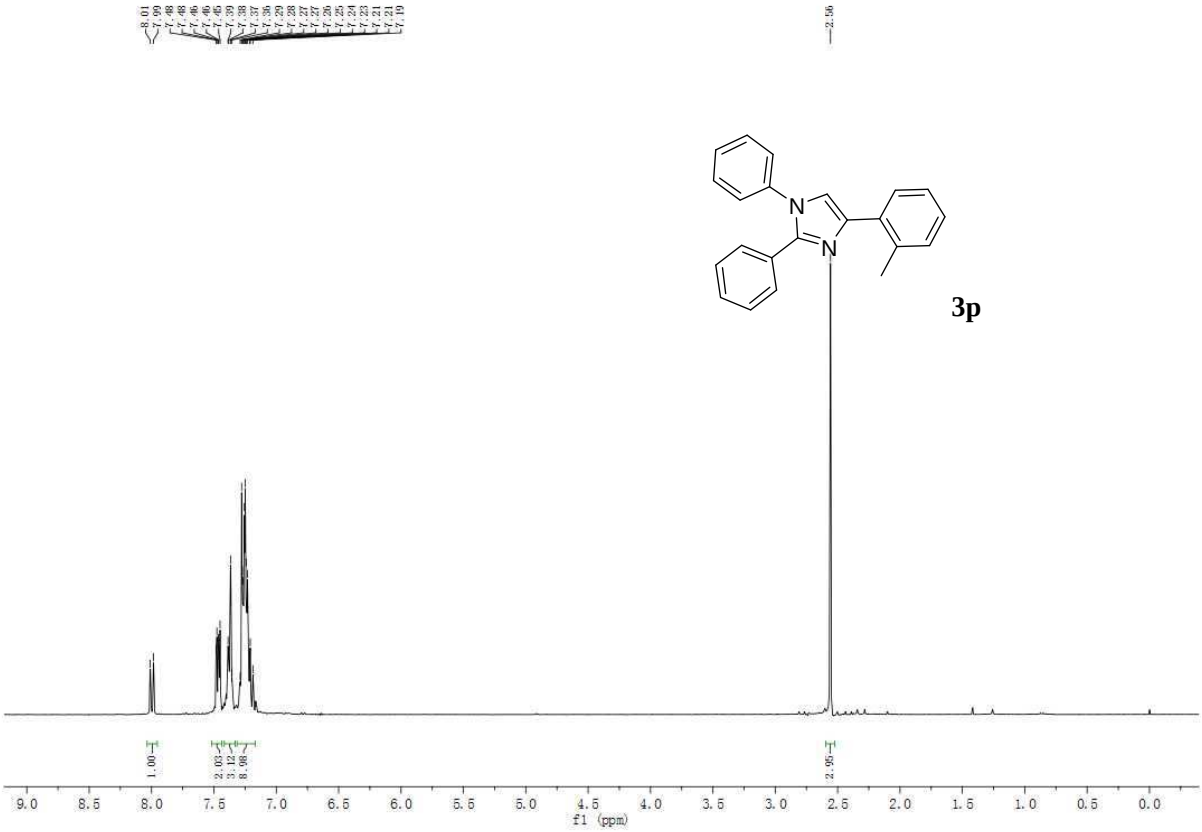

OMe
OMe
OMe
N
N

3n


f1 (ppm)


OMe
3o
f1 (ppm)


OMe
3o
f1 (ppm)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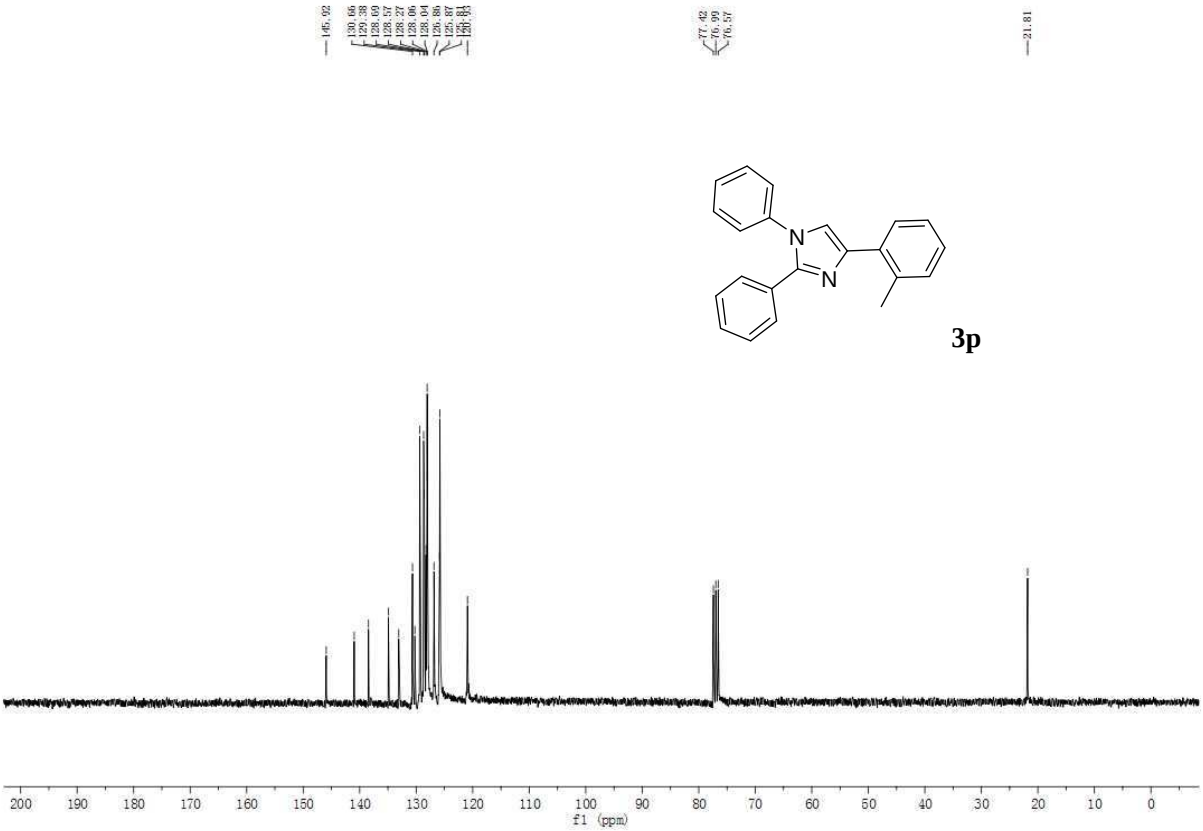
7.26
7.24
7.23
7.21
7.19
2.56
3p
1.00
2.03
3.12
8.98
2.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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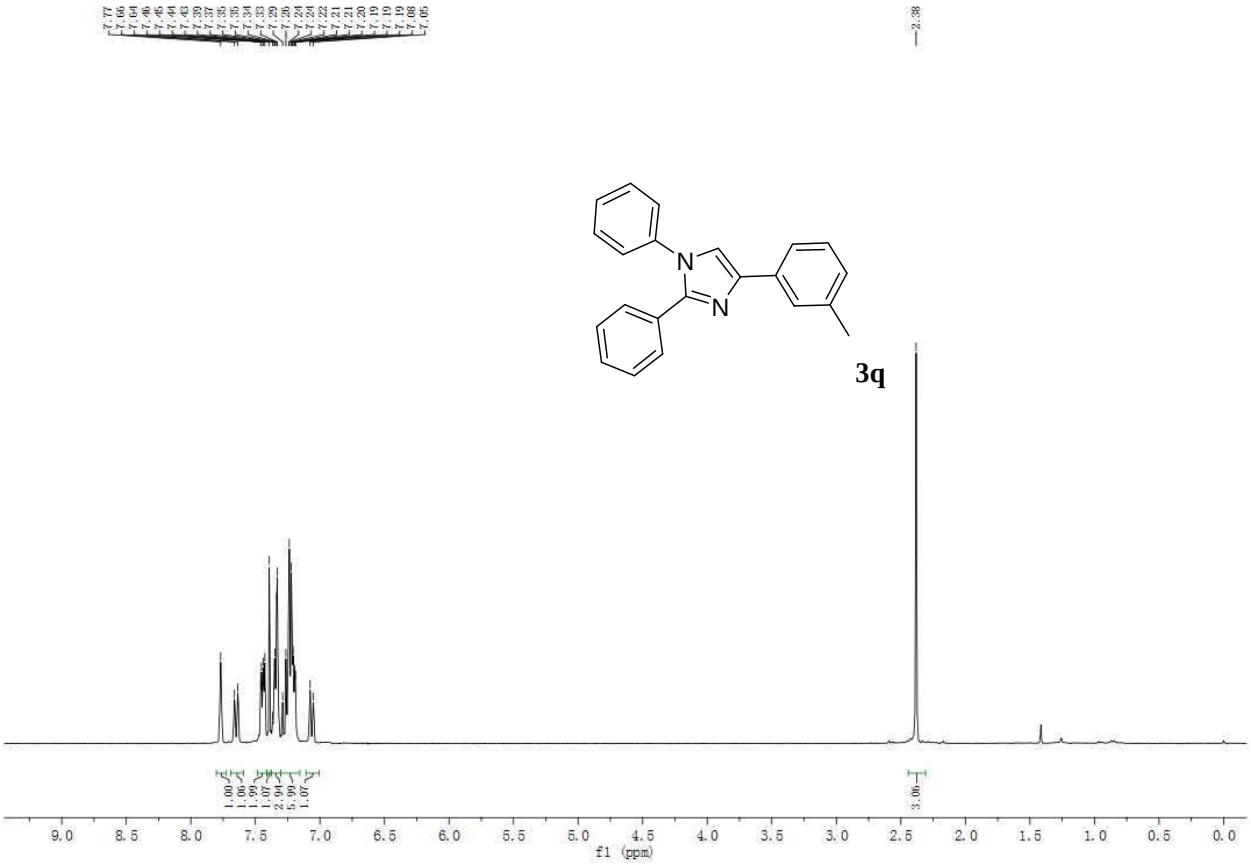
129.38
128.69
128.57
128.27
128.06
126.94
125.86
125.87
125.81
125.80
77.42
76.99
76.57
21.81
3p
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.33
7.29
7.26
7.24
7.22
7.21
7.20
7.19
7.19
7.08
7.05
2.38
N
N
3q
1.00
1.06
1.99
1.07
2.94
5.99
1.07
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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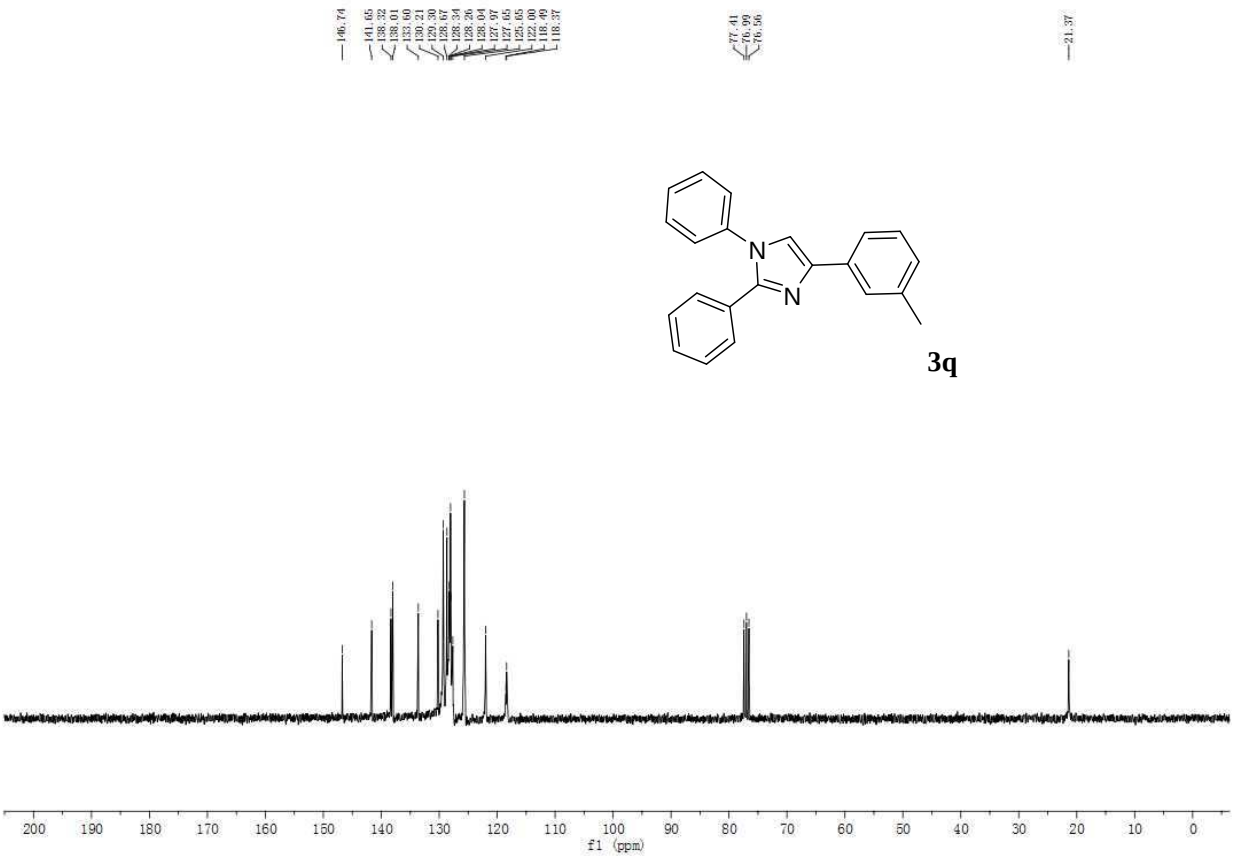
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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130.21
129.30
128.67
128.34
128.26
128.04
127.97
127.65
125.65
122.00
118.49
118.37
77.41
77.00
76.58
21.37
N
N
3q
200
190
180
170
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130
120
110
100
90
80
70
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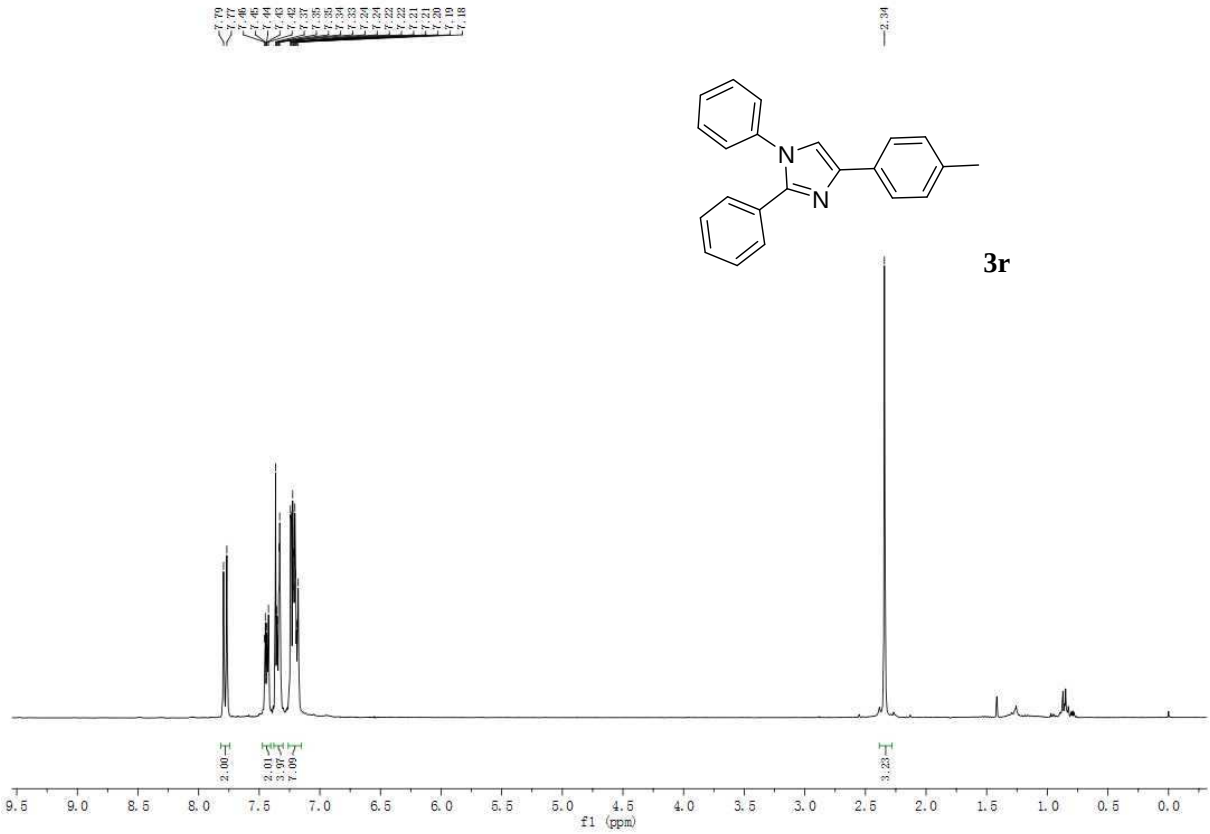
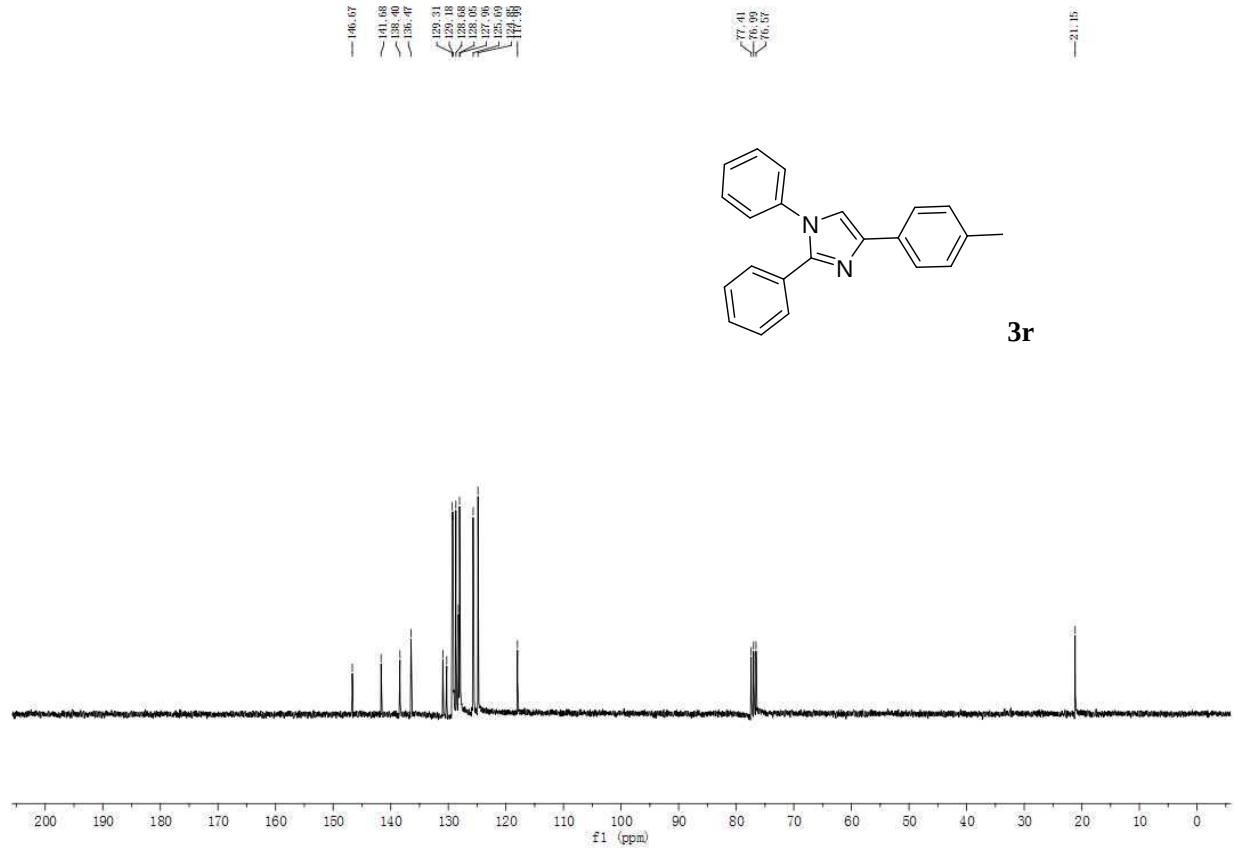
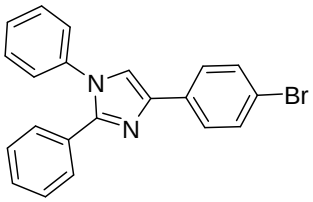
50
40
30
20
10
0
f1 (ppm)


7.79
7.77
7.46
7.45
7.44
7.43
7.42
7.37
7.35
7.34
7.33
7.24
7.23
7.22
7.21
7.20
7.19
7.18
2.34
N
N
2.00
2.01
3.97
7.09
3.23
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

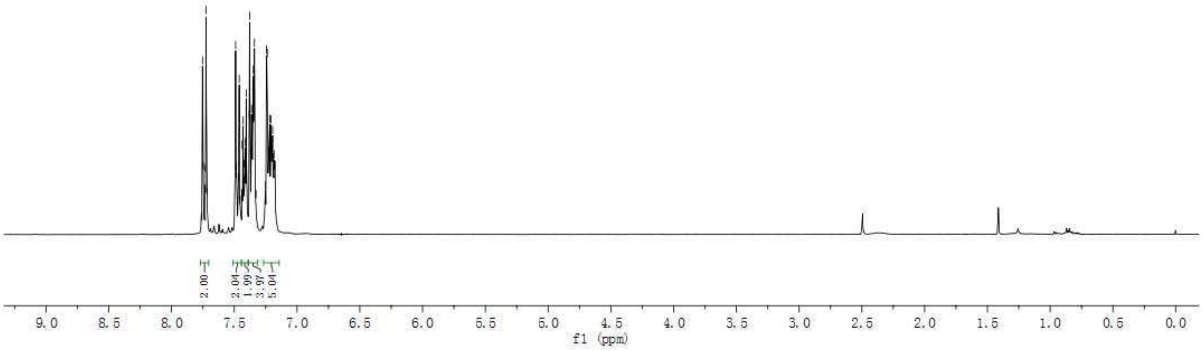
3r

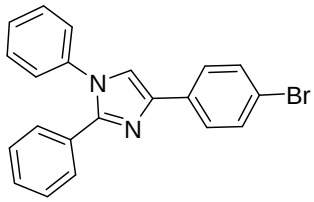

146.67
141.68
138.40
136.47
129.31
129.18
128.68
128.06
127.96
125.69
124.85
117.99
77.41
76.99
76.57
21.15
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3r

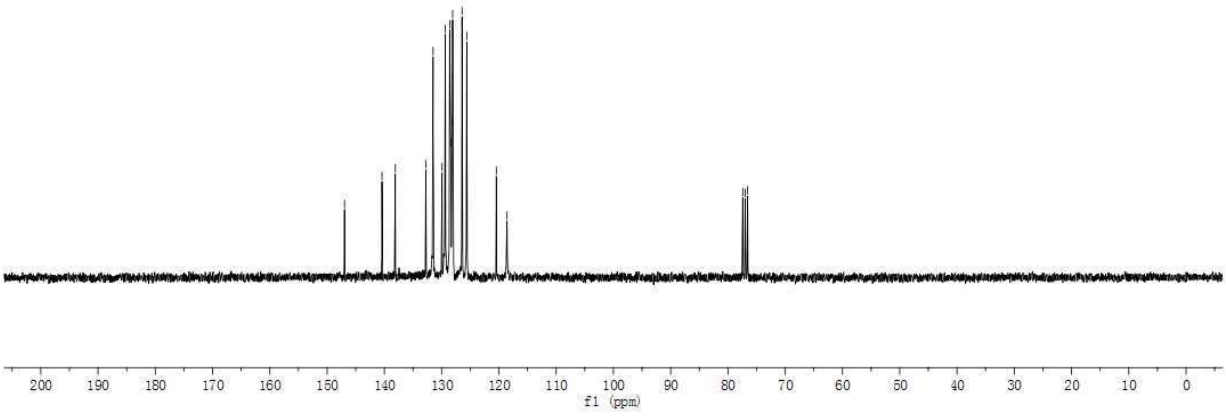

N
N
Br

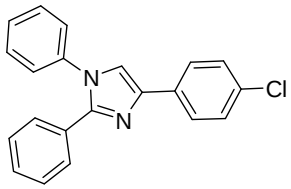
3s


2.00
2.04
1.99
3.97
5.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

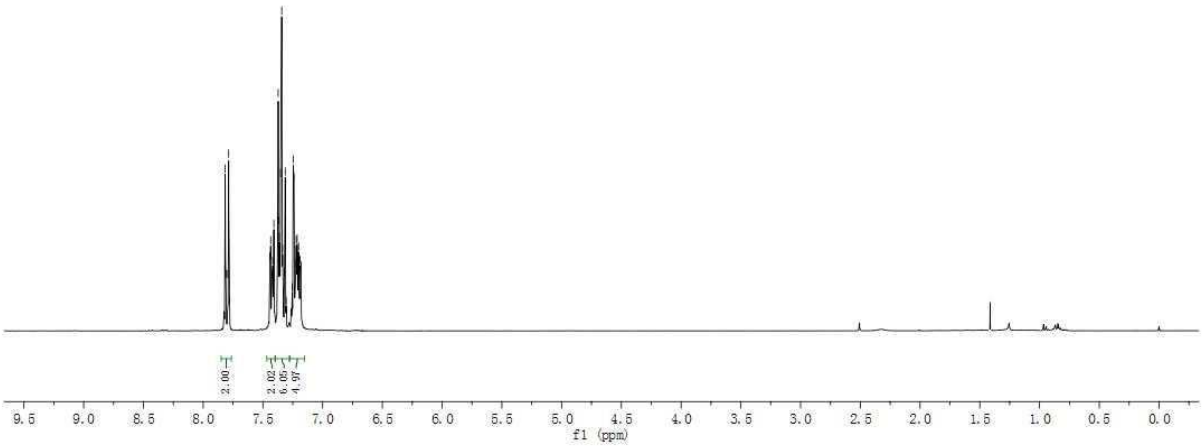

N
N
Br

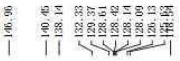
3s

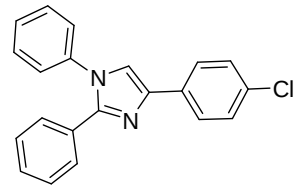

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N
N
Cl

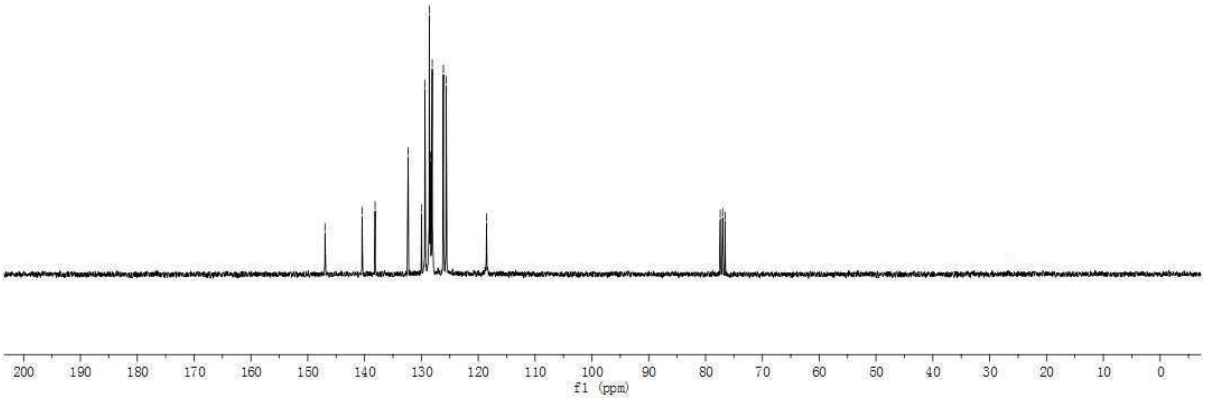
3t

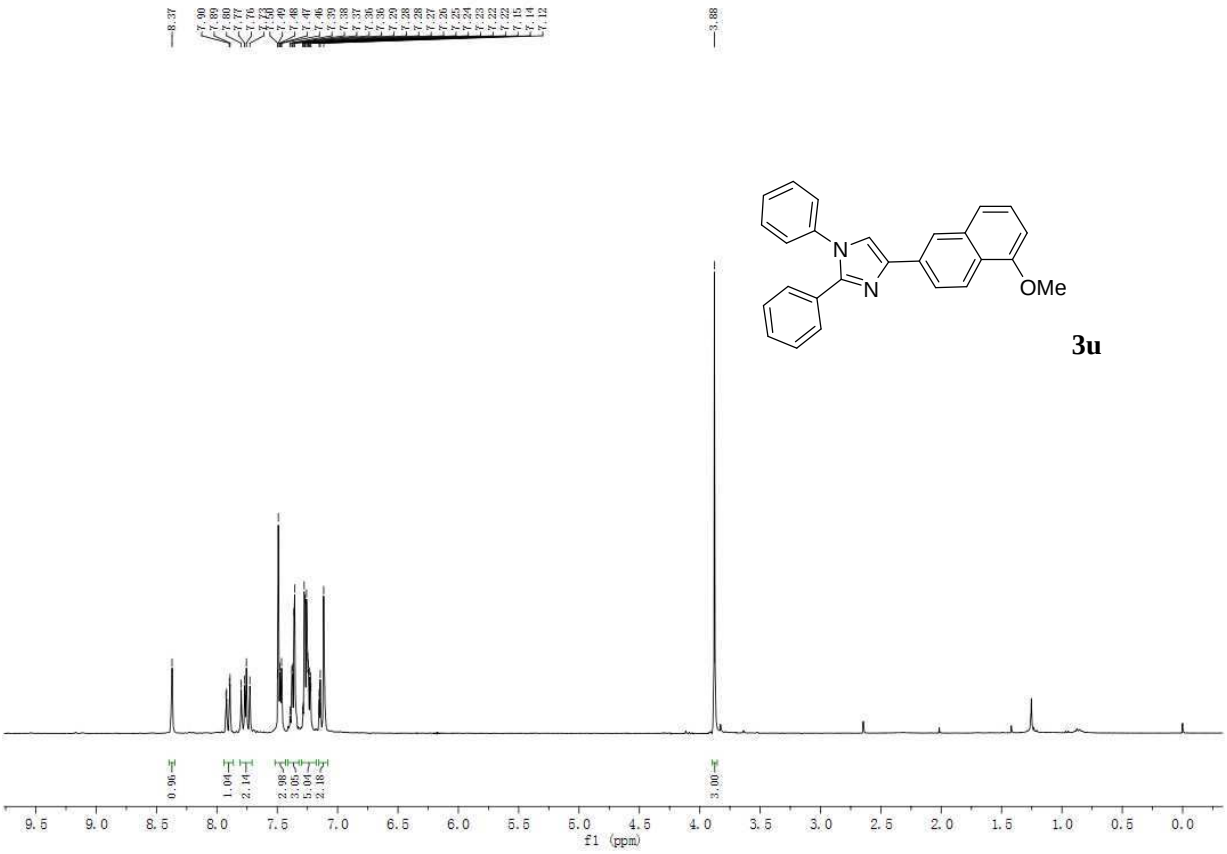

2.00
2.02
6.05
4.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



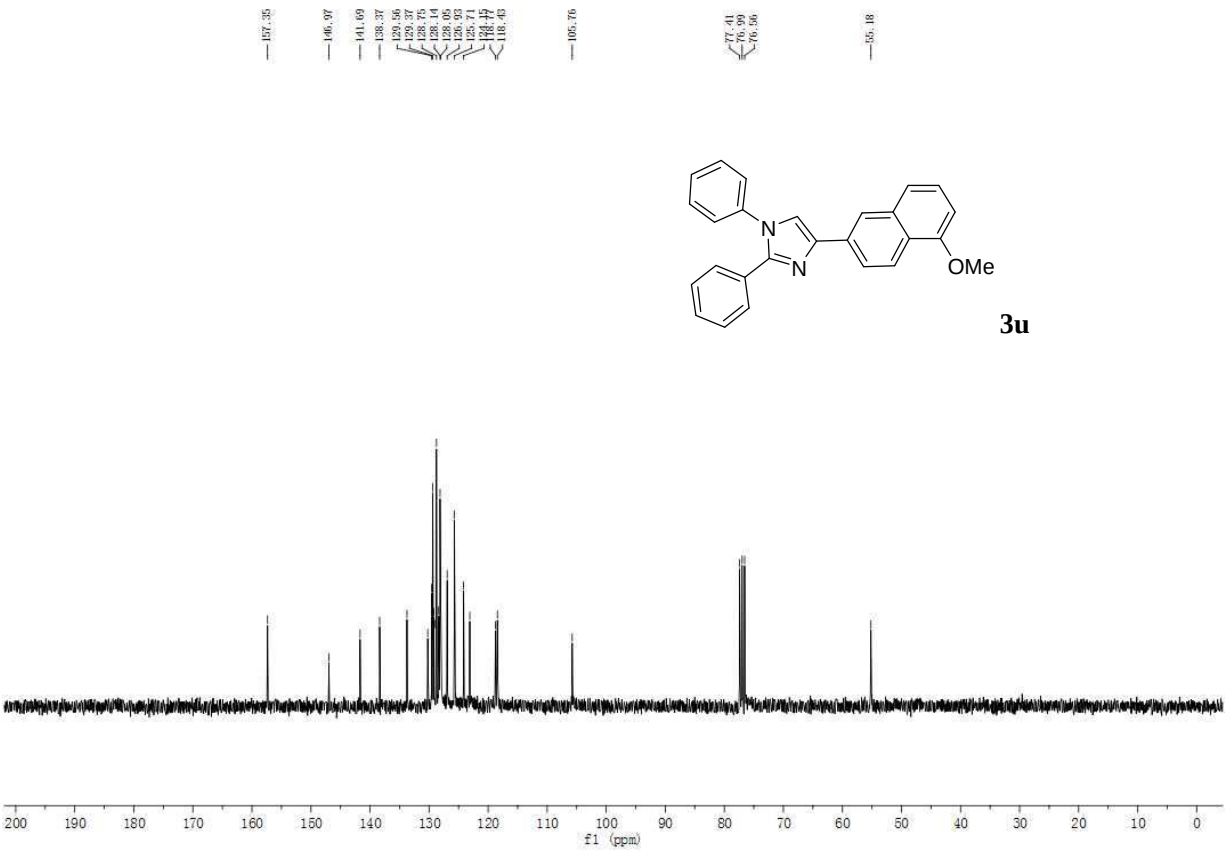

N
N
Cl

3t

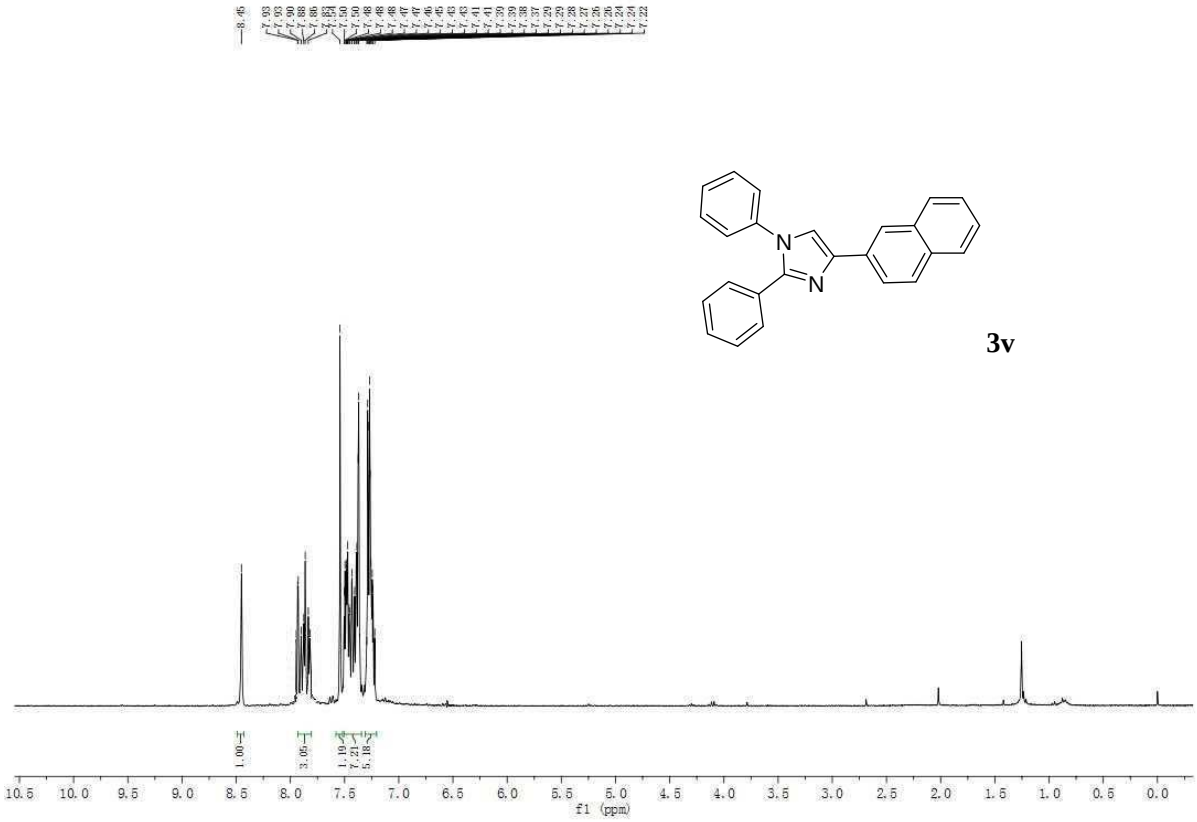

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

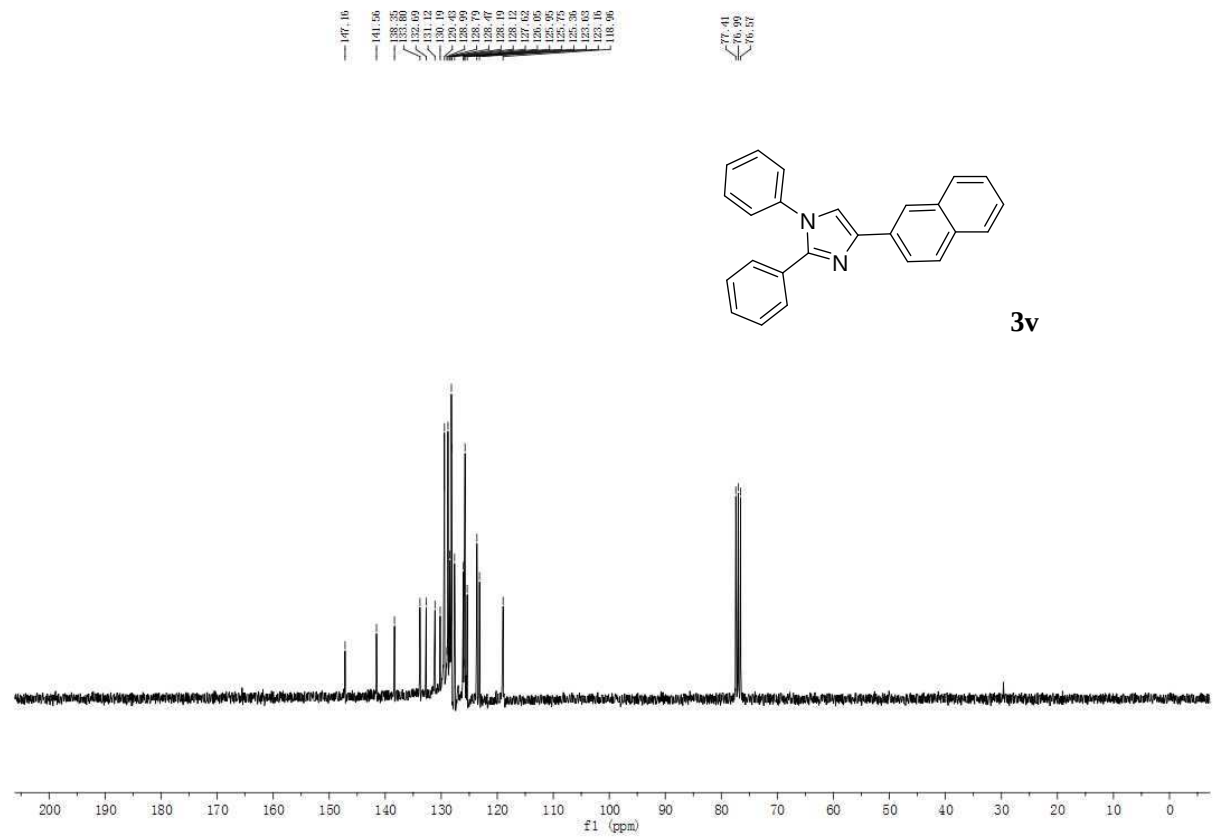

8.37
7.90
7.89
7.80
7.77
7.76
7.73
7.49
7.48
7.47
7.46
7.39
7.38
7.37
7.36
7.35
7.29
7.28
7.27
7.26
7.25
7.24
7.23
7.22
7.15
7.14
7.12
3.88
N
N
OMe
0.96
1.04
2.14
2.98
3.05
5.04
2.18
3.00
f1 (ppm)

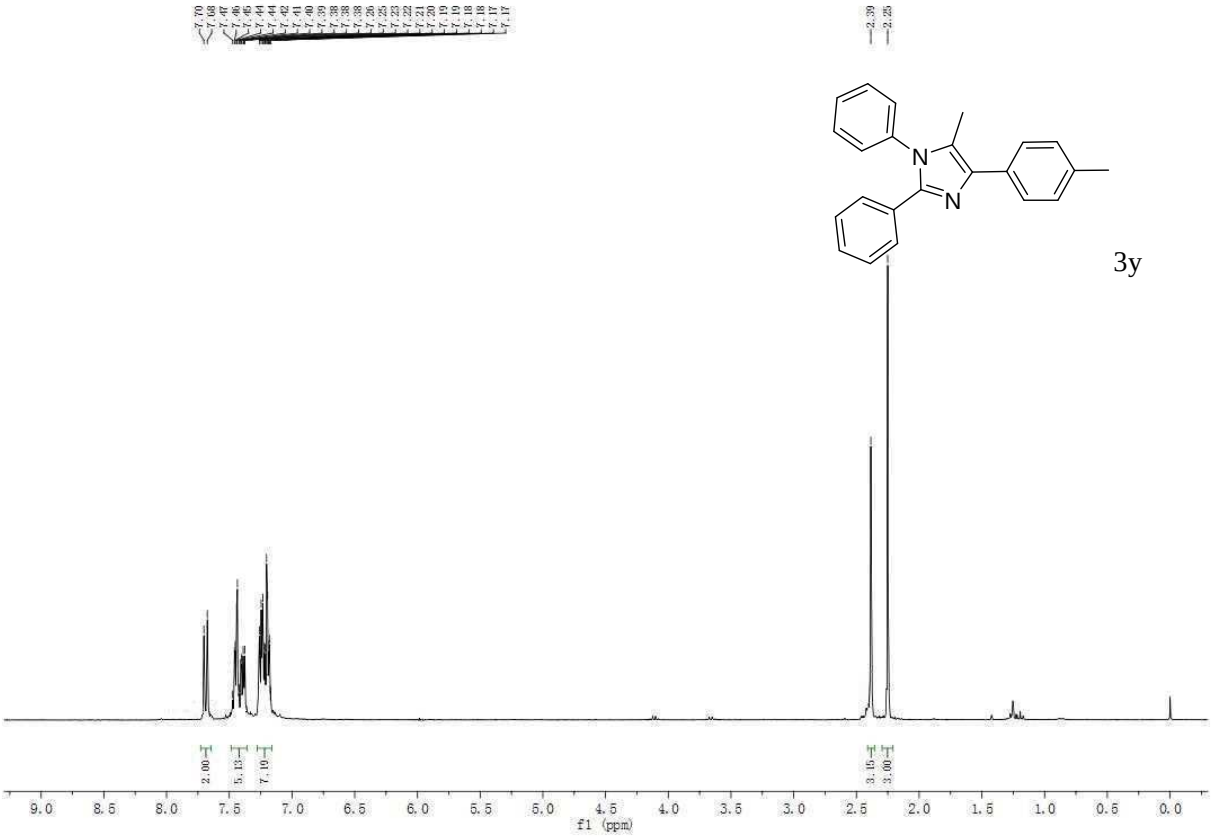
3u


157.35
146.97
141.69
138.37
129.56
129.37
128.75
128.14
128.05
126.93
125.71
118.43
105.76
77.41
76.99
76.56
55.18
N
N
OMe
f1 (ppm)

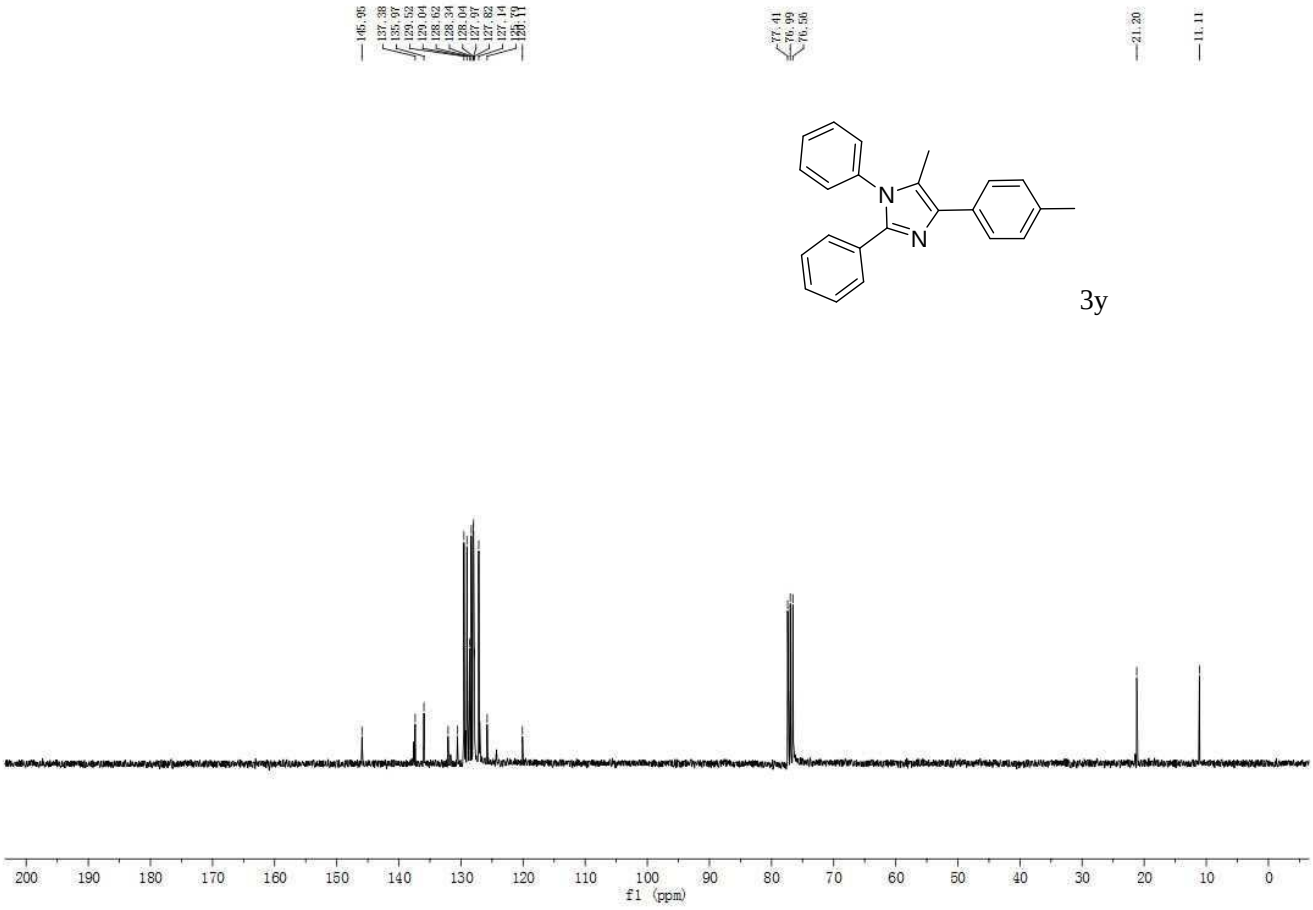
3u


8.45
7.93
7.90
7.88
7.86
7.50
7.48
7.47
7.46
7.45
7.43
7.41
7.39
7.38
7.37
7.29
7.28
7.27
7.26
7.24
7.22
N
N
3v
1.00
3.05
1.19
7.21
5.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


147.16
141.56
138.25
133.80
132.69
131.12
130.19
129.43
128.89
128.79
128.47
128.19
128.12
127.62
126.05
125.95
125.75
125.36
123.63
123.16
118.96
77.41
76.99
76.57
N
N
3v
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.70
7.68
7.47
7.46
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.38
7.25
7.23
7.22
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.17
2.39
2.25
2.00
5.13
7.10
3.15
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3y


146.95
137.38
135.97
129.52
129.04
128.62
128.34
128.04
127.97
127.82
127.14
125.17
77.41
76.99
76.56
21.20
11.11
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3y