Nickel-Catalyzed Isocyanide Insertion Reaction with Aromatic Amines: Direct Access to Open-Chain Guanidines

Zhe Zheng,[a] Hongqiang Ma,[a] Hongwei Jin,[a,b] Bingwei Zhou,[a] Yuanyuan Hu[a,*]

[a]College of Chemical Engineering, Zhejiang University of Technology, Hangzhou, 310014, China.
[b]Eco-industrial Innovation Institute, Zhejiang University of Technology, Quzhou, 324400, China.
E-mail: hyy0907@zjut.edu.cn

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1. General Information

All reactions were carried out in flame-dried reaction vessels with Teflon screw caps under air. Solvents were purified and dried according to standard methods prior to use. Flash column chromatography was performed on silica gel (200-300 mesh) with the indicated solvent mixtures. TLC analysis was performed on pre-coated, glass-backed silica gel plates and visualized with UV light. The heating reaction used oil bath as heat source.

The ^{1}H and ^{13}C spectra were recorded on a Bruker 400 or 500 AV spectrometer. Chemical shifts (δ) were reported as parts per million (ppm) downfield from tetramethylsilane. Coupling constant (J) was reported in hertz unit (Hz). The high-resolution mass spectra (HRMS) were recorded on an Agilent 6210 LC/TOF spectrometer. The crystal measurement was recorded on an Empyrean X-ray diffractometer.

All the amines and *tert*-butyl isocyanide are commercially available and used as received.

2. Nickel-Catalyzed Isocyanide Insertion Reaction with Aromatic Amines

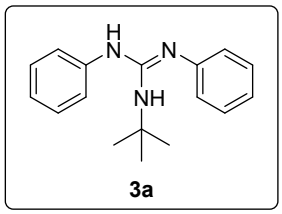
2.1 General procedure and characterization of products

To a 25-mL flame-dried Schlenk tube containing a stir bar was added aromatic amine **1** (0.6 mmol), *tert*-butyl isocyanide **2a** (0.2 mmol, 16.7 mg), $NiBr_2$ (0.01 mmol, 5 mol%, 2.18 mg), anisole (0.5 mL) sequentially. The tube was sealed and stirred at 90 ℃ for 3 h. After the completion, the reaction mixture was concentrated and purified by silica gel column chromatography to give the product **3**.

Characterization of products

Note: The ^{13}C NMR spectra of guanidines seem to be abnormal presumably due to the intrinsic nature of these compounds.

***N*-(1,1-Dimethylethyl)-*N′*,*N″*-diphenylguanidine (3a)[1]**

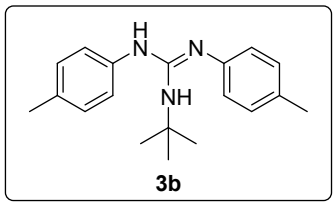


3a

Purified by silica gel column chromatography (silica gel, petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as dark brown solid (27.8 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.0, 7.2 Hz, 4H), 7.03 (d, *J* = 7.2 Hz, 6H), 5.58 (s, 1H), 4.00 (s, 1H), 1.46 (s, 9H).

***N*-(1,1-dimethylethyl) -*N′*,*N″*-di-p-toluenylguanidine (3b)[1]**

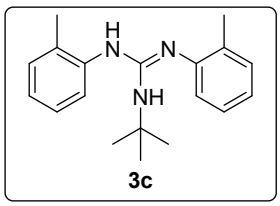


3b

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (38.4 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 6.4 Hz, 4H), 6.95 (s, 4H), 5.55 (s, 1H), 3.95 (s, 1H), 2.34 (s, 6H), 1.48 (s, 9H).

***N*-(1,1-dimethylethyl)-*N′*,*N″*-di-o-methylphenyl guanidine (3c)**

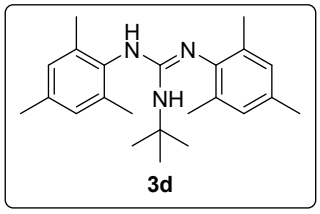


3c

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as red liquid (27.1 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–6.94 (m, 8H), 5.28 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 1H), 2.30 (d, *J* = 44.0 Hz, 6H), 1.53 (d, *J* = 6 Hz, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.6, 130.8, 126.8, 125.2, 122.6, 121.9, 50.9, 29.4, 18.1. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{19}H_{26}N_3$ 296.21212; found 296.21154.

***N*-(1,1-dimethylethyl) -*N′*,*N′′*-bis-2,4,6-trimethylphenyl guanidine (3d)**

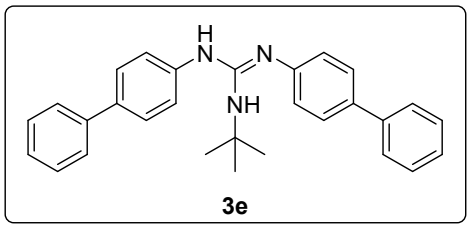


3d

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (38.6 mg, 55% yield). mp: 125-127 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 6.86 (s, 2H), 4.67 (s, 1H), 3.42 (s, 1H), 2.35 (d, *J* = 7.2Hz, 9H), 2.30 (s, 3H), 2.24 (s, 6H), 1.49 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.1, 136.8, 132.3, 131.0, 129.3, 128.8, 29.4, 20.8, 18.5. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{23}H_{34}N_3$ 352.27472; found 352.27381.

***N*-(1,1-dimethylethyl)-*N′*,*N′′*-biphenyl guanidine (3e)**

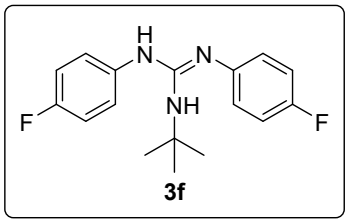


3e

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as dark brown solid (52.8 mg, 63% yield). mp: 64-66 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 15.6, 7.2 Hz, 8H), 7.44 (t, *J* = 7.4 Hz, 4H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 4H), 5.80 (s, 1H), 4.31 (s, 1H), 1.51 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.4, 140.9, 135.4, 128.8, 128.7, 128.1, 126.8, 126.7, 122.6, 51.4, 29.6. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{29}H_{39}N_3$ 420.24342; found 420.24296.

***N-(1,1-dimethylethyl) -N′,N′′-di-p-fluorophenylguanidine* (3f)**

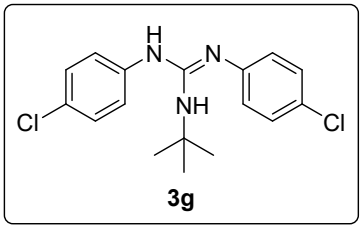


3f

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (24 mg, 55% yield). mp: 129-131 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.6 Hz, 4H), 6.96 (s, 4H), 5.51 (s, 1H), 3.91 (s, 1H), 1.44 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.4, 129.4, 123.4, 51.4, 29.5. **HRMS (ESI) m/z: [M+H]$^+$** calcd for $C_{17}H_{20}F_2N_3$ 304.16198; found 304.16146.

***N*-(1,1-dimethylethyl) -*N′*,*N′′*-di-p-chlorophenylguanidine (3g)[2]**

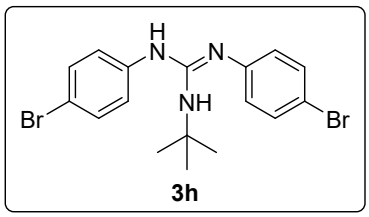


3g

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (34.2 mg, 51% yield). mp: 133-135 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 4H), 6.93 (s, 4H), 5.48 (s, 1H), 3.88 (s, 1H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.4, 129.4, 128.0, 123.5, 51.4, 29.5. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{17}H_{20}N_3Cl_2$ 336.10288; found 336.10254..

***N*-(1,1-dimethylethyl)-*N′*,*N′′*-di-p-bromophenyguanidine (3h)**

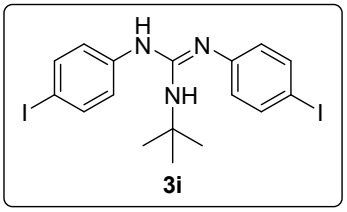


3h

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (42.5 mg, 50% yield). mp: 133-135 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 4H), 6.87 (d, *J* = 9.6 Hz, 4H), 5.46 (s, 1H), 3.90 (s, 1H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.2, 132.3, 123.8, 51.4, 29.6. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{17}H_{20}N_3Br_2$ 424.00185; found 424.00186.

***N*-(1,1-dimethylethyl)-*N′*,*N′′*-bis-p-iodophenylaguanidine (3i)**

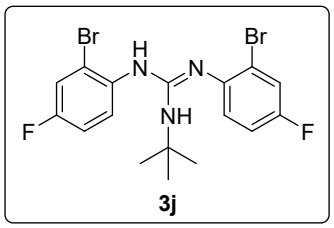


3i

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as white solid (48.8 mg, 47% yield). mp: 134-136 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.8 Hz, 4H), 6.75 (s, 4H), 5.47 (s, 1H), 3.92 (s, 1H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.0, 138.3, 124.1, 51.5, 29.5. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{17}H_{20}I_2N_3$ 519.97411; found 519.97408.

_N_-(1,1-dimethylethyl)- _N′_,_N′′_-di-2-bromo-4-fluorophenylguanidine (3j)

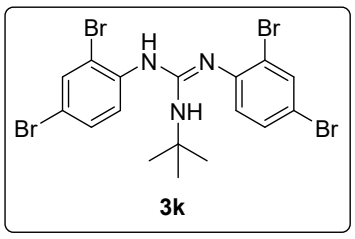


3j

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as dark brown liquid (59.9 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.6 Hz, 3H), 6.97 (s, 3H), 5.75 (s, 1H), 3.85 (s, 1H), 1.47 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.0, 133.9, 124.3, 119.8, 118.2, 115.1, 51.5, 29.8. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{17}H_{18}N_3Br_2F_2$ 459.98301; found 459.98297.

_N_-(1,1-dimethylethyl) -_N′_,_N′′_-bis-2,4-dibromophenyguanidine (3k)

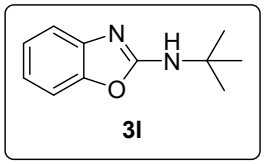


3k

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine = 15:1:0.1) as dark brown liquid (53.5 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 15.2, 6 Hz, 3H), 7.40–7.28 (m, 2H), 6.76 (dd, *J* = 29.6, 8 Hz, 1H), 5.96 (s, 1H), 3.89 (s, 1H), 1.44 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.0, 147.7, 135.1, 134.4, 131.2, 131.0, 52.4, 51.7, 29.9, 28.0. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{17}H_{18}Br_4N_3$ 579.82287; found 579.82282.

_N_-(1,1-Dimethylethyl)-2-benzoxazolamine (3l)[3]

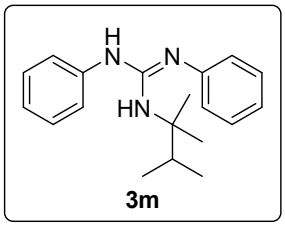


3l

Purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50:1) as dark brown liquid (30.6 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.08 (br, 1H), 1.54 (s, 9H).

1,2-diphenyl-3-(2,4,4-trimethylpentan-2-yl)guanidine (3m)

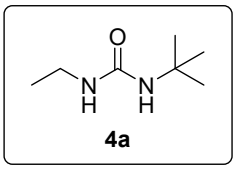


3m

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine =10:1:0.1) as white solid (23.3 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 4H), 6.92 (s, 6H), 5.45 (s, 1H), 3.86 (s, 1H), 1.77 (s, 2H), 1.38 (s, 6H), 0.92 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.9, 129.4, 122.9, 55.0, 51.8, 31.7, 31.62, 29.9. **HRMS (ESI) m/z:** $[M+H]^+$ calcd for $C_{21}H_{30}N_3$ 324.24342; found 324.24337.

1-(tert-butyl)-3-ethylurea (4a)[4]



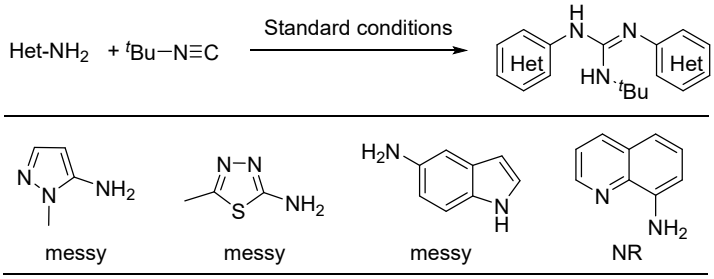
4a

Purified by silica gel column chromatography (petroleum ether/ethyl acetate/triethylamine =10:1:0.1) as white solid (10.9 mg, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 1H), 4.09 (s, 1H), 3.15 (dd, *J* = 7.2, 5.6 Hz, 2H), 1.33 (s, 9H), 1.11 (t, *J* = 7.2 Hz, 3H).

2.2 Test on the reactivity of heteroaromatic amines

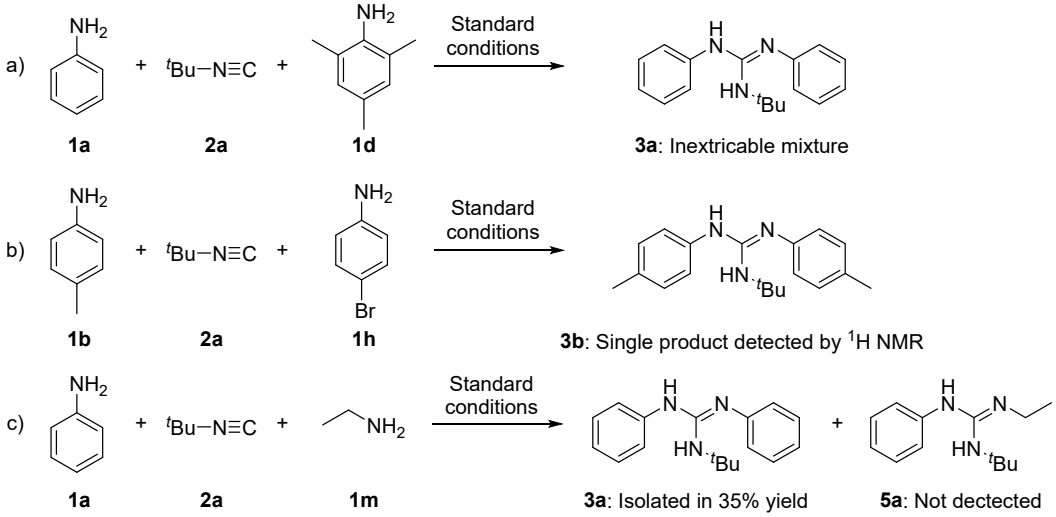
The substrate scope of heterocyclic amines has been evaluated under the standard conditions. As exhibited in Scheme S1, five-membered heterocyclic amines based on pyrazole, thiadiazole and indole frameworks resulted in messy mixtures. This is probably ascribed to the electron-rich property for decomposition under the reaction conditions. In contrast, quinolin-8-amine was totally inert in the reaction. We speculated that the coordination effect of the N-atom to the nickel catalyst might inhibit the expected reaction.



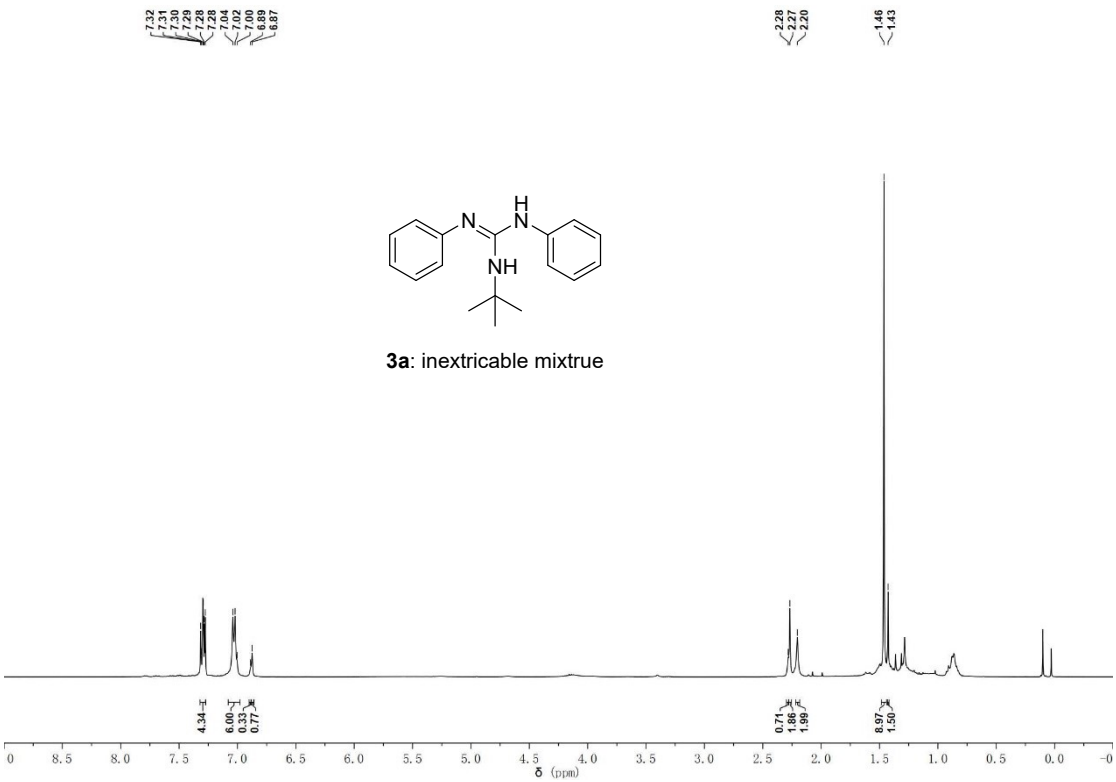
Scheme S1. The reactivity survey of heteroaromatic amines

2.3 Cross-over reactions of two different amines with isocyanide

The isocyanide insertion reactions with two different aromatic amines were examined. First, in the cross-over reaction of aniline **1a** and 2,4,6-trimethylaniline **1d**, an inextricable mixture was detected (Scheme S2a). After meticulous analysis of its ^{1}H NMR spectrum, guanidine **3a** was determined as major product. Next, the cross-over reaction with *p*-toluidine **1b** and 4-bromoaniline **1h** was explored (Scheme S2b). Peculiarly, guanidine **3b** was exclusively detected by ^{1}H NMR analysis, which indicated that the electron-rich aromatic amines might be preferable than electron-deficient ones in this isocyanide insertion protocol. In addition, the reaction of aniline **1a** and ethanamine **1m** was also tested under the standard reaction conditions (Scheme S2c). As shown, only guanidine **3a** was isolated in 35% yield and the unsymmetric guanidine **5a** could not be detected.

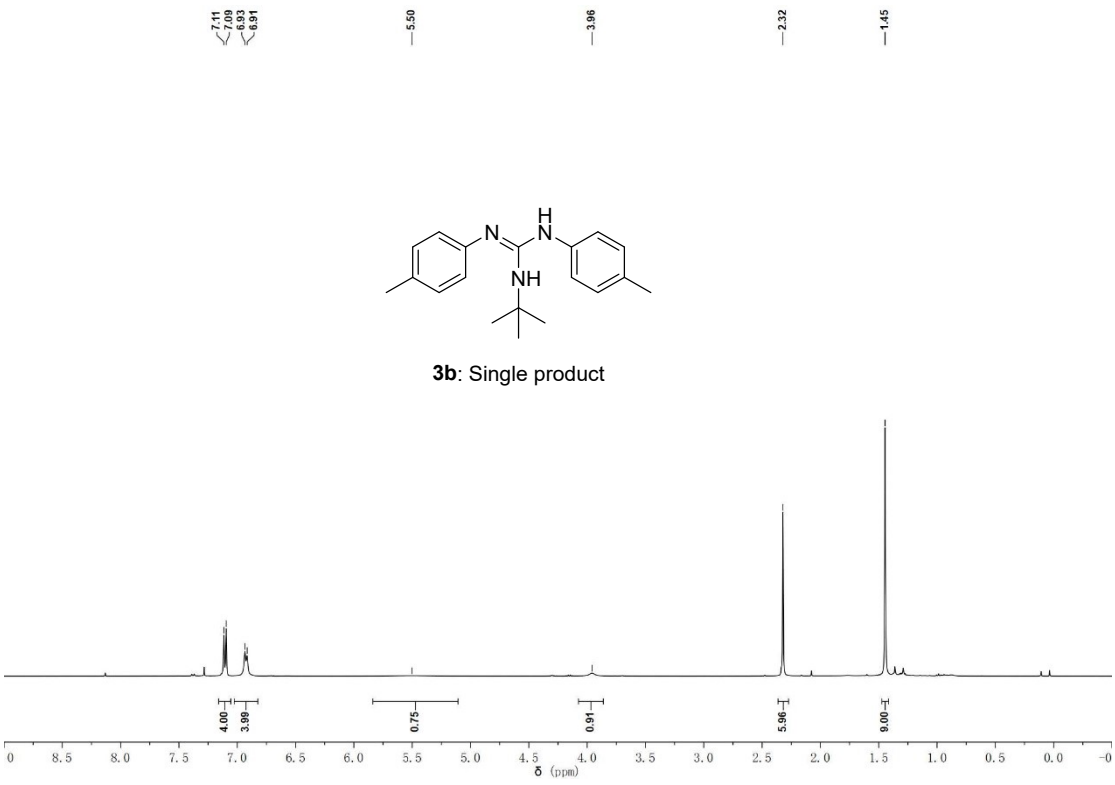


Scheme S2. Cross-over reactions of two different amines with isocyanide



3a: inextricable mixtrue

Figure S1. ^{1}H NMR spectrum of inextricable mixture in Scheme S2a



3b: Single product

Figure S2. ^{1}H NMR spectrum of product **3b** in Scheme S2b

3. References

1. T.-H. Zhu, S.-Y. Wang, T.-Q. Wei and S.-J. Ji, *Adv. Synth. Catal.*, 2015, **357**, 823.

2. H. Yu, M. Zhang, W. Sun, Y. Li and R. Gao, *Lett. Org. Chem.*, 2010, **7**, 566.

3. B. Liu, M. Yin, H. Gao, W. Wu and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3009.

4. J. Pawlas, J.-H. Choi, C. von Bargen, S. Maibom-Thomsen, J. H. Rasmussen and O. Ludemann-Hombourger, *Org. Process Res. Dev.* 2023, **27**, 1348.

4. X-Ray Crystallographic Data of 3a

The crystal of **3a** was crystallized by slow vapor diffusion of acetate and petroleum ether.

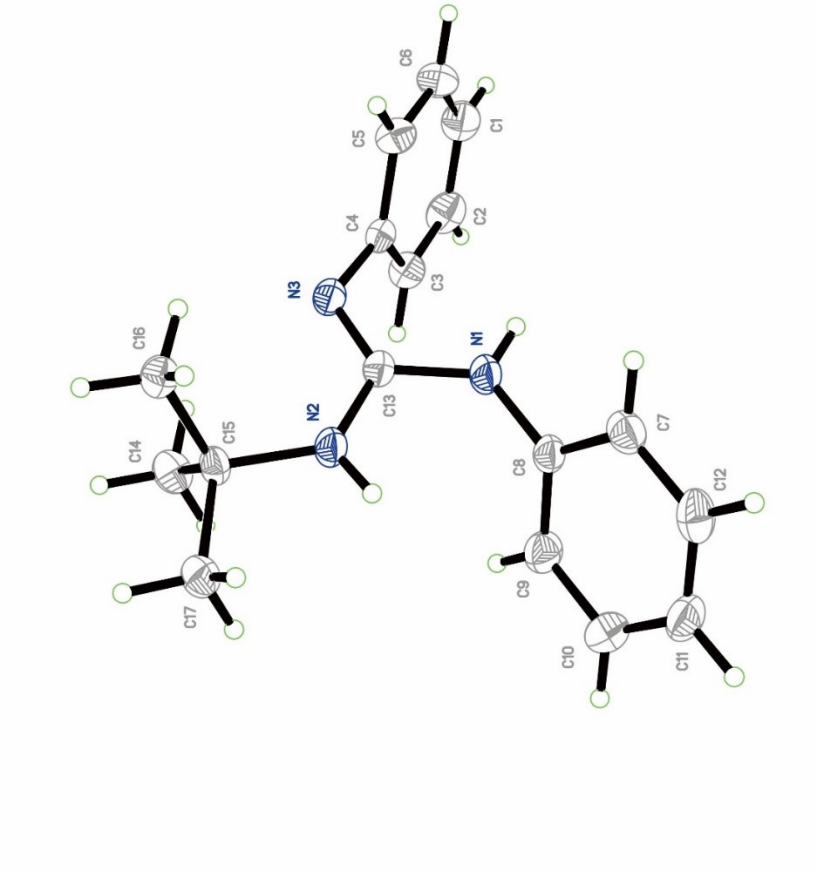


Figure S1. Ortep drawing of compound **3a** with 50% ellipsoids

Datablock: mo_JS_10045_0m_tw

Bond precision: C-C = 0.0065 A Wavelength=0.71073

Cell: a=5.9783(10) b=10.038(2) c=25.696(5)
alpha=90.518(8) beta=91.336(7) gamma=93.881(7)
Temperature: 223 K

	Calculated	Reported
Volume	1538.0(5)	1537.9(5)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C17 H21 N3	C17 H21 N3
Sum formula	C17 H21 N3	C17 H21 N3
Mr	267.37	267.38
Dx,g cm-3	1.155	1.155
Z	4	4
Mu (mm-1)	0.070	0.070
F000	576.0	576.3
F000'	576.17	
h,k,lmax	7,12,30	7,12,30
Nref	5634	5512
Tmin,Tmax	0.990,0.993	0.024,0.047
Tmin'	0.990	

Correction method= # Reported T Limits: Tmin=0.024 Tmax=0.047
AbsCorr = PSI-SCAN

Data completeness= 0.978 Theta(max)= 25.350

R(reflections)= 0.1013(4038) wR2(reflections)= 0.2901(5512)

S = 1.056 Npar= 368

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

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PLAT420_ALERT_2_C D-H Bond Without Acceptor N2 --H2 . Please Check
PLAT420_ALERT_2_C D-H Bond Without Acceptor N4 --H4 . Please Check
PLAT420_ALERT_2_C D-H Bond Without Acceptor N5 --H5 . Please Check
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PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ..... 2.927 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L= 0.600 120 Report

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(90 More Missing: see the .ckf listing file)

Alert level G

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PLAT073_ALERT_1_G H-atoms ref., but hydrogen treatment Reported as     constr Check
PLAT769_ALERT_4_G CIF Embedded Explicitly Supplied Scattering Data          3 Note
PLAT870_ALERT_4_G ALERTS Related to Twinning Effects Suppressed ..          ! Info
PLAT910_ALERT_3_G Missing FCF Reflection(s) Below Theta(Min)[Deg]=       2.03 Note
                   0  0  1,    0  0  2,
PLAT930_ALERT_2_G FCF-based   Twin Law ( 0 1 0)         Est.d BASF       0.39 Check
PLAT931_ALERT_5_G CIFcalcFCF  Twin Law ( 0 1 0)         Est.d BASF       0.39 Check
PLAT933_ALERT_2_G Number of HKL-OMIT Records in Embedded .res File        104 Note
                  -5 -2 13,   -5  0 12,   -4 -7  5,   -4 -4  2,   -4 -3  1,   -4 -2  1,
                  -4 -2  3,   -4  5  0,   -1 -5 19,   -1 -3 23,   -1  1 18,   -1  4 21,
                  -1  5 23,    0 -9  3,    0 -7  2,    0 -7 10,    0 -6  1,    0 -6  4,
                   0 -5  1,    0 -5  2,    0 -5  3,    0 -5  5,    0 -5  8,    0 -4  2,
                   0 -4  5,    0 -4  6,    0 -3  3,    0 -3  4,    0 -3  5,    0 -3  6,
                   0 -3 17,    0 -2  1,    0 -2  3,    0 -2  4,    0 -2  5,    0 -2  6,
                   0 -2 10,    0 -2 11,    0 -1  1,    0 -1  2,    0  0  6,    0  1  6,
                   0  2  1,    0  2  2,    0  2  3,    0  2  4,    0  2  5,    0  3  2,
                   0  3  7,    0  4  0,
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity .....          1.0 Low
PLAT948_ALERT_5_G Externally Supplied Scattering Factors       CIF          3 Note
PLAT969_ALERT_5_G The 'Henn et al.' R-Factor-gap value .....        3.404 Note
                Predicted wR2: Based on SigI**2  8.52 or SHELX Weight 27.47
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   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   9 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  12 ALERT level G = General information/check it is not something unexpected

   2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   7 ALERT type 2 Indicator that the structure model may be wrong or deficient
   7 ALERT type 3 Indicator that the structure quality may be low
   2 ALERT type 4 Improvement, methodology, query or suggestion
   3 ALERT type 5 Informative message, check
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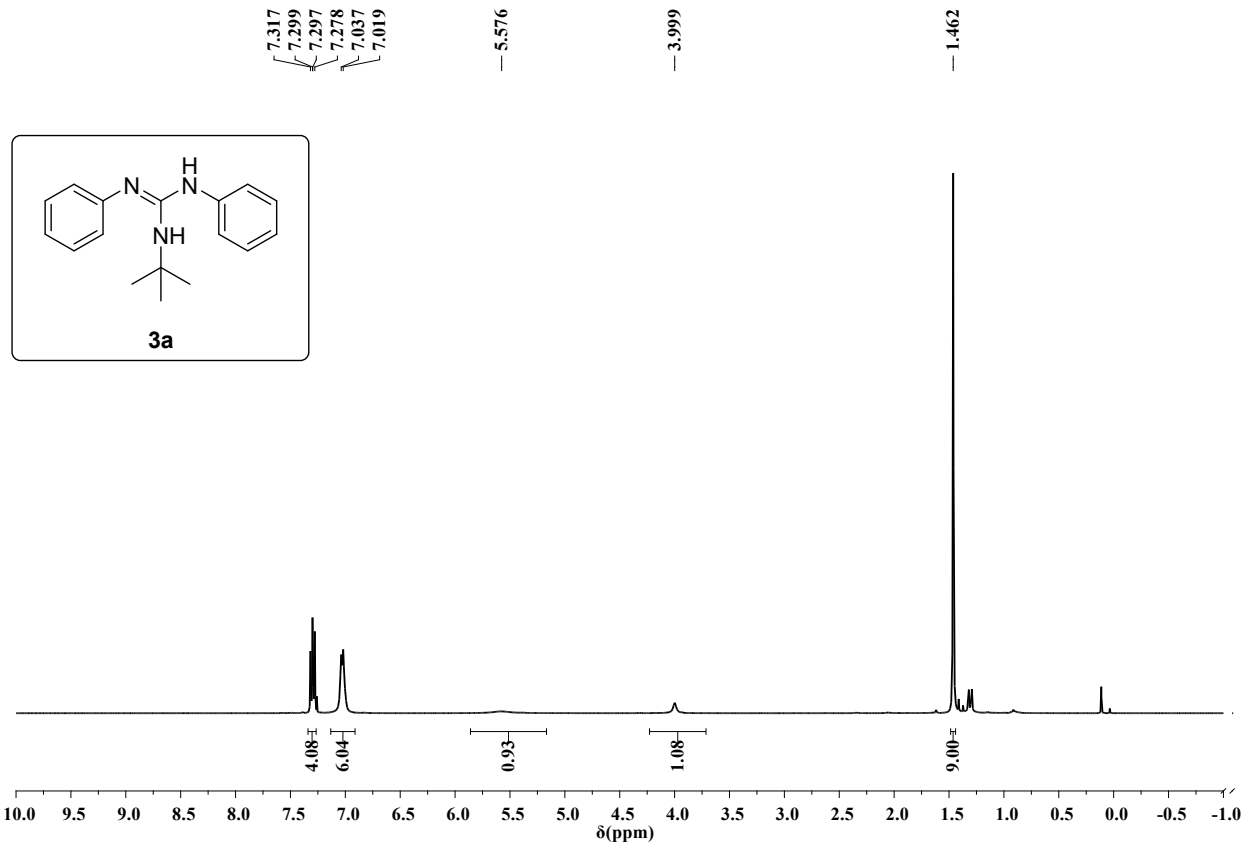
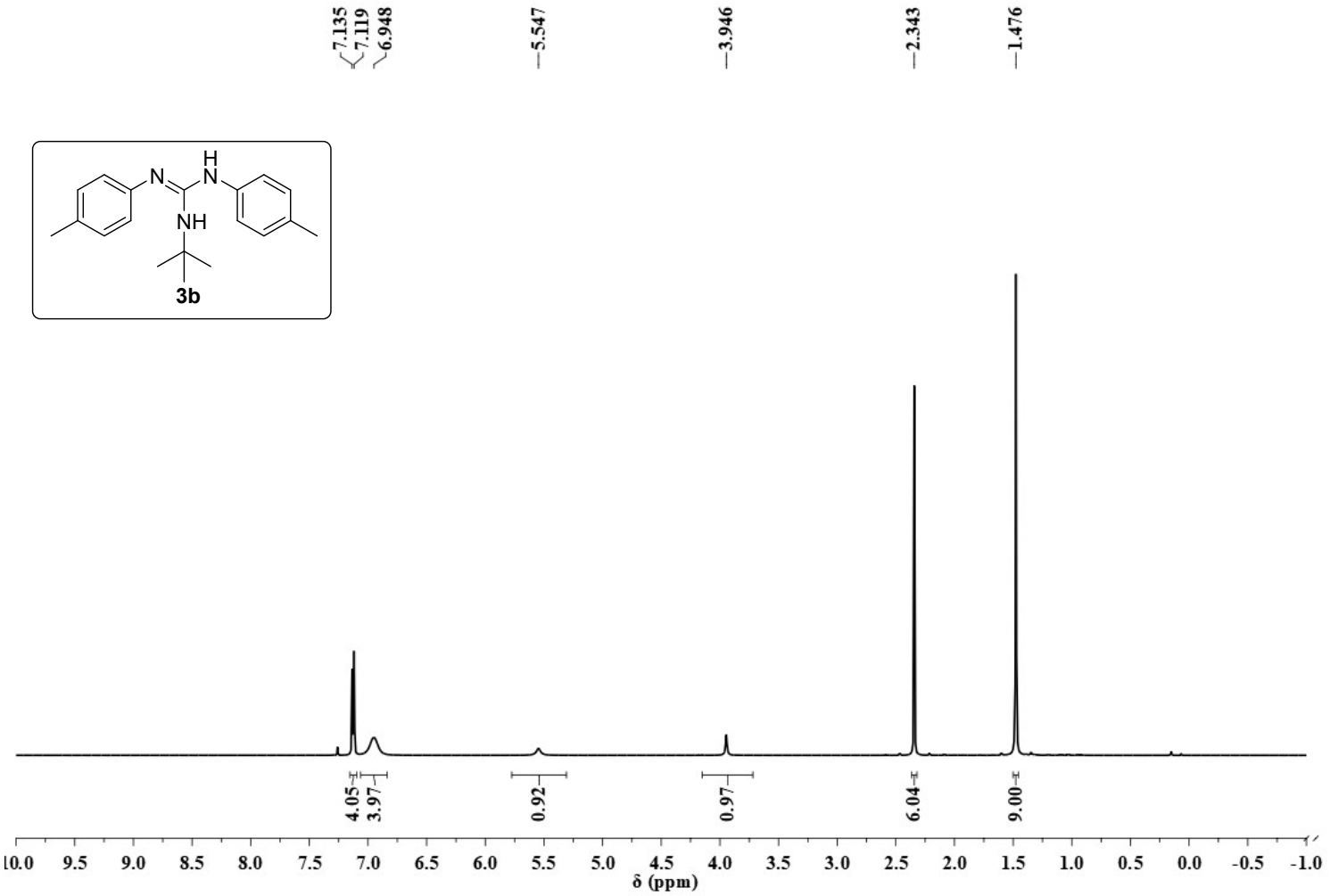
5. ^{1}H and ^{13}C NMR Spectra

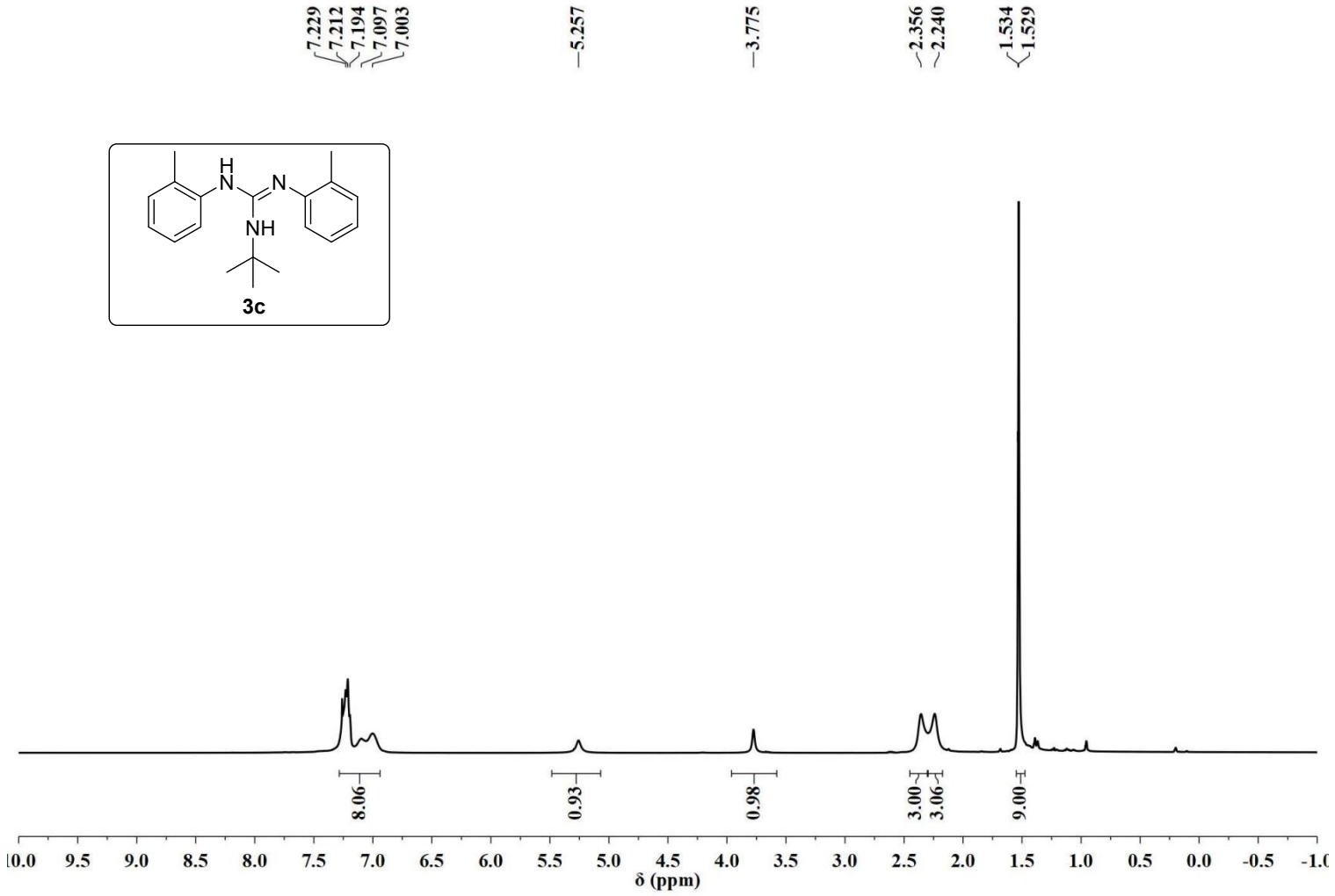
^{1}H NMR of 3a (400 MHz, $CDCl_3$)



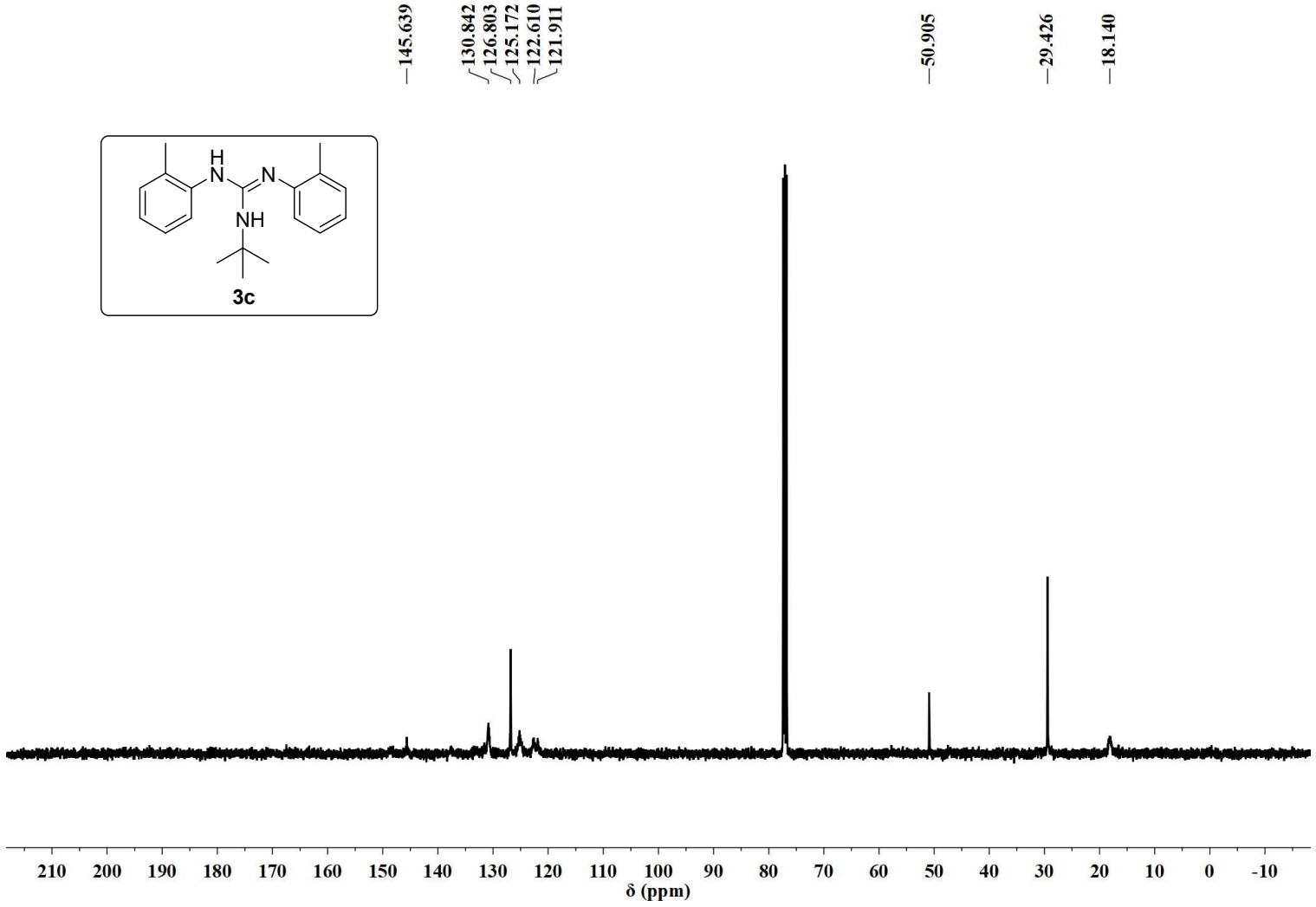
^{1}H NMR of 3b (400 MHz, $CDCl_3$)



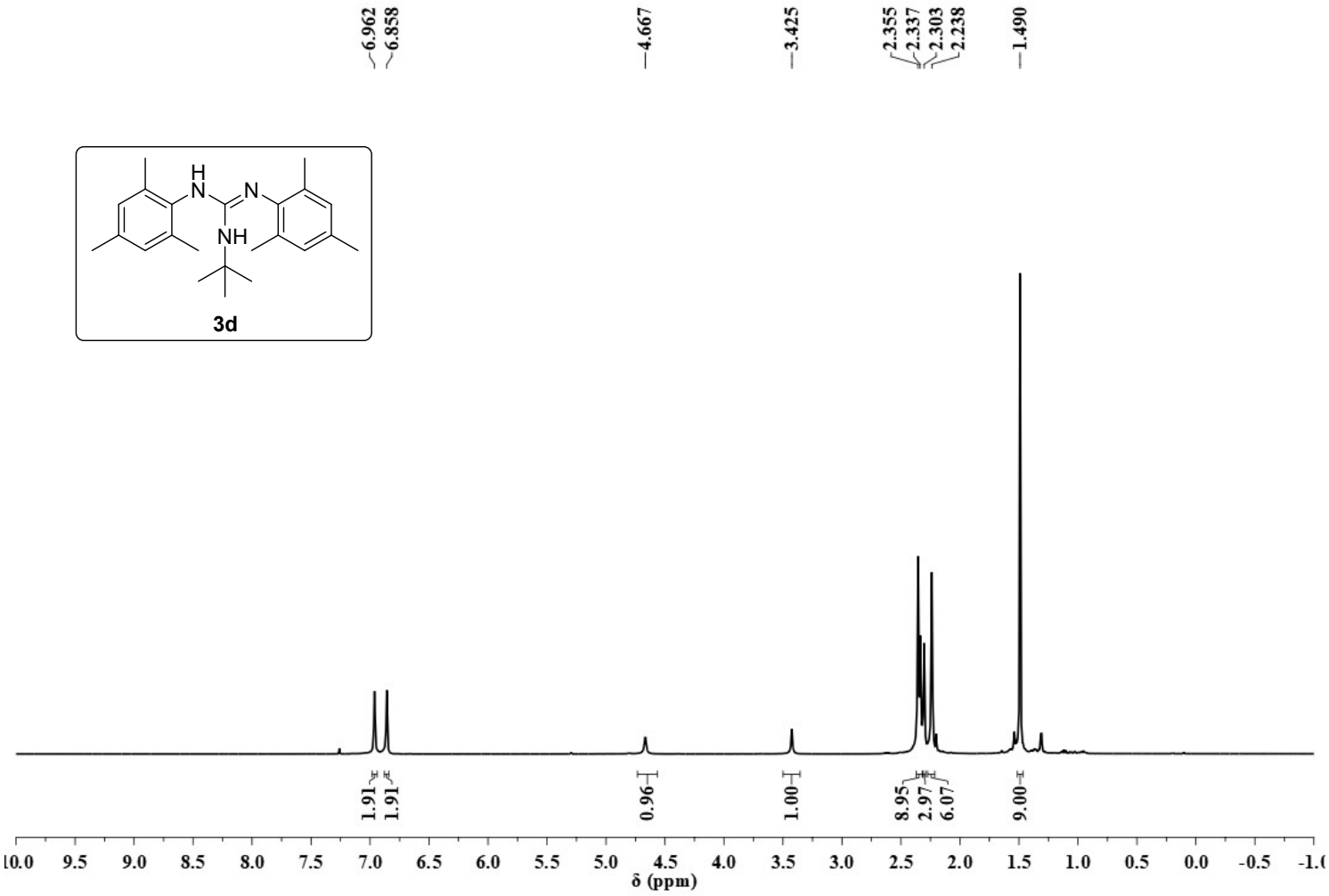
^{1}H NMR of 3c (400 MHz, $CDCl_3$)



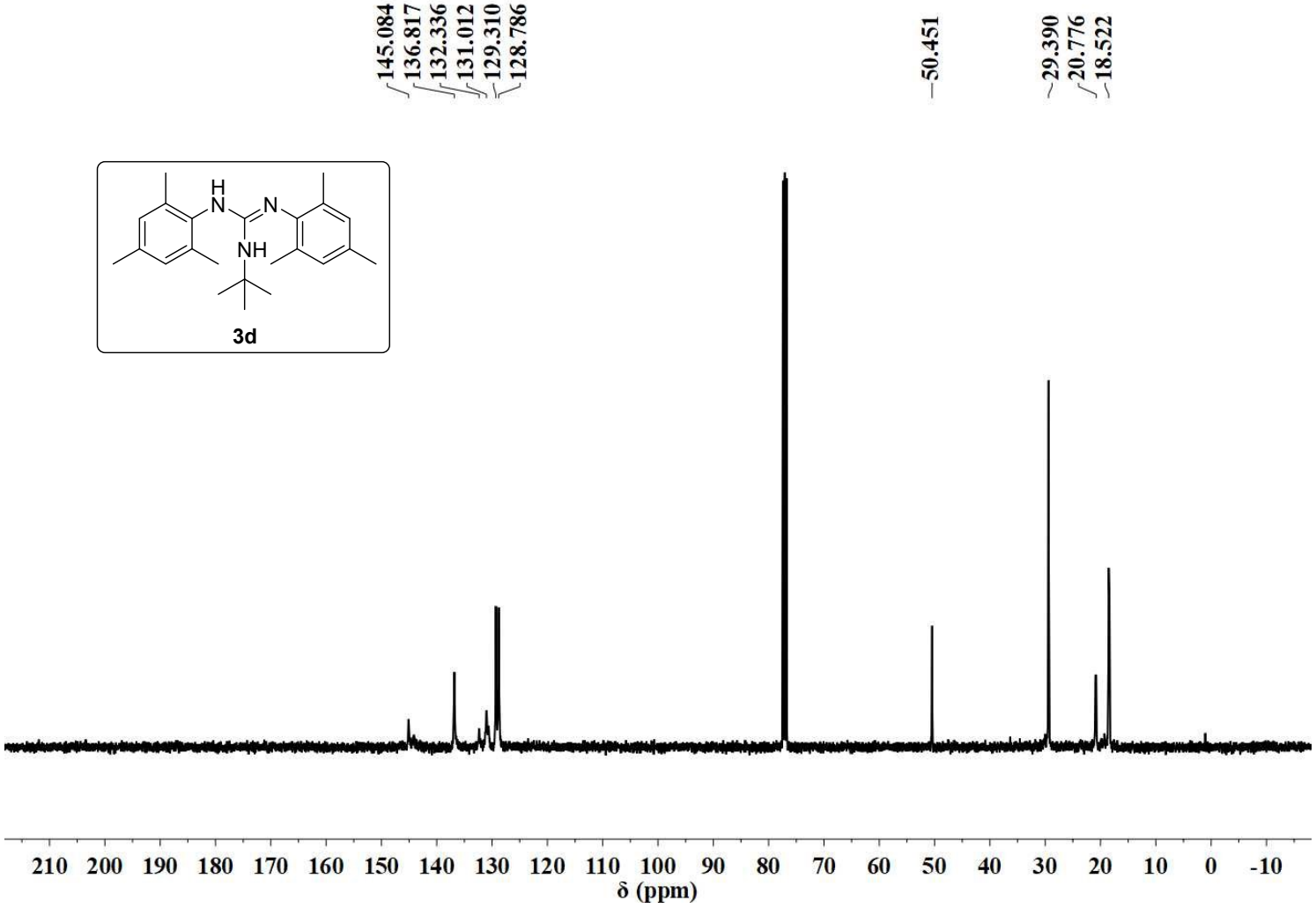
^{13}C NMR of 3c (101 MHz, $CDCl_3$)



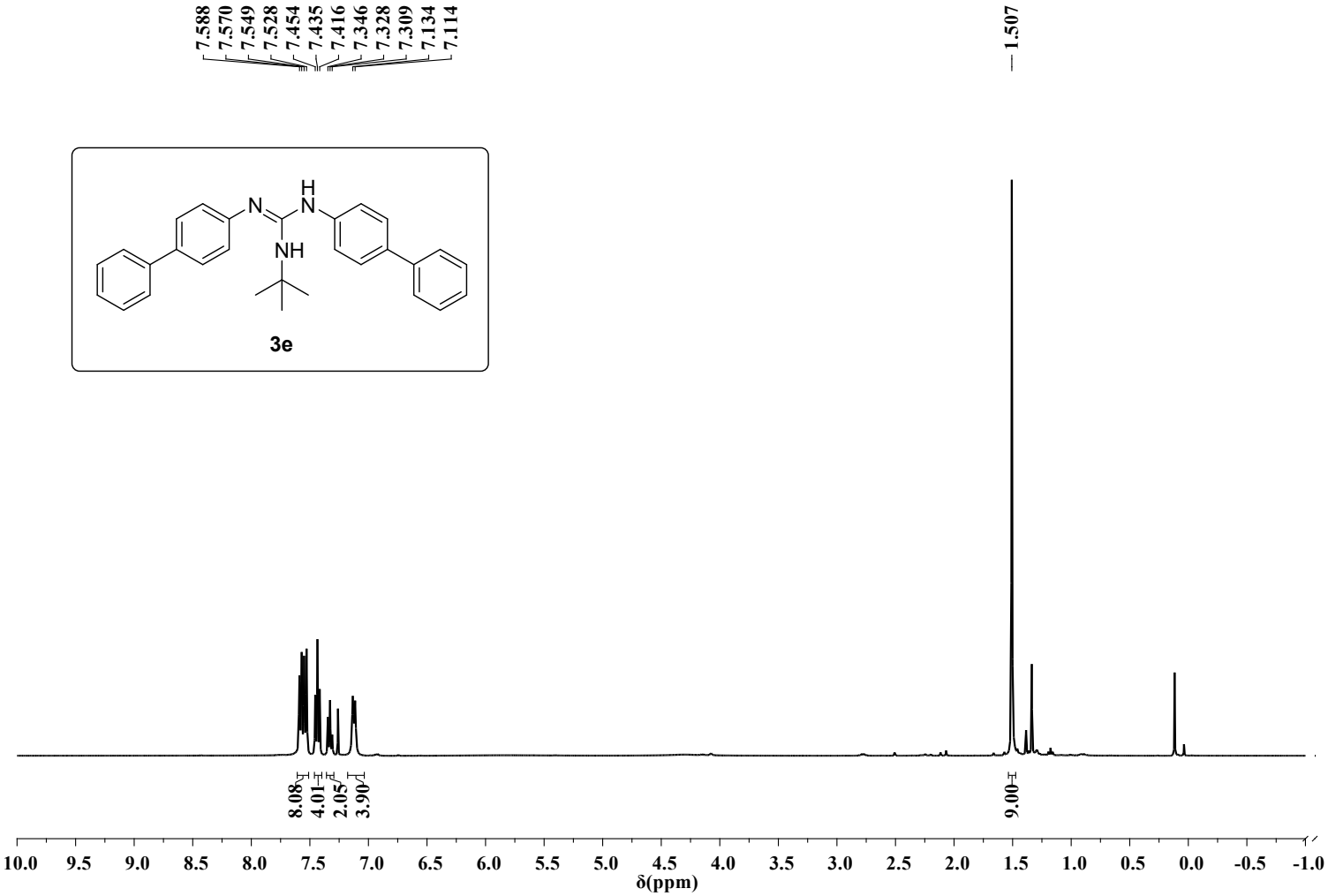
^{1}H NMR of 3d (400 MHz, $CDCl_3$)



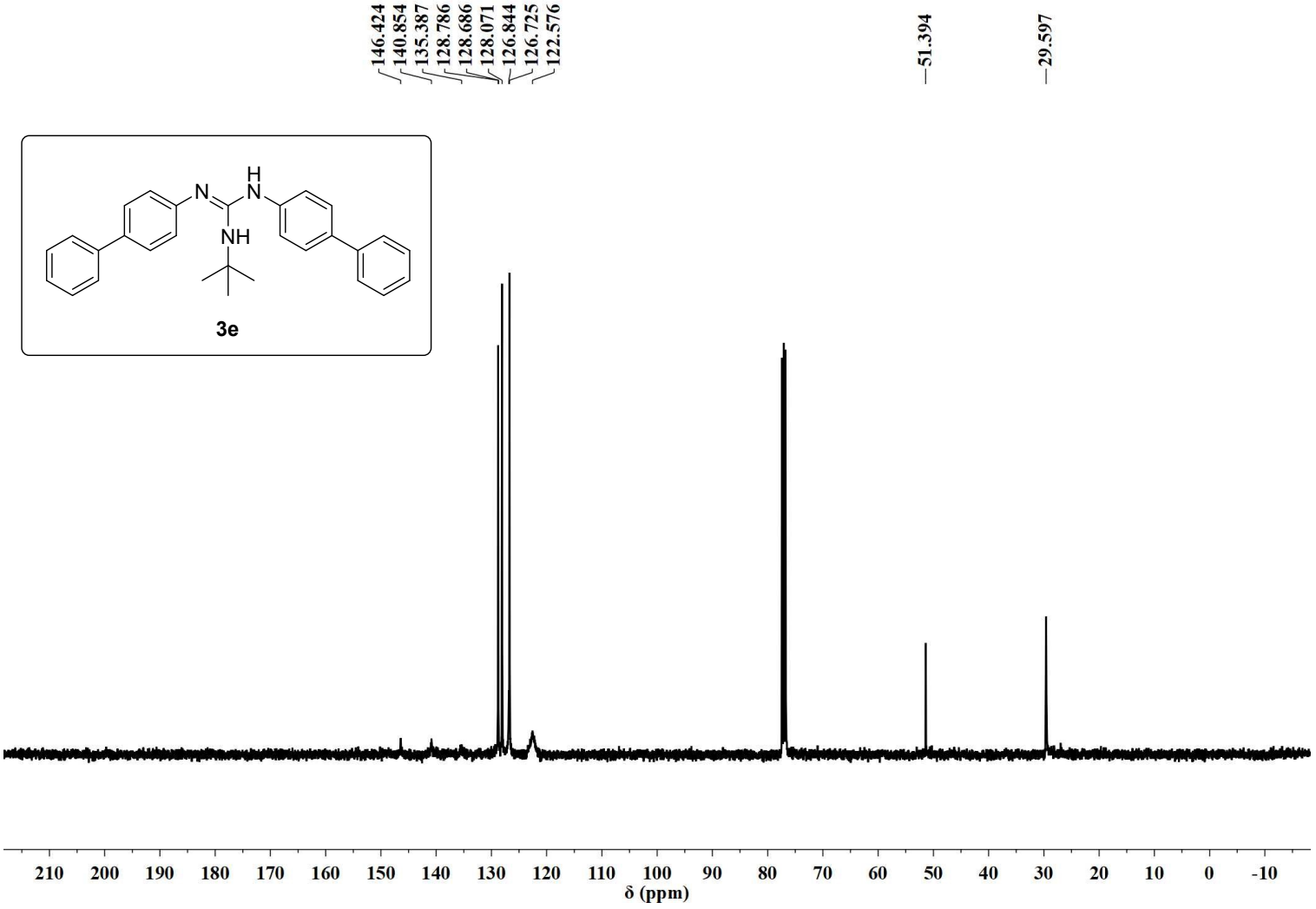
^{13}C NMR of 3d (101 MHz, $CDCl_3$)



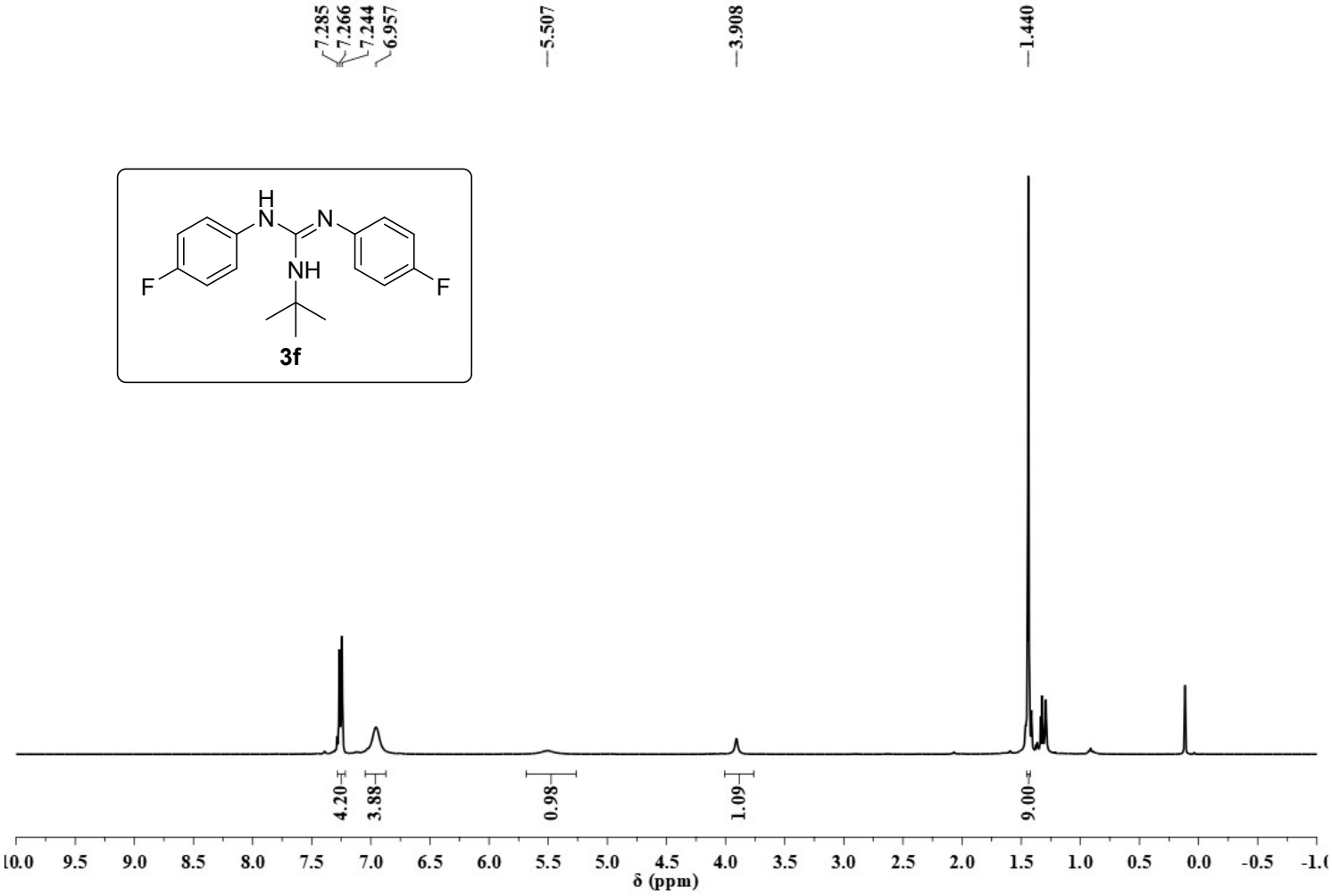
^{1}H NMR of 3e (400 MHz, $CDCl_3$)



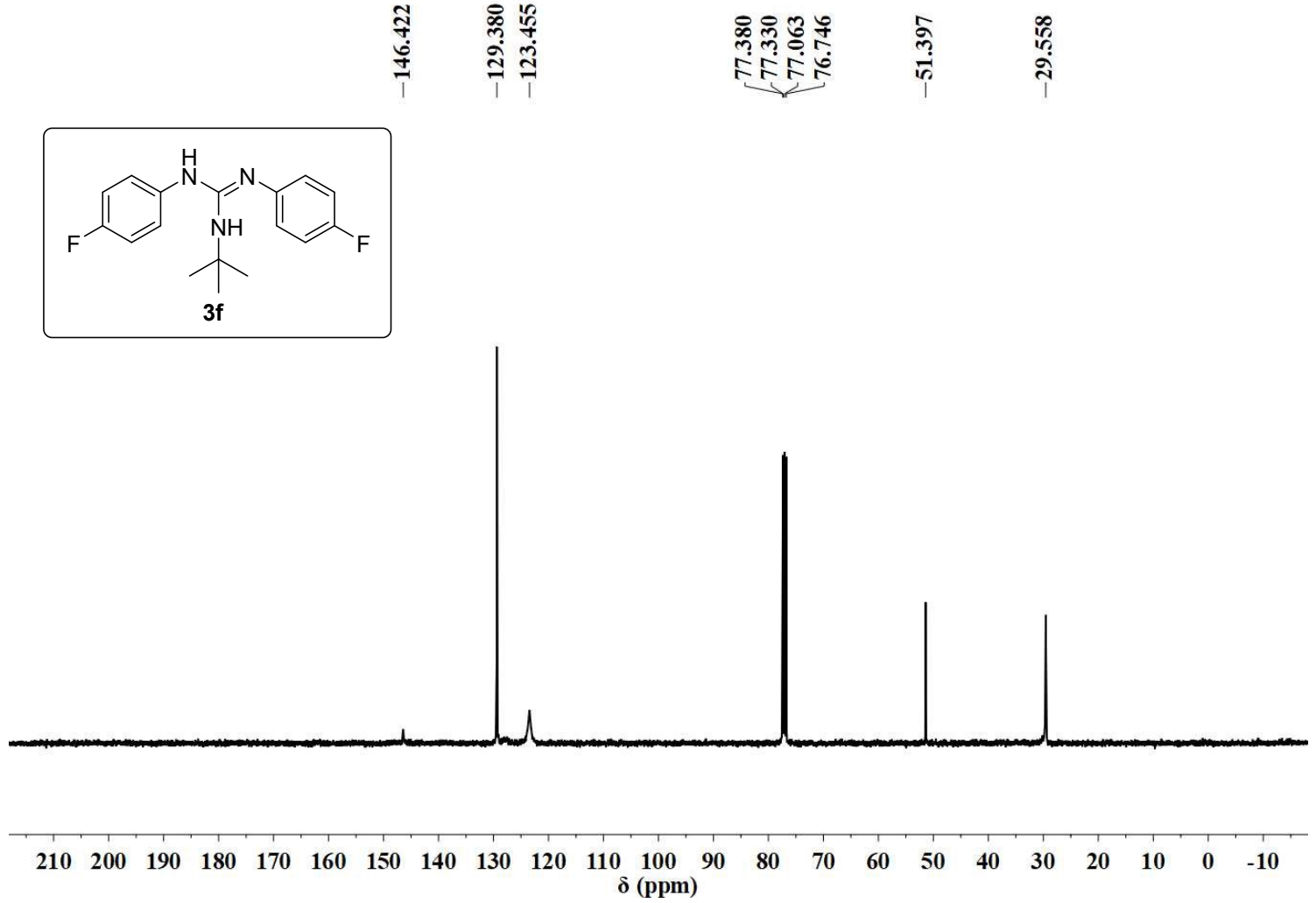
^{13}C NMR of 3e (101 MHz, $CDCl_3$)



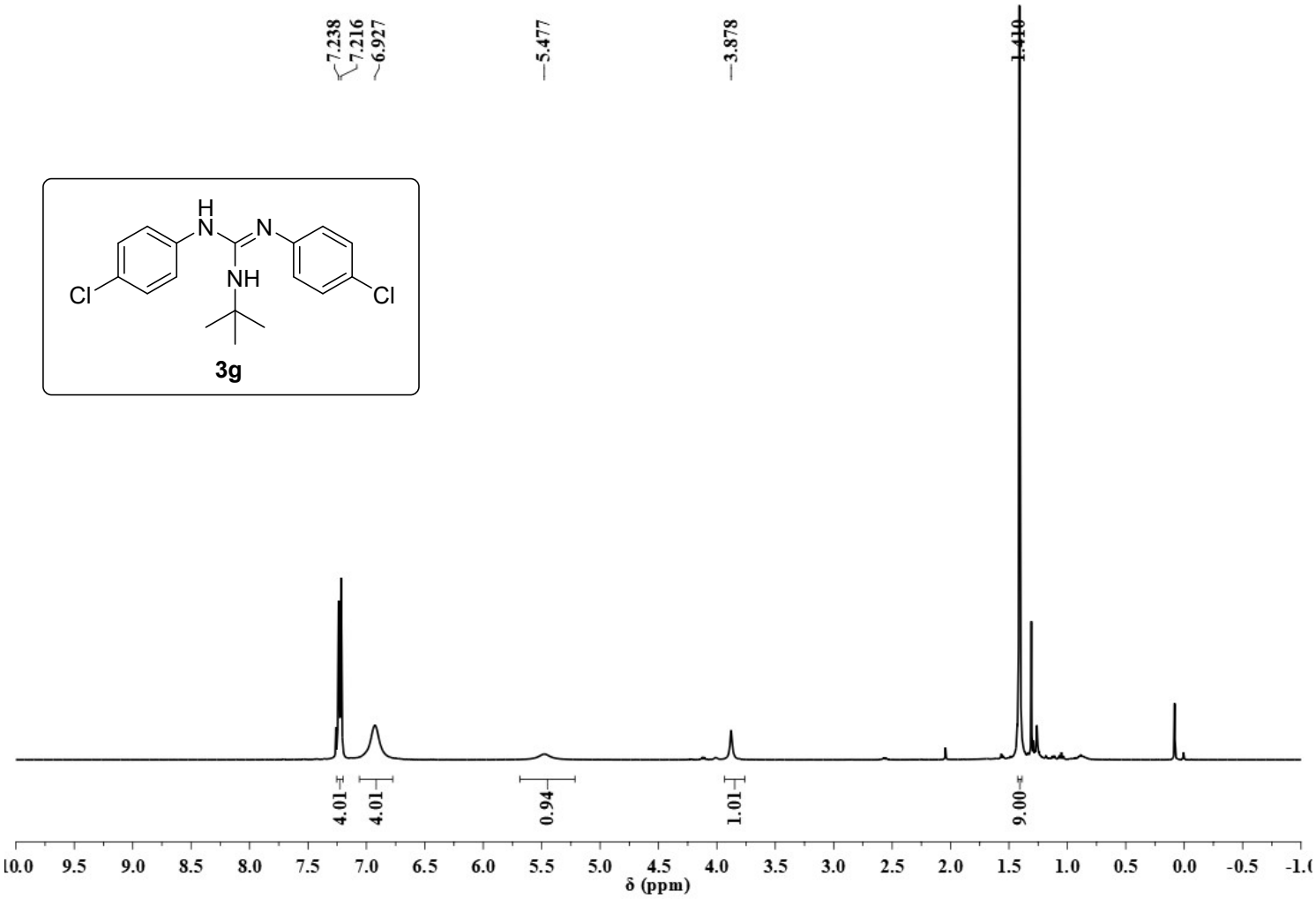
^{1}H NMR of 3f (400 MHz, $CDCl_3$)



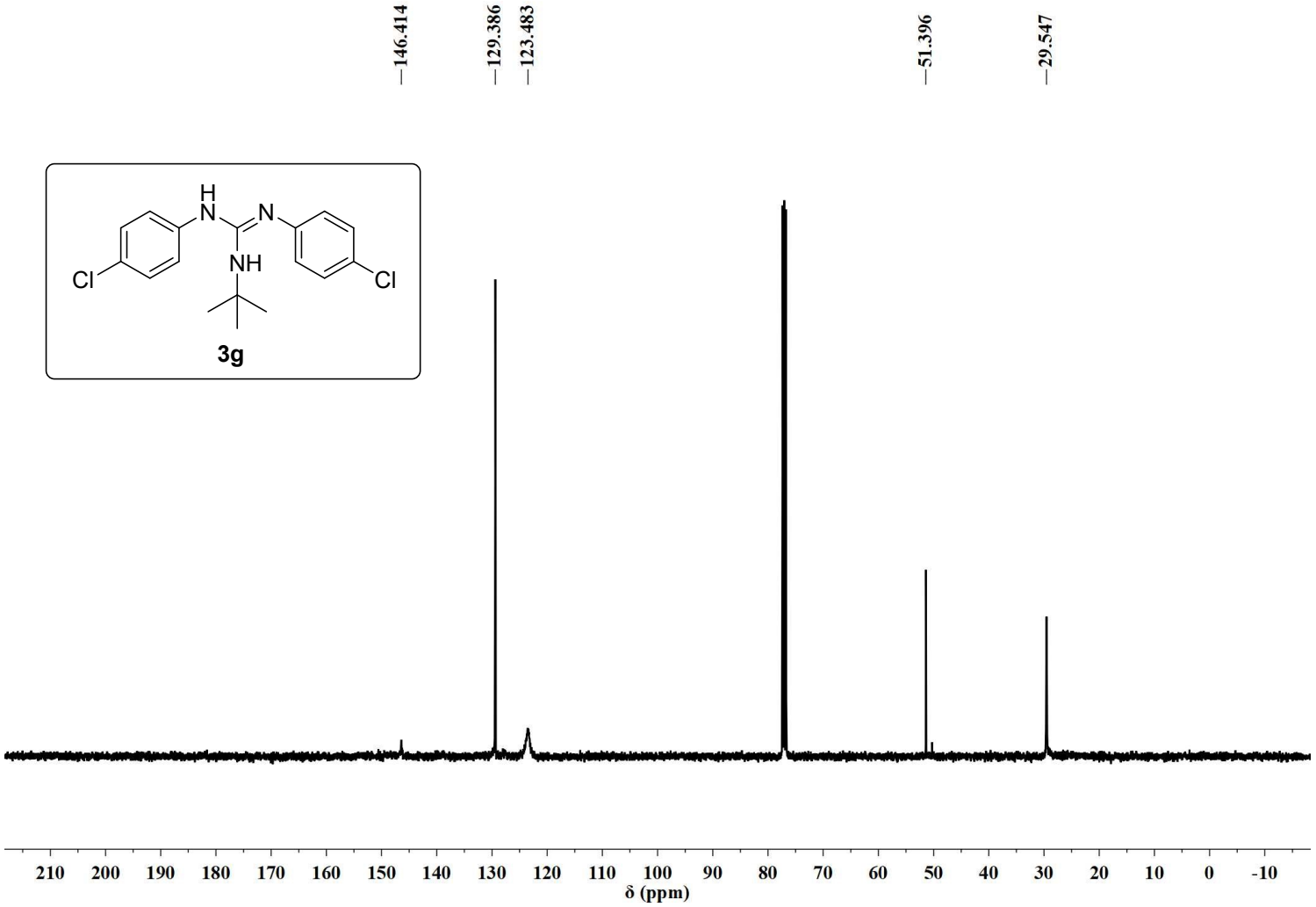
^{13}C NMR of 3f (101 MHz, $CDCl_3$)



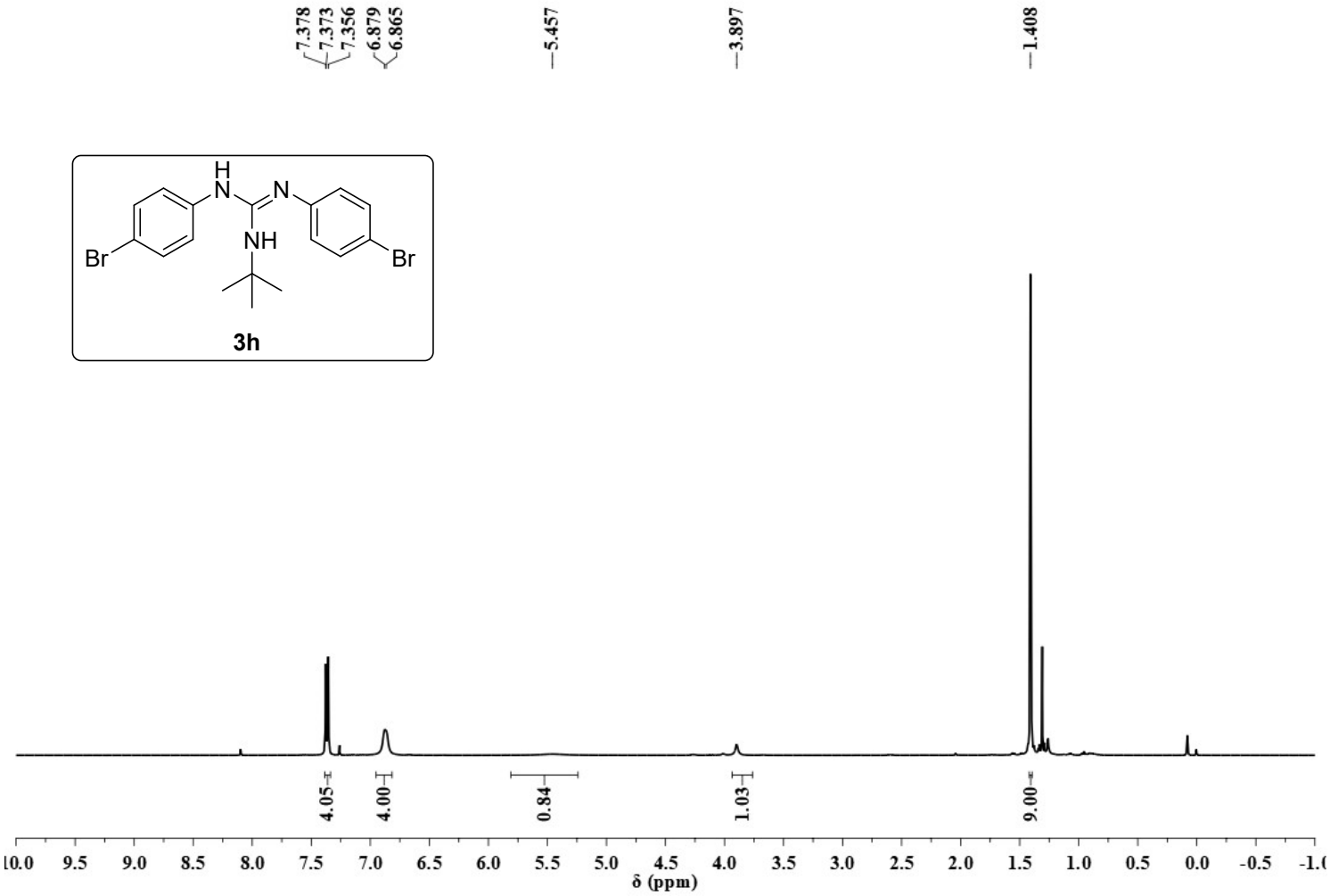
^{1}H NMR of 3g (400 MHz, $CDCl_3$)



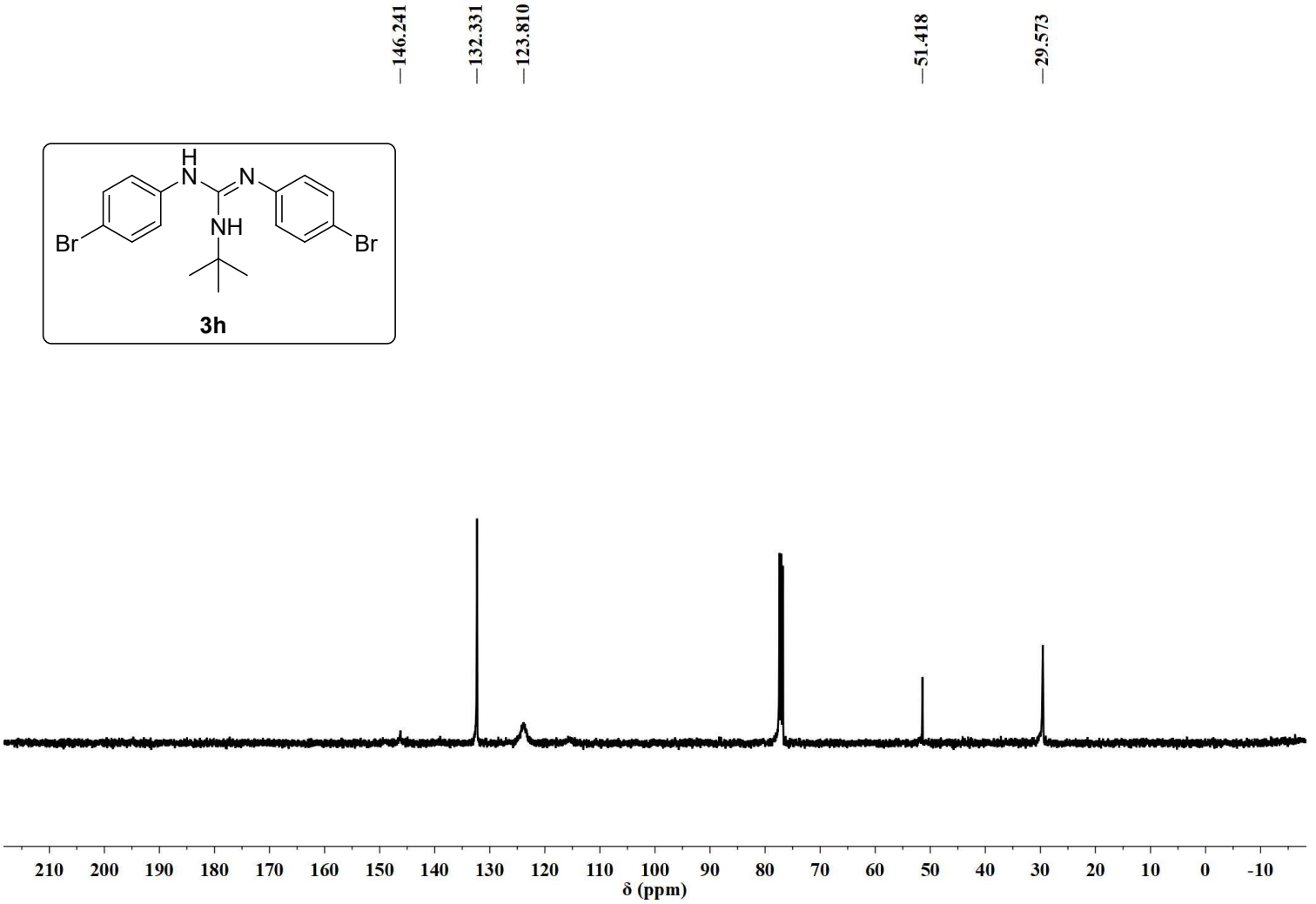
^{13}C NMR of 3g (101 MHz, $CDCl_3$)



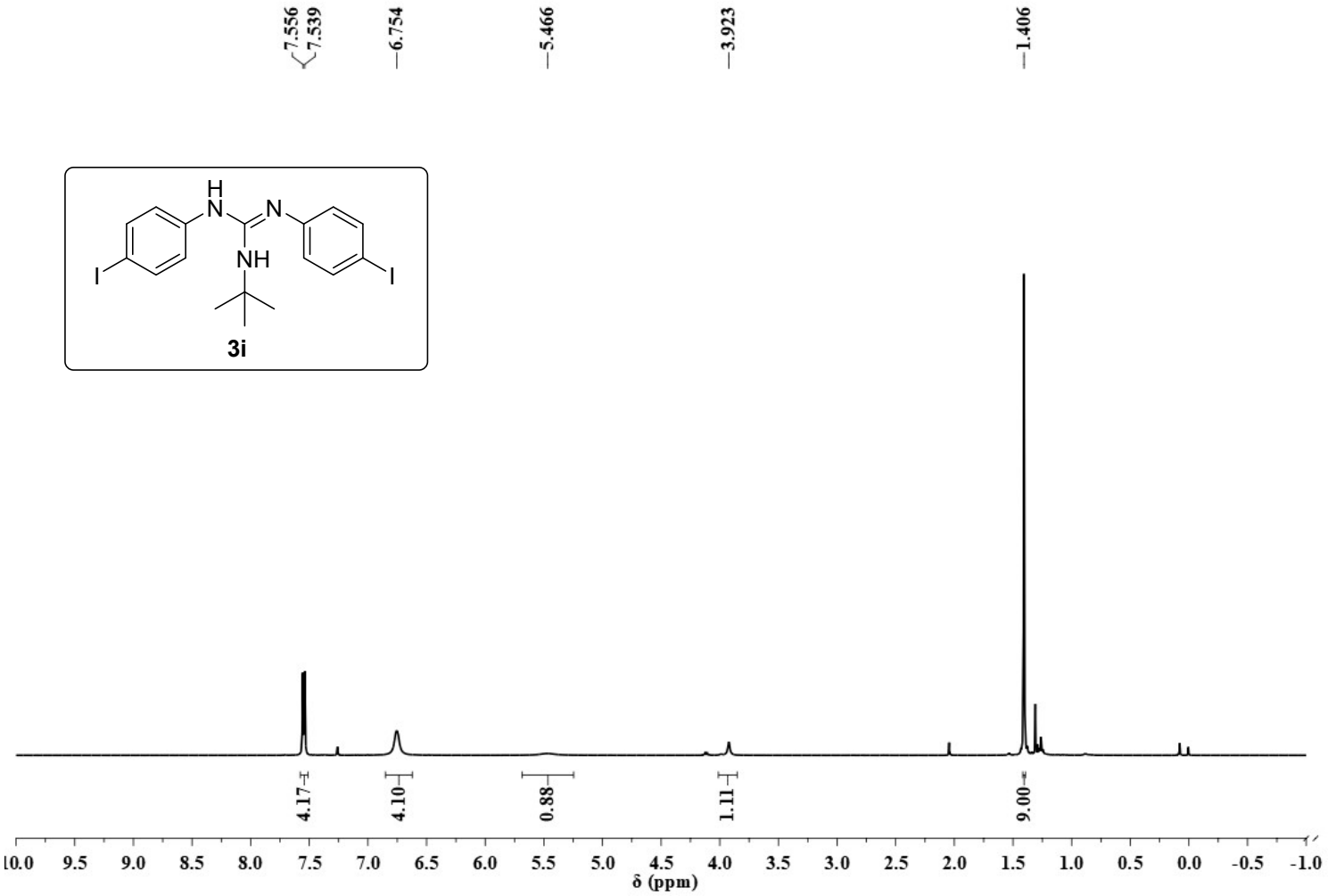
^{1}H NMR of 3h (400 MHz, $CDCl_3$)



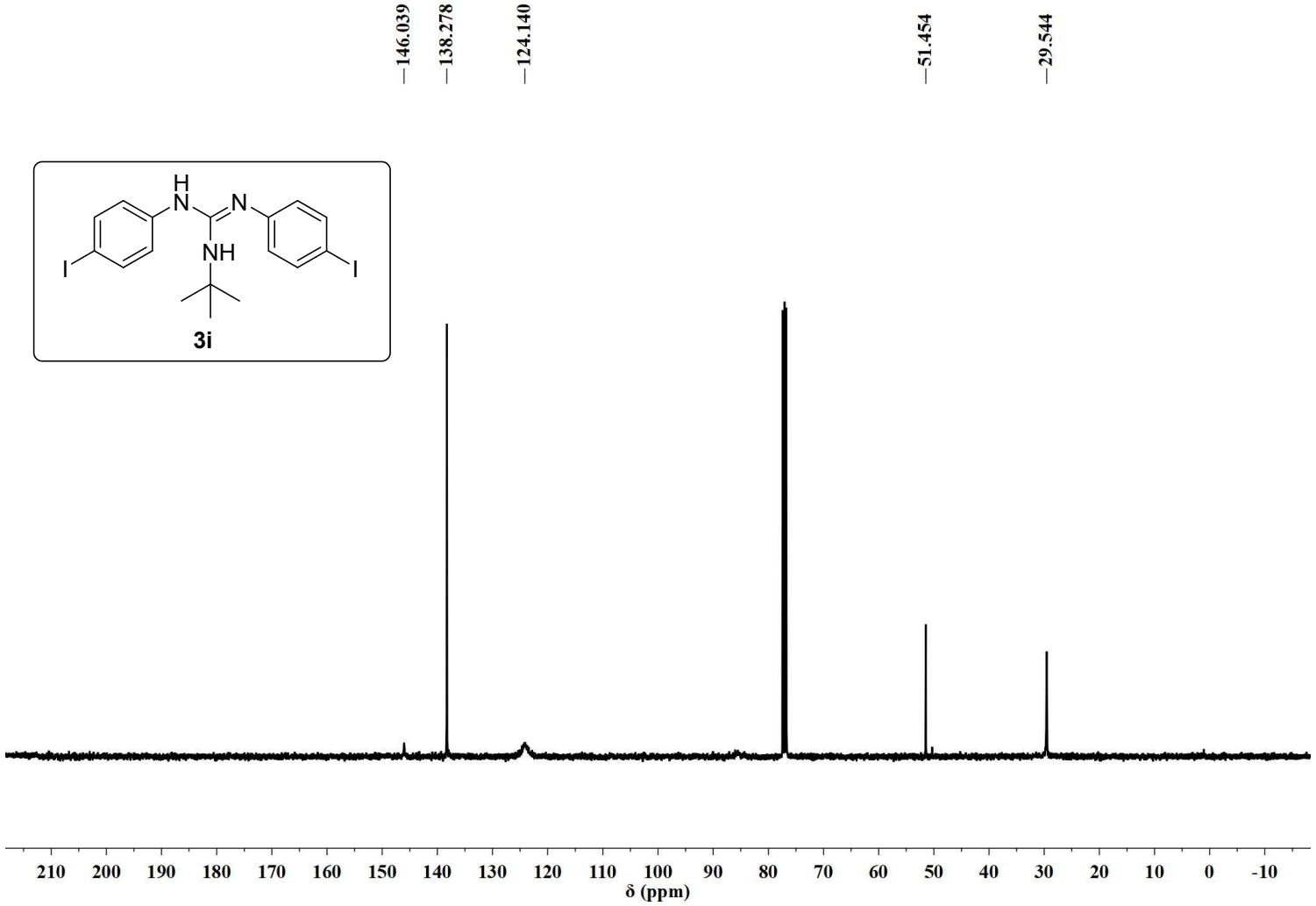
^{13}C NMR of 3h (101 MHz, $CDCl_3$)



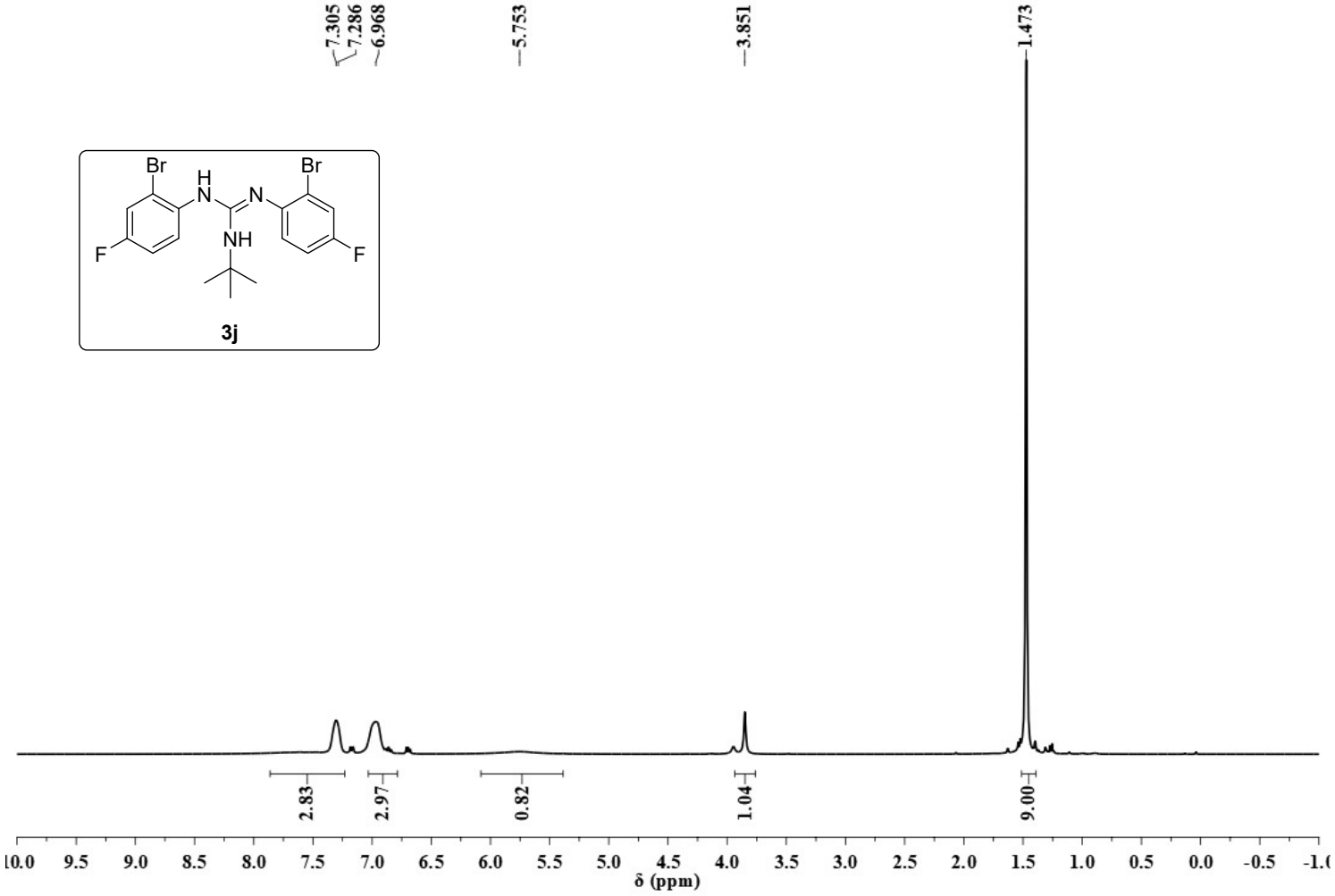
^{1}H NMR of 3i (400 MHz, $CDCl_3$)



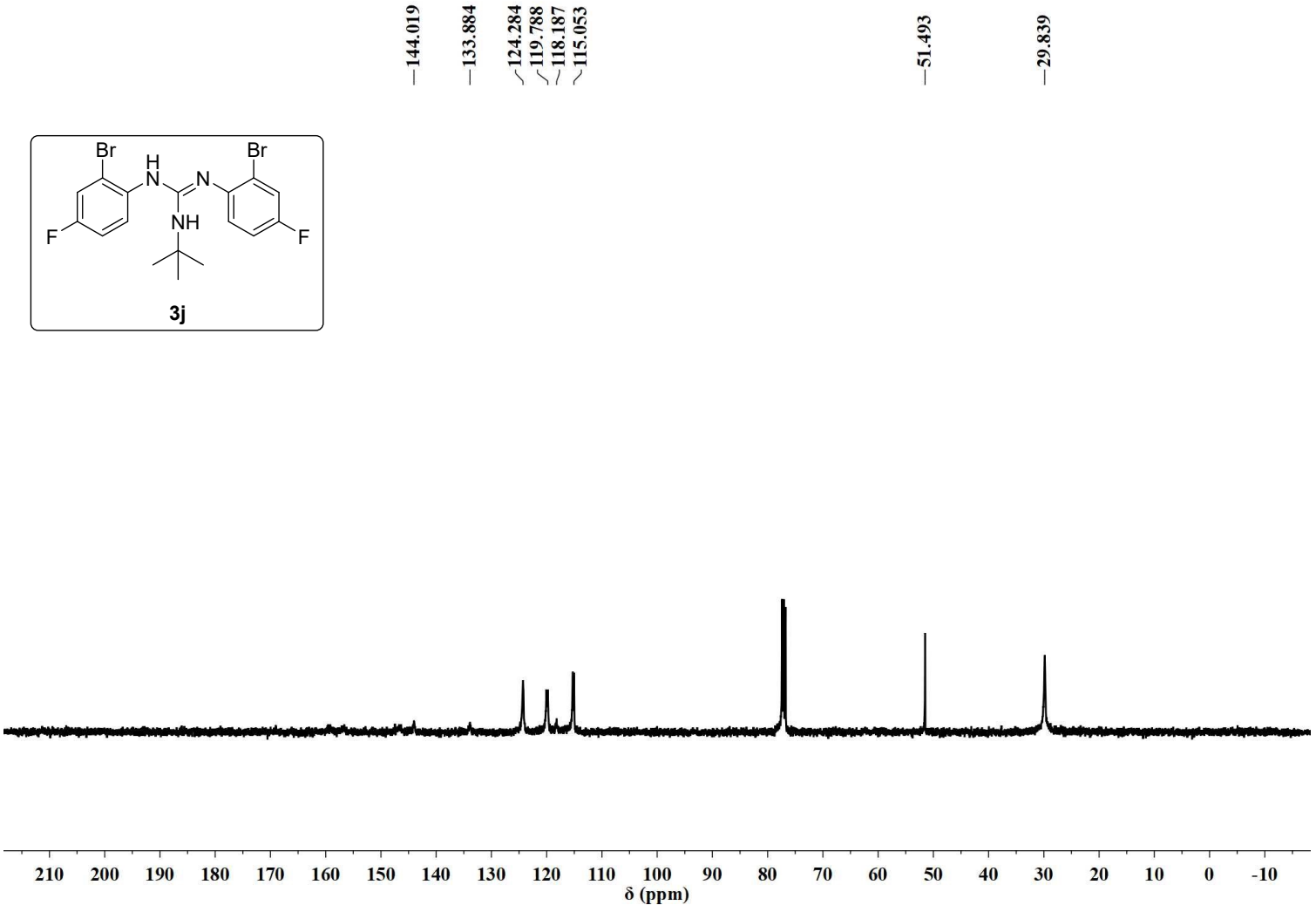
^{13}C NMR of 3i (400 MHz, $CDCl_3$)



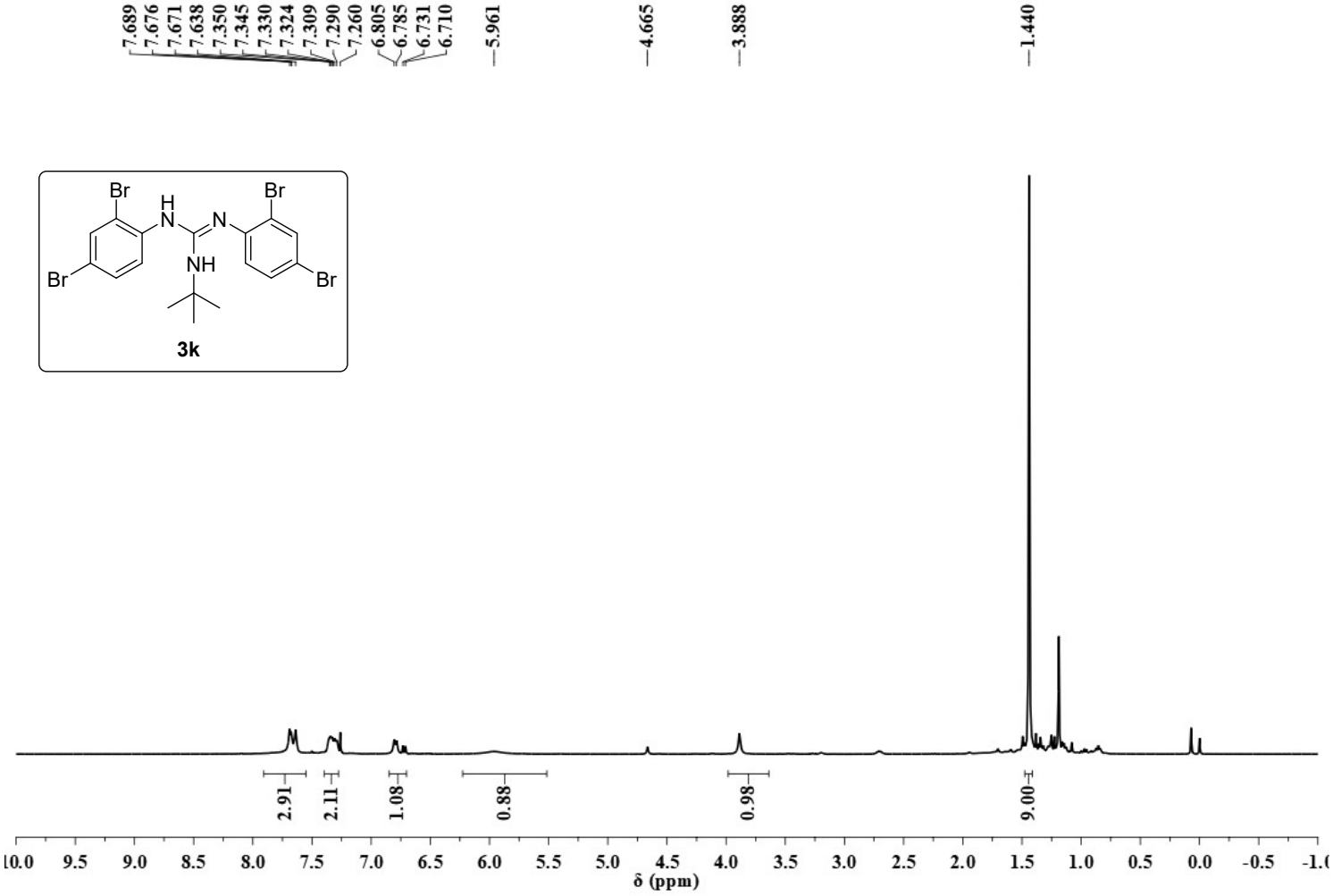
^{1}H NMR of 3j (400 MHz, $CDCl_3$)



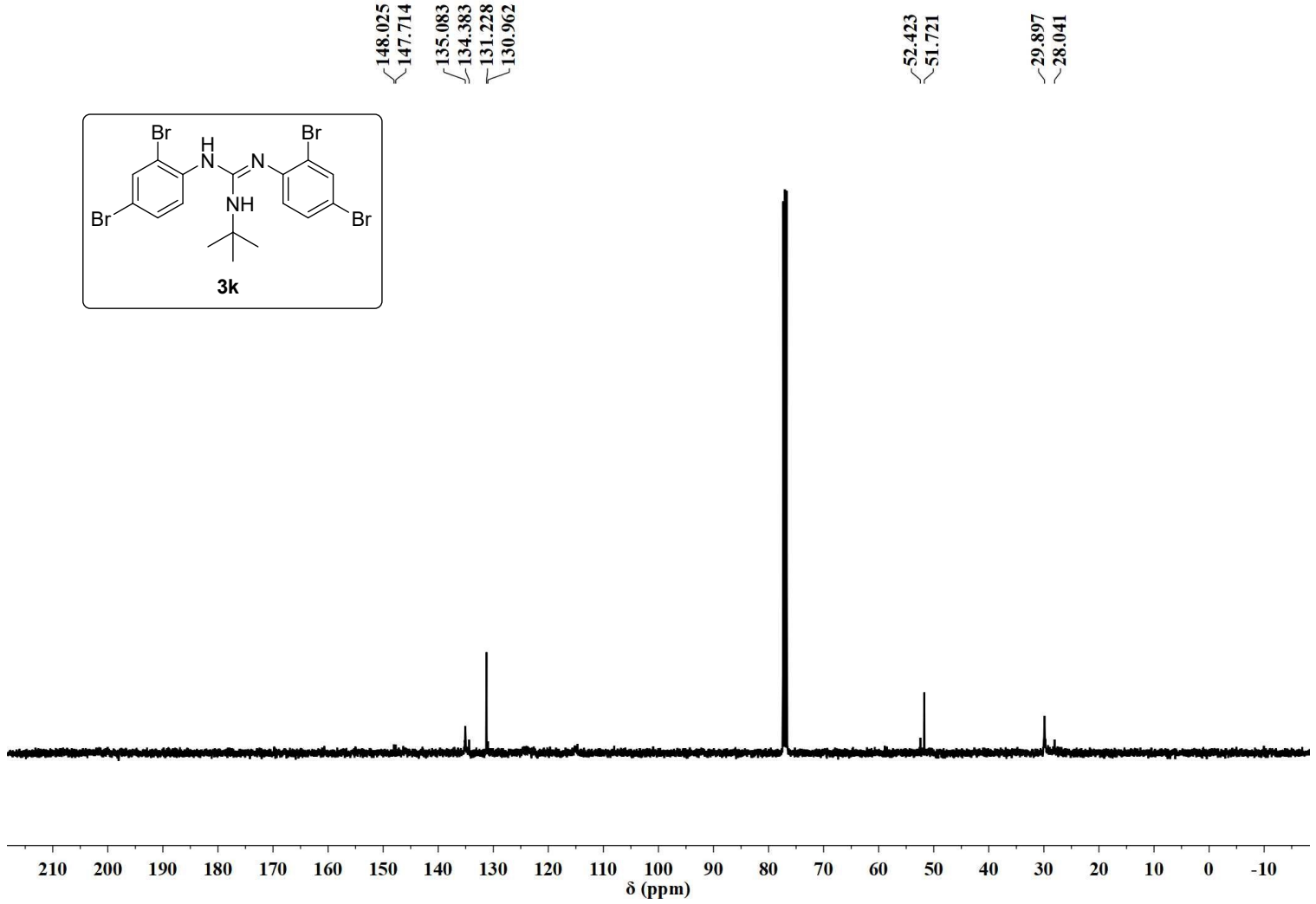
^{13}C NMR of 3j (101 MHz, $CDCl_3$)



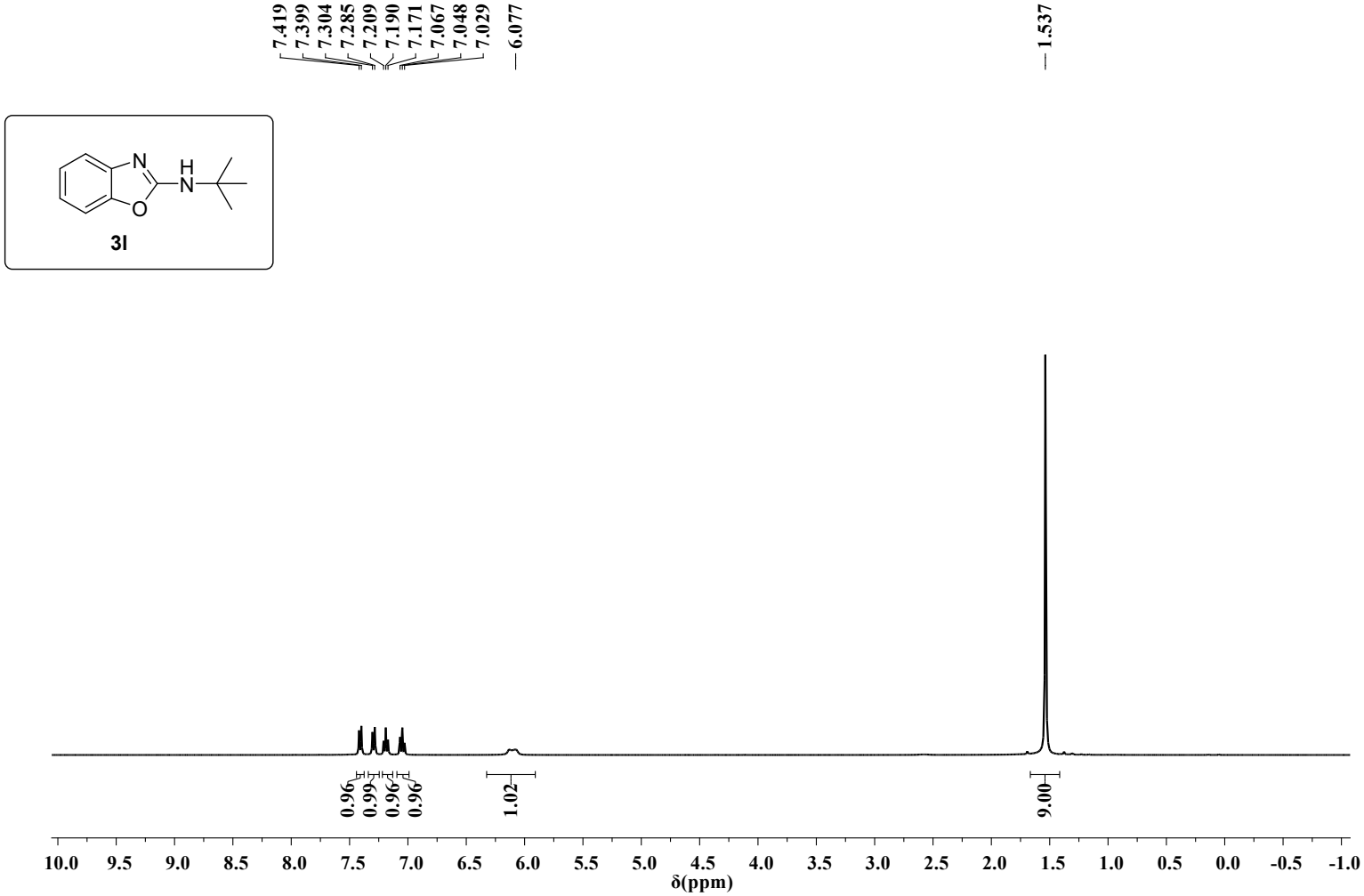
^{1}H NMR of 3k (400 MHz, $CDCl_3$)



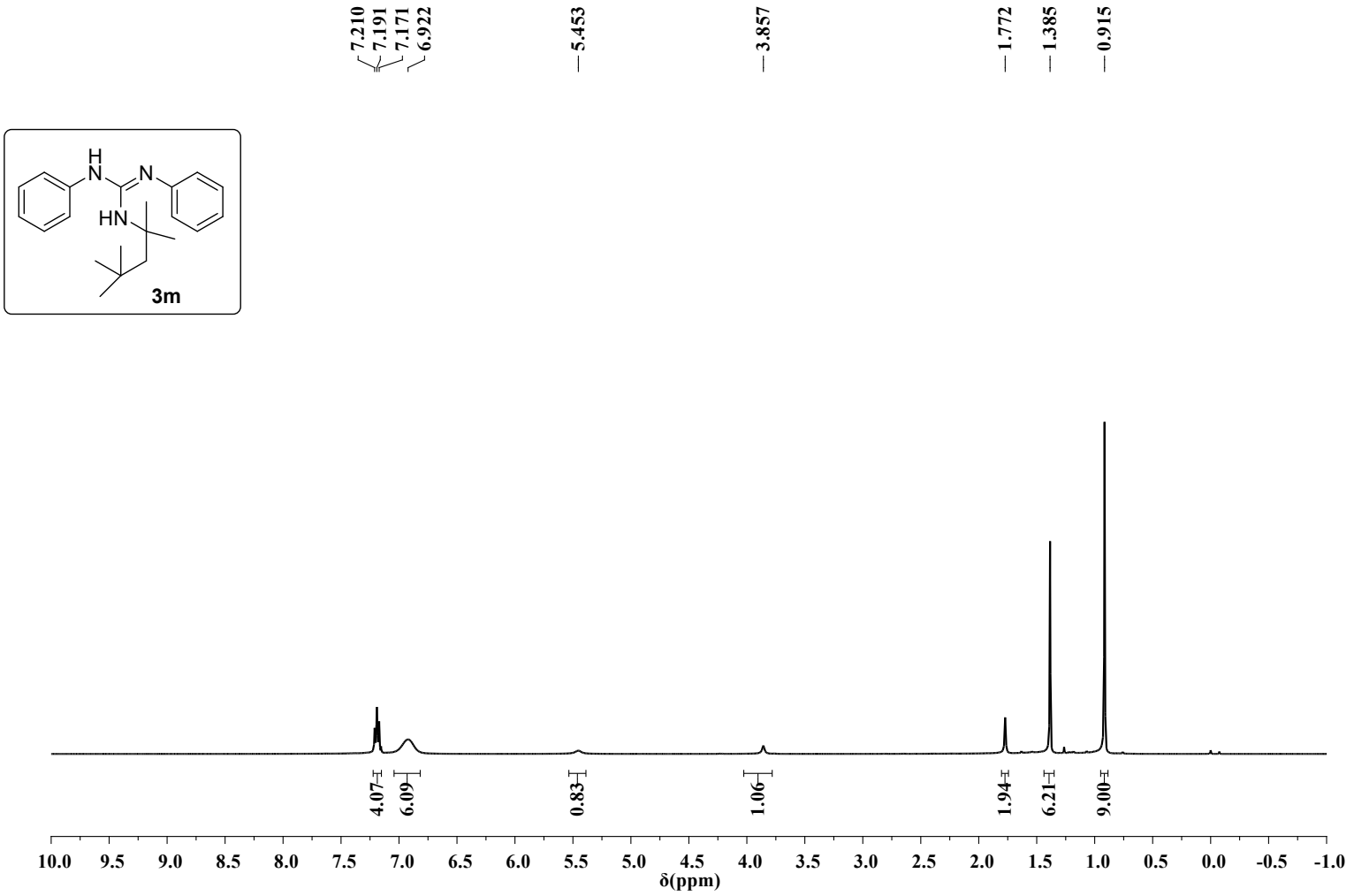
^{13}C NMR of 3k (101 MHz, $CDCl_3$)



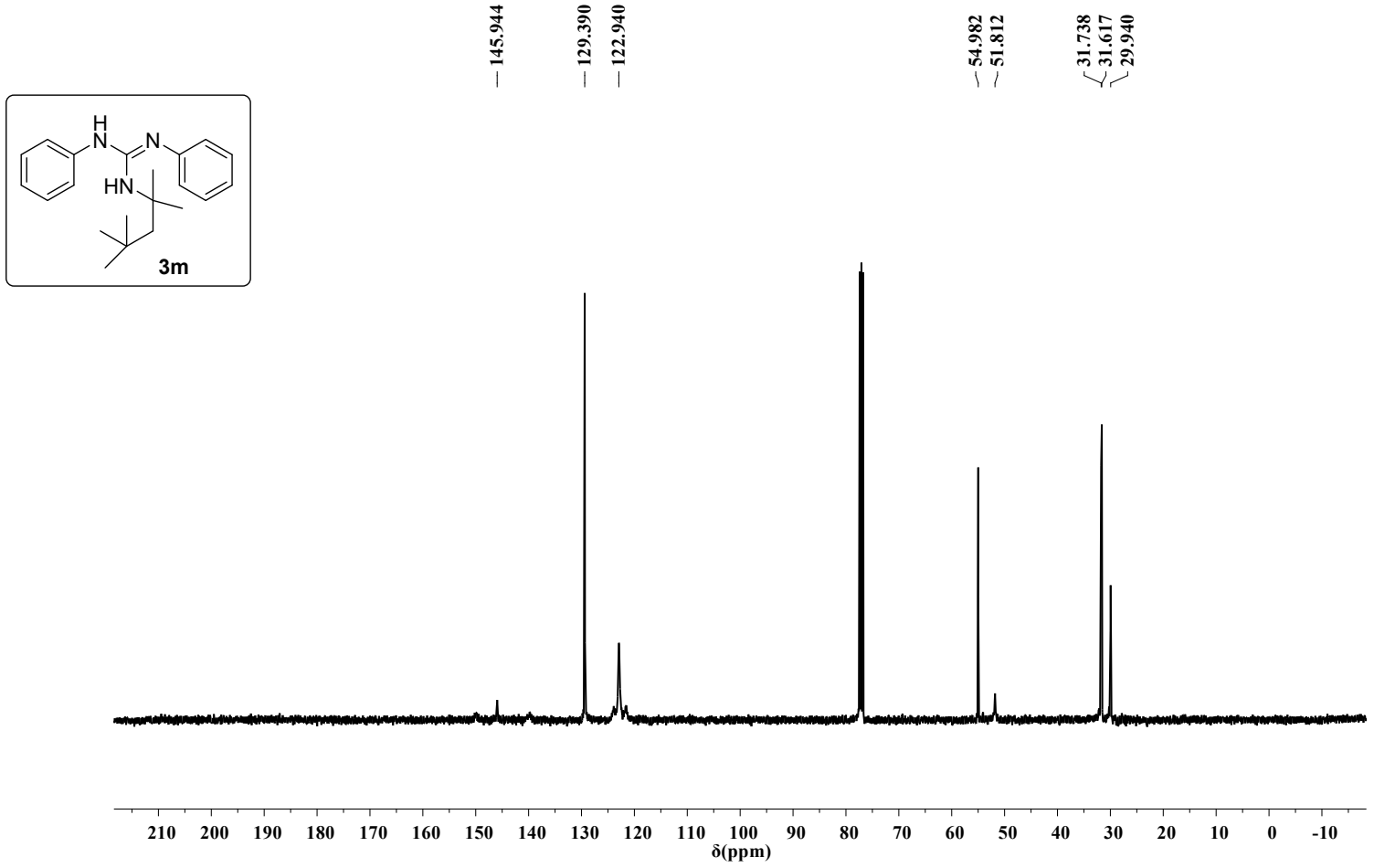
^{1}H NMR of 3l (400 MHz, $CDCl_3$)



^{1}H NMR of 3m (400 MHz, $CDCl_3$)



^{13}C NMR of 3m (101 MHz, $CDCl_3$)



^{1}H NMR of 4a (400 MHz, $CDCl_3$)