Supporting Information

Copper-Catalyzed Nucleophilic Trifluoromethylation of Benzylic Chlorides

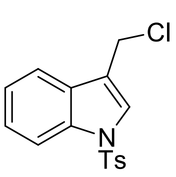
Yoshihiro Miyake, Shin-ichi Ota, Masashi Shibata, Kazunari Nakajima and Yoshiaki Nishibayashi*

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan

General Methods.

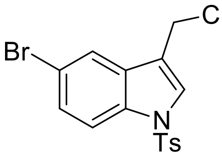
^{1}H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were measured on a JEOL Excalibur 270 spectrometer using $CDCl_3$ as solvent. ^{19}F NMR (471 MHz) spectra were recorded on a JEOL JNM-ECP 500 spectrometer. Elemental analyses were performed at Microanalytical Center of The University of Tokyo. Mass spectra were measured on a JEOL JMS-700 mass spectrometer. Specific rotations were measured on a JASCO DIP-1000 polarimeter.

All reactions were carried out under dry nitrogen atmosphere. Solvents were dried by the usual methods, then distilled under N_2 and degassed before use. CF_3SiMe_3 is commercially available and was distilled before use. Potassium fluoride (KF) was dried under vacuum at 190 °C overnight and stored in a glove box. Copper (I) thiophene 2-carboxylate (CuTC) was prepared according to the reported method.[S1] Benzylic chlorides **1a** and **1b** were commercially available. Trifluoromethylated product **2a**[S2] was a known compound. Benzylic chlorides **1c**,[S3] **1e**,[S4] **1g**,[S5] **1h**,[S5] **1j**,[S6] and **1k**[S7] were prepared by the reaction of corresponding alcohols with $SOCl_2$. Benzylic chlorides **1d**,[S8] **1f**,[S9] and **1i**[S10] were prepared from corresponding alcohols by the reported methods. **(*R*)-1i** was prepared by the reaction of the corresponding (*S*)-alcohol (96% *ee*) with $POCl_3$ and pyridine.[S11]



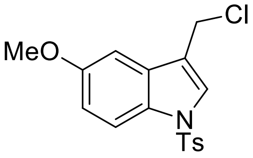
1f

1f:[S9] A white solid. ^{1}H NMR δ 7.96-7.99 (m, 1H), 7.76-7.79 (m, 2H), 7.61-7.65 (m, 2H), 7.22-7.38 (m, 4H), 4.73 (s, 2H), 2.35 (s, 3H). ^{13}C NMR δ 145.2, 135.3, 135.1, 130.0, 129.0, 126.9, 125.2, 125.0, 123.4, 119.7, 118.8, 113.7, 37.3, 21.6.



1g

1g:[S5] A white solid. ^{1}H NMR δ 7.74-7.86 (m, 4H), 7.60 (s, 1H), 7.44 (dd, *J* = 8.8 and 1.9 Hz, 1H), 7.24-7.27 (m, 2H), 4.68 (s, 2H), 2.36 (s, 3H). ^{13}C NMR δ 145.6, 134.8, 134.0, 130.7, 130.1, 128.2, 126.9, 126.1, 122.6, 118.2, 117.1, 115.2, 36.9, 21.6.



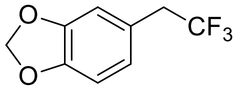
1h

1h:[S5] A white solid. ^{1}H NMR δ 7.86 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.56 (s, 1H), 7.21-7.26 (m, 2H), 6.94-7.04 (m, 2H), 4.70 (s, 2H), 3.84 (s, 3H), 2.34 (s, 3H). ^{13}C NMR δ 156.5, 145.1, 135.0, 130.0, 129.9, 126.8, 125.7, 118.7, 114.7, 114.4, 102.0, 55.7, 37.4, 21.5.

Copper-Catalyzed Trifluoromethylation of Benzylic Chlorides (1)

A typical experimental procedure for the reaction of *p*-methoxybenzyl chloride (**1a**) with CF_3SiMe_3 is described below. In a 20 mL Schlenk flask were placed CuTC (4.7 mg, 0.025 mmol) and KF (87.1 mg, 1.5 mmol). Anhydrous and degassed THF (3.0 mL) was added, and then the mixture was magnetically stirred at room temperature. After the addition of **1a** (78.8 mg, 0.50 mmol) and CF_3SiMe_3 (220 μL, 1.5 mmol), the reaction flask was kept at 60 °C for 48 h. The solution was poured into water (5 mL) and the resulting mixture was extracted with diethyl ether (30 mL x 3). The combined extracts were washed with brine, and dried over anhydrous $MgSO_4$. After the concentration under reduced pressure, the resulting residue was purified by column chromatography (SiO_2, eluent: hexane /AcOEt = 90 / 10) to give **2a** as a yellow oil (80.9 mg, 0.425 mmol, 85% isolated yield).[S2]

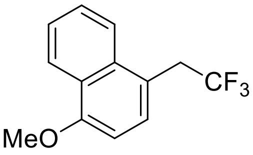
Isolated yields and spectroscopic data of other products are as follows.



2c

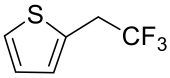
2c: 94% Yield. A colorless oil. ^{1}H NMR δ 6.72-6.80 (m, 3H), 5.97 (s, 2H), 3.27 (q, *J* = 11.2 Hz, 2H) ^{13}C NMR δ 147.9, 147.5, 125.7 (q, $^1J_{C\text{-}F}$ = 276 Hz**)**, 123.6, 123.5 (q, $^3J_{C\text{-}F}$ = 3.3 Hz), 110.3. 108.4, 101.2, 39.9 (q, $^2J_{C\text{-}F}$ = 29.9 Hz)**.** ^{19}F NMR δ -69.0 (t, *J* = 11.2 Hz). HRMS (EI) Calcd for $C_9H_7F_3O_2$

[M]: 204.0398. Found: 204.0400.



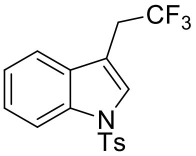
2d

2d: 93% Yield. A white solid, m.p. 37.8-39.1 °C. ^{1}H NMR δ 8.33 (d, J = 7.0 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.48-7.92 (m, 2H), 7.38 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H), 3.77 (q, J = 11.1 Hz, 2H). ^{13}C NMR δ 155.8, 133.1, 129.5, 127.0, 126.2 (q, $^{1}J_{\text{C-F}}$ = 277 Hz), 125.9, 125.2, 123.4 (q, $^{4}J_{\text{C-F}}$ = 1.1 Hz), 122.7, 118.3 (q, $^{3}J_{\text{C-F}}$ = 2.8 Hz), 103.2, 55.5, 36.4 (q, $^{2}J_{\text{C-F}}$ = 30.1 Hz). ^{19}F NMR δ -67.7 (t, J = 11.1 Hz). HRMS (EI) Calcd for $C_{13}H_{11}F_{3}O$ [M]: 240.0762. Found: 240.0760.



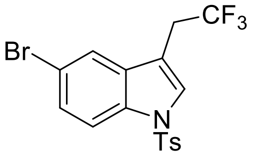
2e

2e: 82% NMR yield. A colorless oil. ^{1}H NMR δ 7.29 (dd, J = 1.8 and 4.7 Hz, 1H), 6.99-7.02 (m, 2H), 3.60 (q, J = 11.0 Hz, 2H). ^{13}C NMR δ 130.6 (q, $^{3}J_{\text{C-F}}$ = 3.3 Hz), 128.7, 127.1, 126.0, 125.0 (q, $^{1}J_{\text{C-F}}$ = 276 Hz), 34.6 (q, $^{2}J_{\text{C-F}}$ = 32.2 Hz). ^{19}F NMR δ -69.4 (t, J = 11.0 Hz). HRMS (EI) Calcd for $C_{6}H_{5}F_{3}S$ [M]: 166.0064. Found: 166.0066.



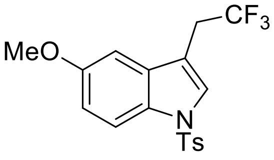
2f

2f: 86% Yield. A white solid, m. p. 123.7-125.2°C. ^{1}H NMR δ 7.98 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.21-7.37 (m, 4H), 3.47 (q, J = 11.0 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR δ 145.2, 134.9, 134.8, 130.1, 129.9, 126.7, 126.0, 125.6 (q, $^{1}J_{\text{C-F}}$ = 276.4 Hz), 125.0, 123.4, 119.3 (q, $^{4}J_{\text{C-F}}$ = 1.1Hz), 113.6, 111.3 (q, $^{3}J_{\text{C-F}}$ = 3.3 Hz), 30.2 (q, $^{2}J_{\text{C-F}}$ = 31.8 Hz), 21.4. ^{19}F NMR δ -68.2 (t, J = 11.0 Hz). Anal. Calcd for $C_{17}H_{14}F_{3}NO_{2}S$: C, 57.78; H, 3.99; N, 3.96. Found: C, 57.45; H, 4.10; N, 3.83.



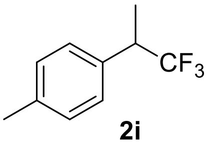
2g

2g: 90% Yield. A white solid, m. p. 151.3-153.2°C. ^{1}H NMR δ 7.85 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.58-7.62 (m, 2H), 7.43 (dd, J = 8.8 and 1.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 3.42 (q, J = 11.0 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR δ 145.5, 134.7, 133.6, 131.9, 130.1, 128.0, 127.2, 126.8, 125.6 (q, ${}^1J_{\text{C-F}}$ = 276.4 Hz), 122.2, 117.1, 115.1, 110.7 (q, ${}^3J_{\text{C-F}}$ = 3.3 Hz), 30.3 (q, ${}^2J_{\text{C-F}}$ = 32.0 Hz), 21.6. ^{19}F NMR δ -68.2 (t, J = 11.0 Hz). Anal. Calcd for $C_{17}H_{13}BrF_3NO_2S$: C, 47.24; H, 3.03; N, 3.24. Found: C, 47.15; H, 3.18; N, 3.23.



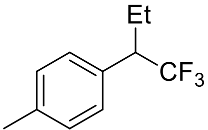
2h

2h: 89% Yield. A white solid, m. p. 124.7-126.5°C. ^{1}H NMR δ 7.87 (d, J = 9.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.20-7.26 (m, 2H), 6.90-6.97 (m, 2H), 3.82 (s, 3H), 3.43 (q, J = 11.0 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR δ 156.6, 145.0, 135.0, 131.2, 129.9, 129.6, 126.8, 126.7, 125.6 (q, ${}^1J_{\text{C-F}}$ = 276.3 Hz), 114.6, 114.1, 111.4 (q, ${}^3J_{\text{C-F}}$ = 3.2 Hz), 101.7, 55.6, 30.4 (q, ${}^2J_{\text{C-F}}$ = 32.0 Hz), 21.5. ^{19}F NMR δ -68.1 (t, J = 11.0 Hz). Anal. Calcd for $C_{18}H_{16}F_3NO_3S$: C, 56.39; H, 4.21; N, 3.65. Found: C, 56.29; H, 4.34; N, 3.38.



2i

2i: 75% Yield. A colorless oil. ^{1}H NMR δ 7.21 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.32-3.48 (m, 1H), 2.35 (s, 3H), 1.49 (d, J = 7.3 Hz, 3H). ^{13}C NMR δ 137.8, 133.4 (q, ${}^3J_{\text{C-F}}$ = 1.9 Hz), 129.3, 128.3, 127.2 (q, ${}^1J_{\text{C-F}}$ = 278.8 Hz), 43.8 (q, ${}^2J_{\text{C-F}}$ = 27.5 Hz), 21.0, 14.6 (q, ${}^3J_{\text{C-F}}$ = 2.8 Hz). ^{19}F NMR δ -74.2 (d, J = 11.3 Hz). HRMS (EI) Calcd for $C_{10}H_{11}F_3$ [M]: 188.0813. Found: 188.0806.



2j

2j: 42% Yield. A colorless oil. ^{1}H NMR δ 7.16 (br, 4H), 3.00-3.16 (m, 1H), 2.35 (s, 3H), 1.98-2.13 (m, 1H), 1.76-1.93 (m, 1H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 137.7, 131.7 (q, ${}^3J_{\text{C-F}}$ = 2.2 Hz), 129.3, 128.9, 127.1 (q, ${}^1J_{\text{C-F}}$ = 279.3 Hz), 51.4 (q, ${}^2J_{\text{C-F}}$ = 26.2 Hz), 22.0 (q, ${}^3J_{\text{C-F}}$ = 2.3 Hz), 21.1, 11.5. ^{19}F NMR δ -72.5 (d, J = 11.3 Hz). . HRMS (EI) Calcd for $C_{11}H_{13}F_3$ [M]: 202.0969. Found: 202.0963.

Copper-Catalyzed Trifluoromethylation of (*R*)-1i

In a 20 mL Schlenk flask were placed CuTC (4.8 mg, 0.025 mmol) and KF (87.4 mg, 1.5 mmol). Anhydrous and degassed THF (3.0 mL) was added, and then the mixture was magnetically stirred at room temperature. After the addition of (*R*)-**1i** (77.4 mg, 0.50 mmol, 60% *ee*) and CF_3SiMe_3 (220 μL, 1.5 mmol), the reaction flask was kept at 60 °C for 48 h. The solution was poured into water (5 mL) and the resulting mixture was extracted with diethyl ether (30 mL x 3). The combined extracts were washed with brine, and dried over anhydrous $MgSO_4$. After the concentration under reduced pressure, the resulting residue was purified by column chromatography (SiO_2, eluent: hexane only) to give **2i** as a colorless oil (61.7 mg, 0.328 mmol, 66% isolated yield). $[\alpha]^{25}_{D} = -0.4$ (c = 0.705, $CHCl_3$).

References and Notes

(S1) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

(S2) Riss, P. J.; Aigbirhio, F. I. *Chem. Commun.* **2011**, *47*, 11873.

(S3) Porcal, W.; Merlino, A.; Boiani, M.; Gerpe, A.; González, M.; Cerecetto, H. *Org. Process. Res. Dev.* **2008**, *12*, 156.

(S4) Diliën, H.; Chambon, S.; Cleij, T. J.; Lutsen, L.; Vanderzande, D.; Adriaensens, P. J. *Macromolecules* **2011,** *44*, 4711.

(S5) Ramakrishna, V. S. N.; Shirsath, V. S.; Kambhampati, R. S.; Rao, V. S. V. V.; Jasti, V. *N-Arylsulfonyl-3-substituted indoles having serotonin receptor affinity, process for their preparation and pharmaceutical composition containing them.* WO 2004048330 A1, Jun 10, 2004.

(S6) Liu, K.-T.; Chang, L.-W.; Yu, D.-G.; Chen, P.-S.; Fan, J.-T. *J. Phys. Org. Chem.* **1997**, *10*, 879.

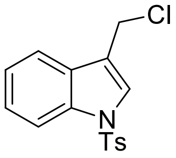
(S7) Waibel, M.; Kieser, K. J.; Carlson, K. E.; Stossi, F.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Eur. J. Med. Chem.* **2009**, *44*, 3560.

(S8) Foster, B.; Gaillard, B.; Mathur, N.; Pincock, A. L.; Pincock, J. A.; Sehmbey, C. *Can. J. Chem.* **1987**, *65*, 1599.

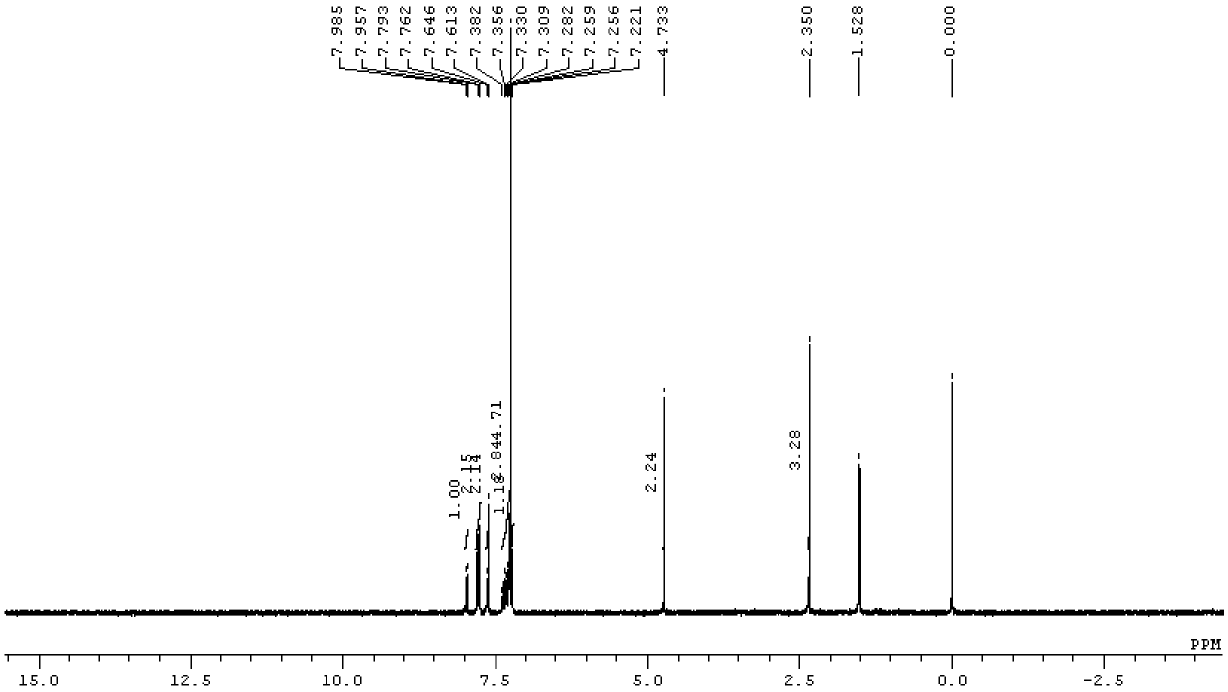
(S9) Badiger, S.; Behnke, D; Betschart, C.; Chaudhari, V.; Cotesta, S.; Hinrichs, J. H.-H.; Ofner, S.; Pandit, C. *Diaza-spiro[5.5]undecanes as orexin receptor antagonists.* WO 2011076747 A1, Jun 30, 2011.

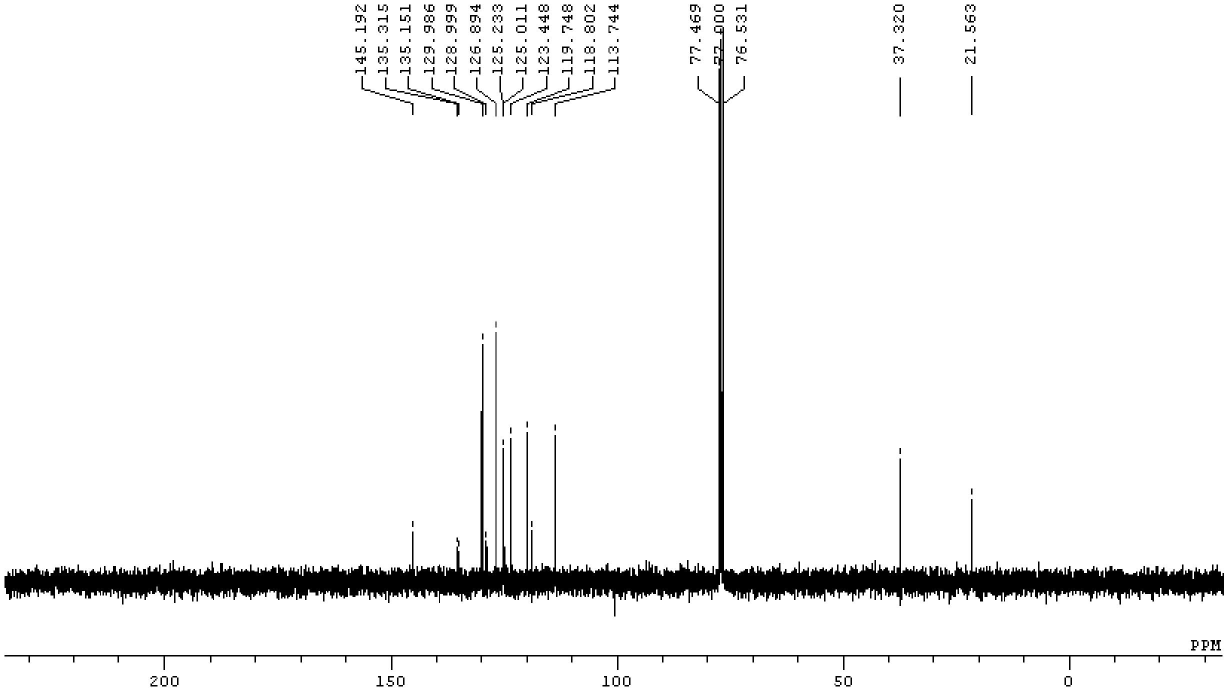
(S10) Kiyokawa, K.; Yasuda, M.; Baba, A. *Org. Lett.* **2010**, *12*, 1520.

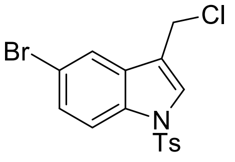
(S11) Burwell, R. T., Jr.; Shields, A. D.; Hart, H. *J. Am. Chem. Soc.* **1954**, *76*, 908.


Cl
N
Ts

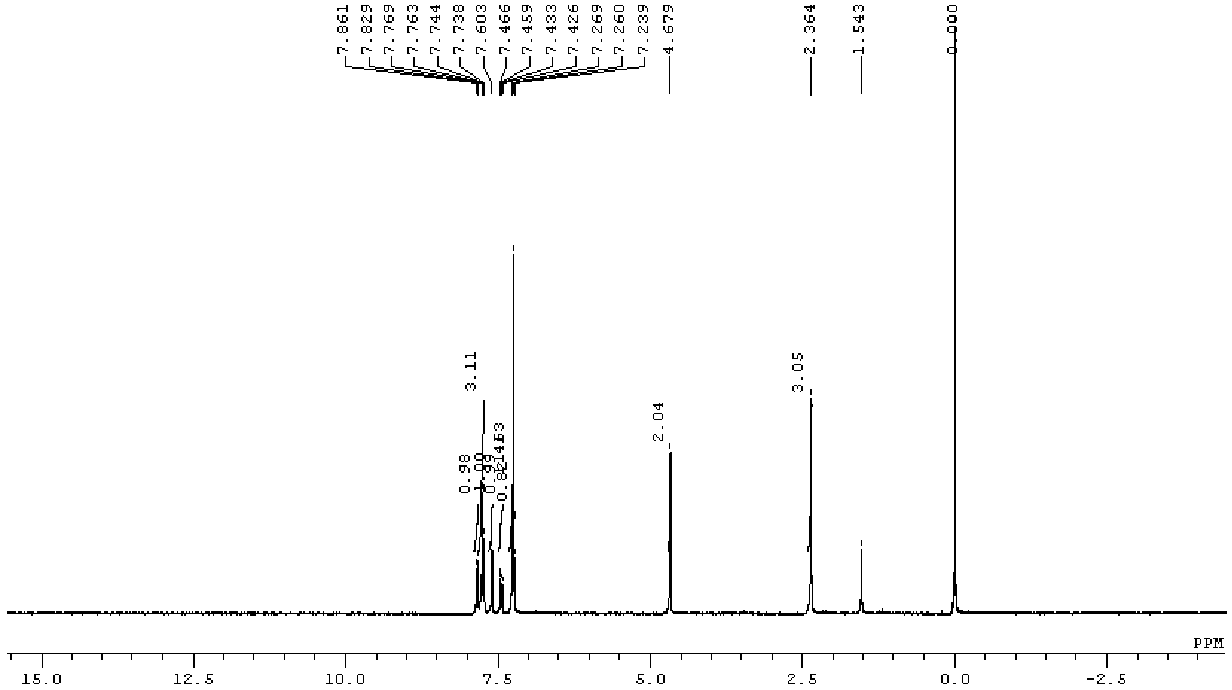
1f

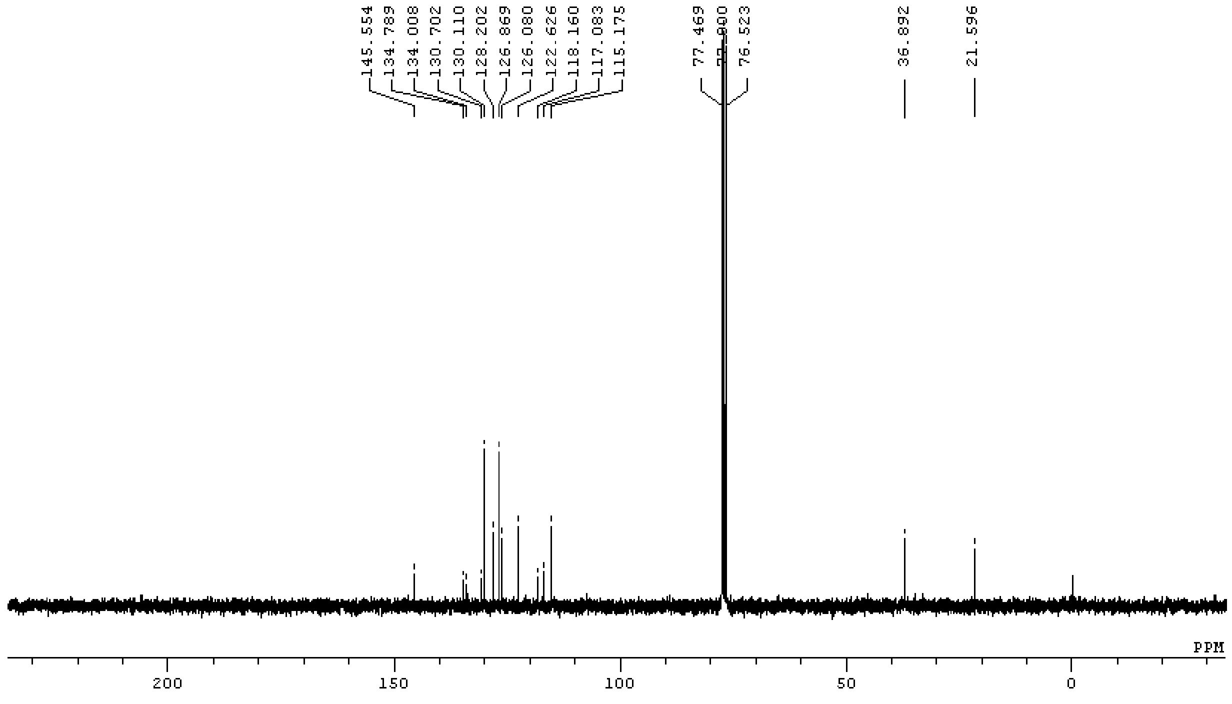

7.985
7.957
7.793
7.762
7.646
7.613
7.382
7.356
7.330
7.309
7.282
7.259
7.256
7.221
4.733
2.350
1.528
0.000
1.00
2.15
2.14
1.18
4.84
4.71
2.24
3.28
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

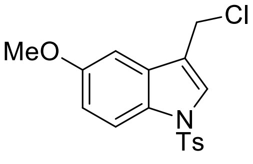

145.192
135.315
135.151
129.986
128.999
126.894
125.233
125.011
123.448
119.748
118.802
113.744
77.469
77.000
76.531
37.320
21.563
PPM
200
150
100
50
0


Br
Cl
N
Ts

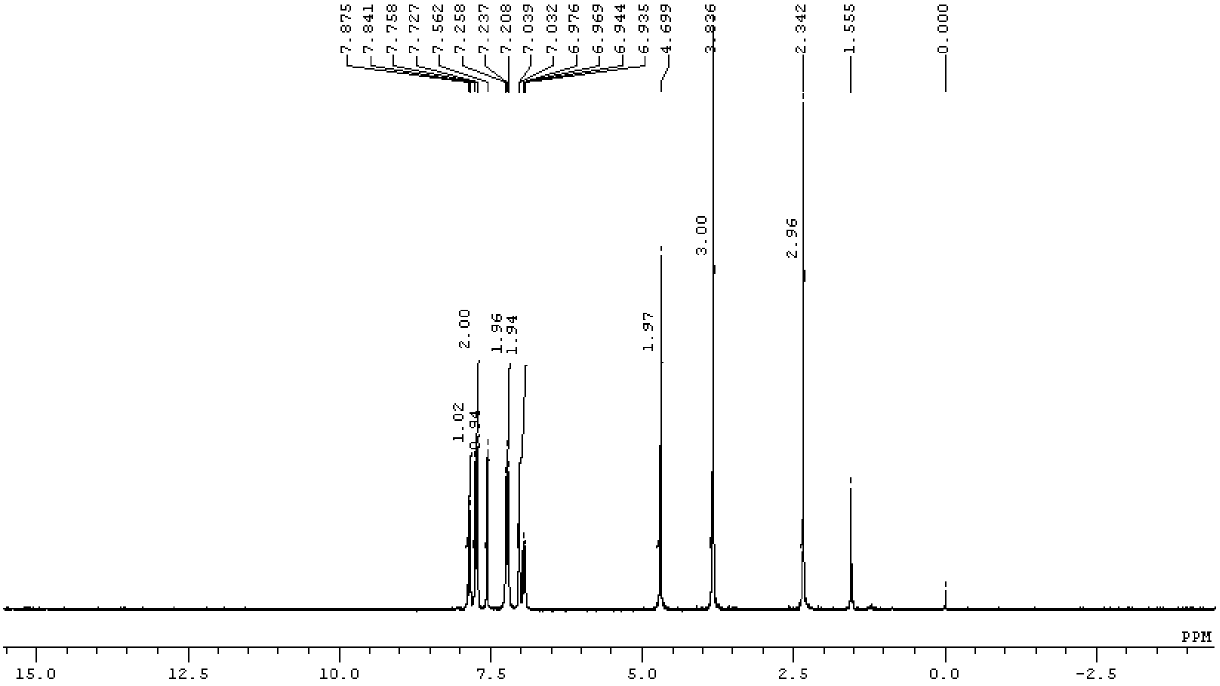
1g

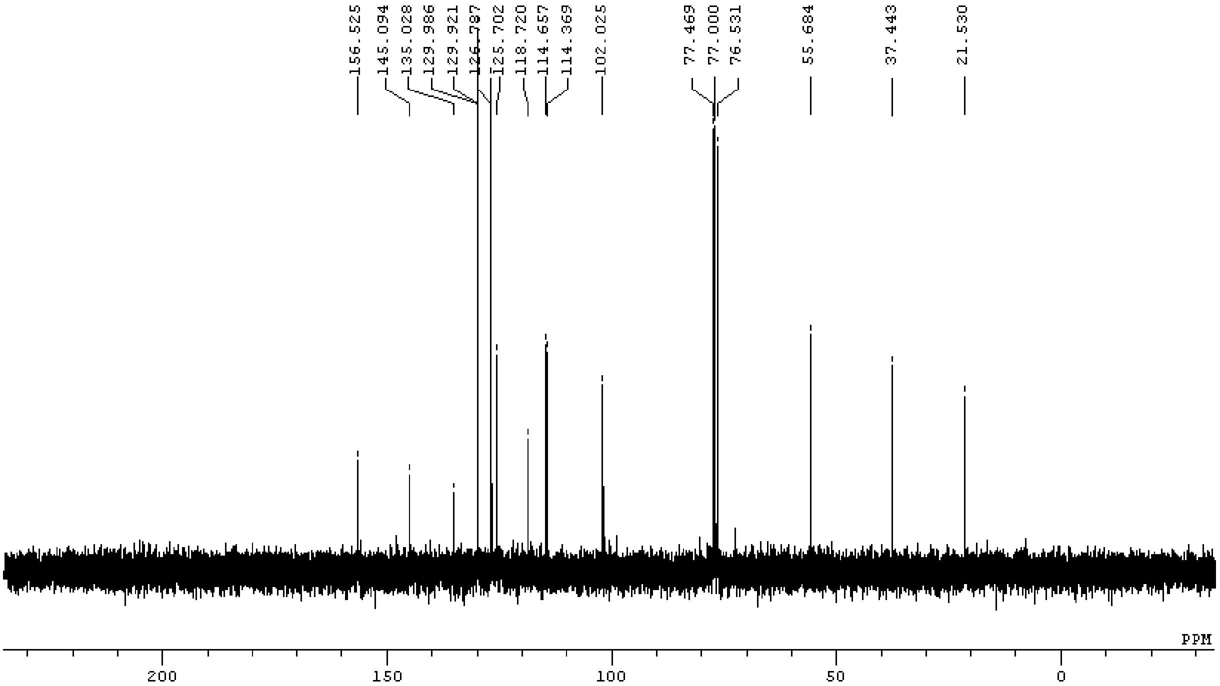

7.861
7.829
7.769
7.763
7.744
7.738
7.603
7.466
7.459
7.433
7.426
7.269
7.260
7.239
4.679
2.364
1.543
0.000
3.11
0.98
1.00
0.99
0.82
2.04
3.05
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

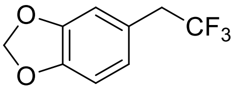

145.554
134.789
134.008
130.702
130.110
128.202
126.869
126.080
122.626
118.160
117.083
115.175
77.469
77.000
76.523
36.892
21.596
PPM
200
150
100
50
0


MeO
Cl
N
Ts

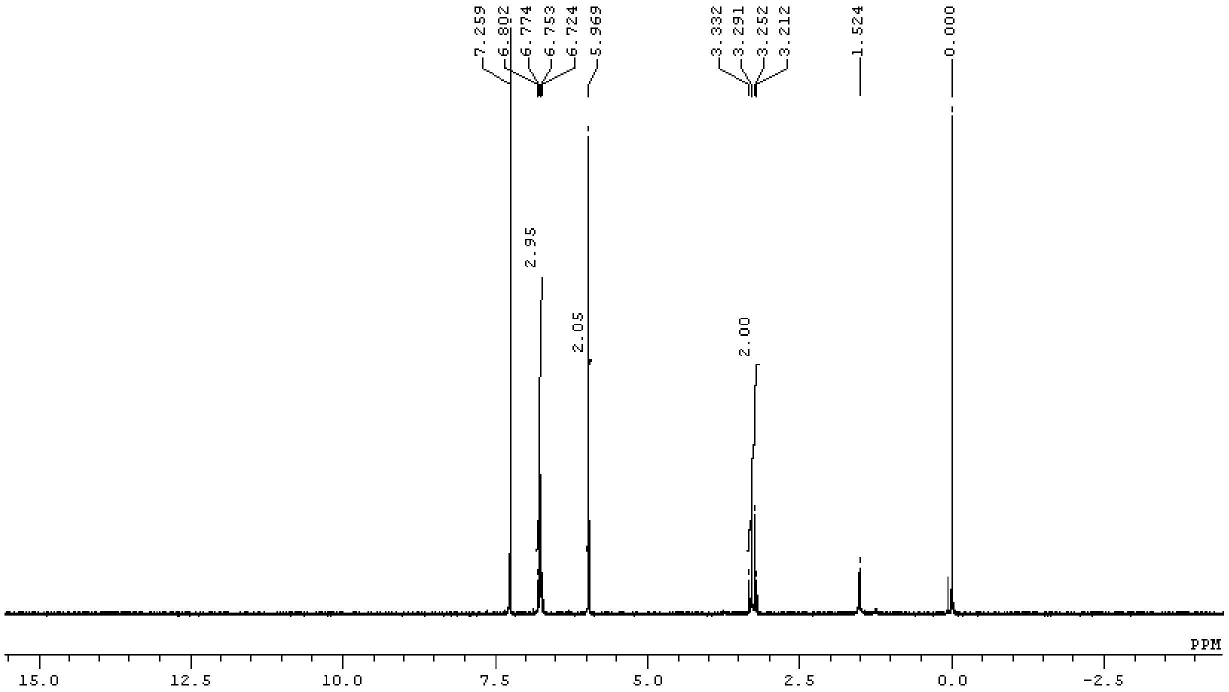
1h

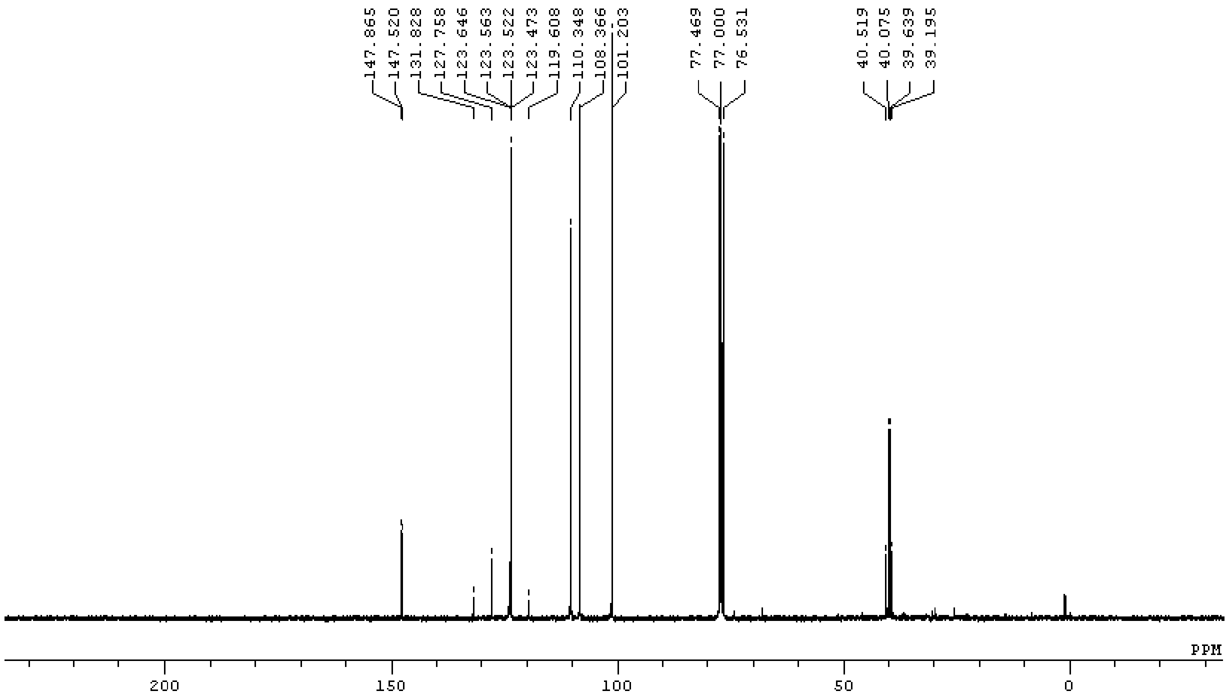

7.875
7.841
7.758
7.727
7.562
7.258
7.237
7.208
7.039
7.032
6.976
6.969
6.944
6.935
4.699
3.836
2.342
1.555
0.000
1.02
0.94
2.00
1.96
1.94
1.97
3.00
2.96
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

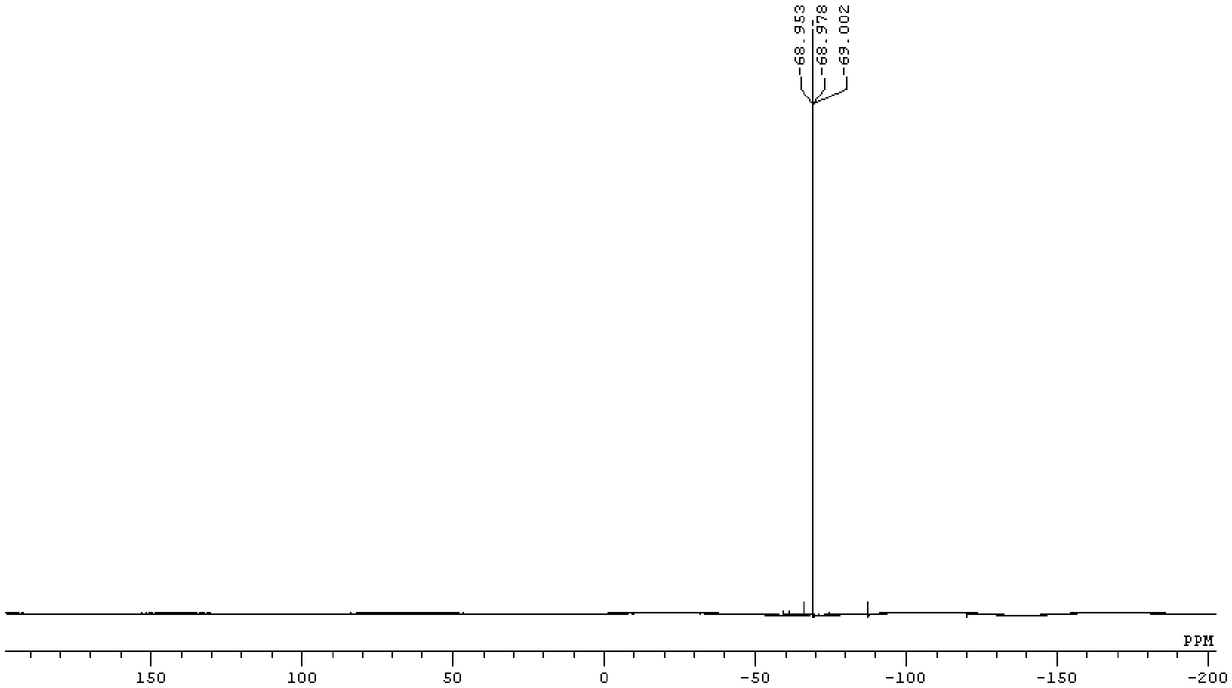

156.525
145.094
135.028
129.986
129.921
126.787
125.702
118.720
114.657
114.369
102.025
77.469
77.000
76.531
55.684
37.443
21.530
PPM
200
150
100
50
0

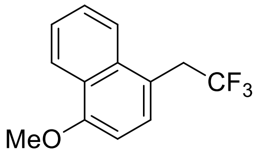

O
O
CF3

2c

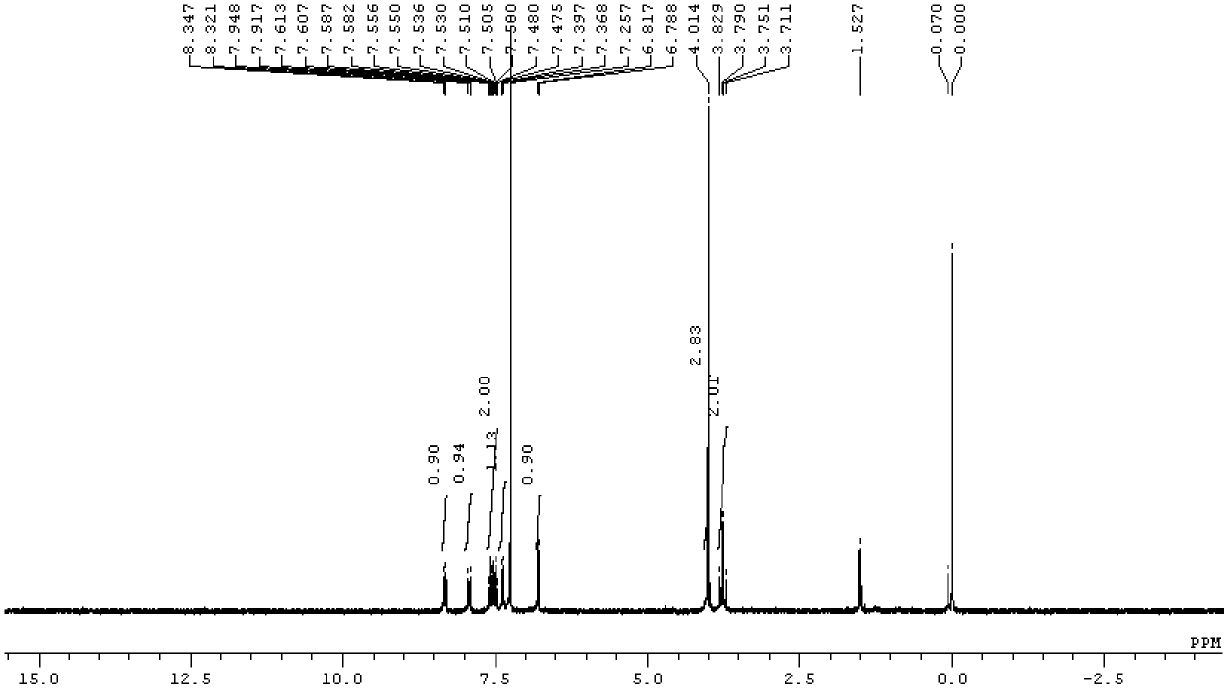

7.259
6.802
6.774
6.753
6.724
5.969
3.332
3.291
3.252
3.212
1.524
0.000
2.95
2.05
2.00
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

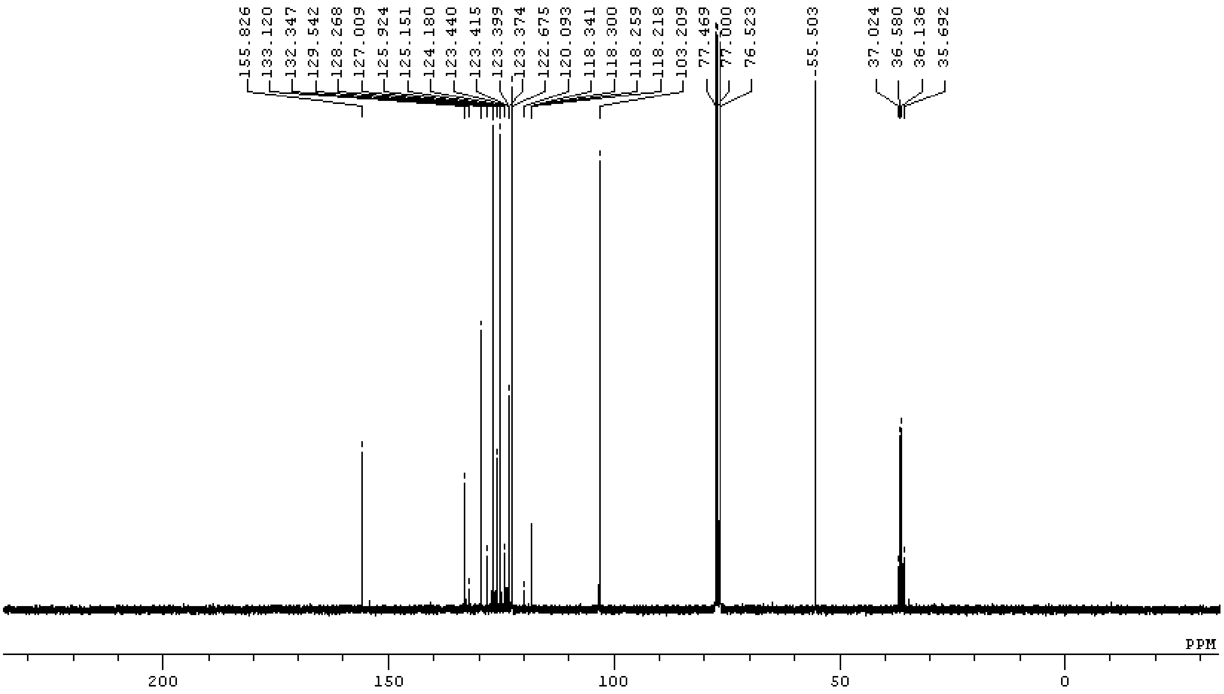

147.865
147.520
131.828
127.758
123.646
123.563
123.522
123.473
119.608
110.348
108.366
101.203
77.469
77.000
76.531
40.519
40.075
39.639
39.195
PPM
200
150
100
50
0

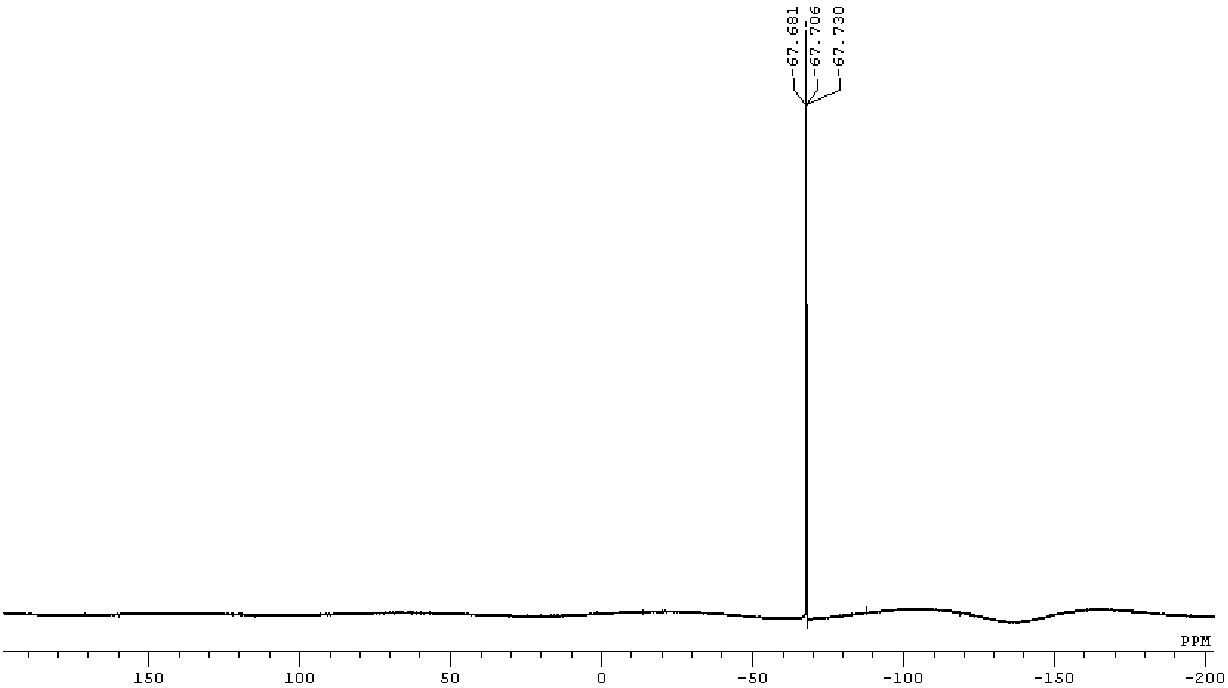

-68.953
-68.978
-69.002
PPM
150
100
50
0
-50
-100
-150
-200

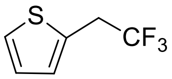

CF3
MeO

2d

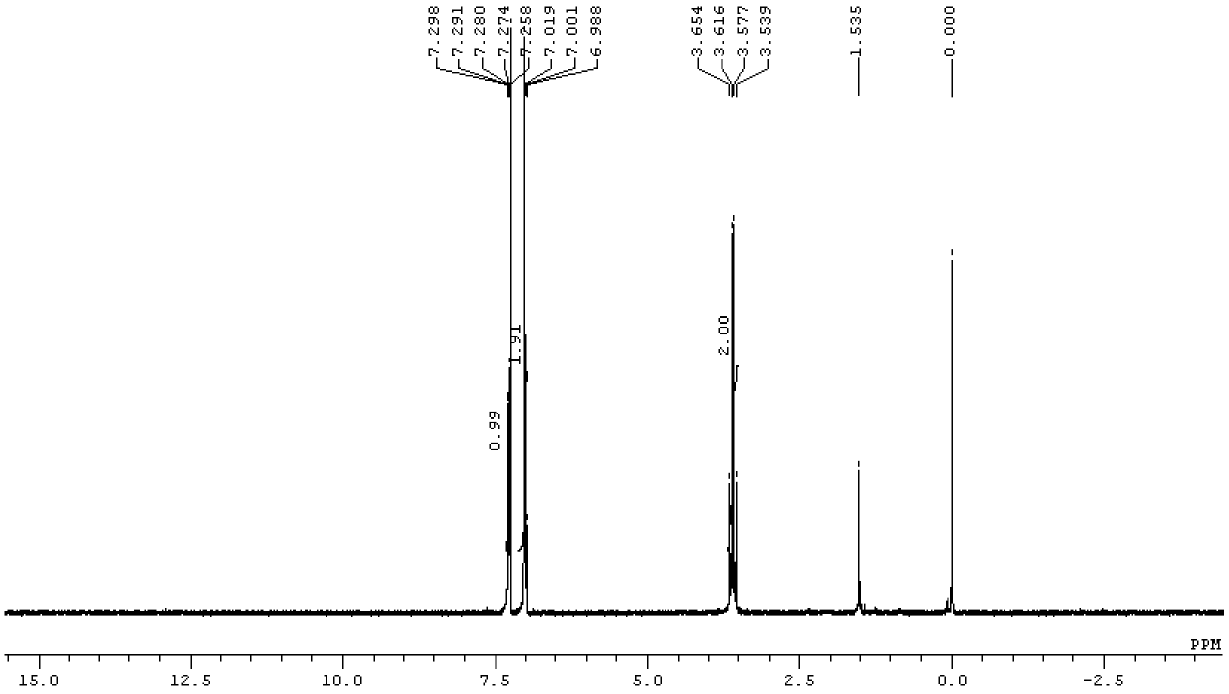

8.347
8.321
7.948
7.917
7.613
7.607
7.587
7.582
7.556
7.550
7.536
7.530
7.510
7.505
7.580
7.480
7.475
7.397
7.368
7.257
6.817
6.788
4.014
3.829
3.790
3.751
3.711
1.527
0.070
0.000
0.90
0.94
1.13
2.00
0.90
2.83
2.01
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

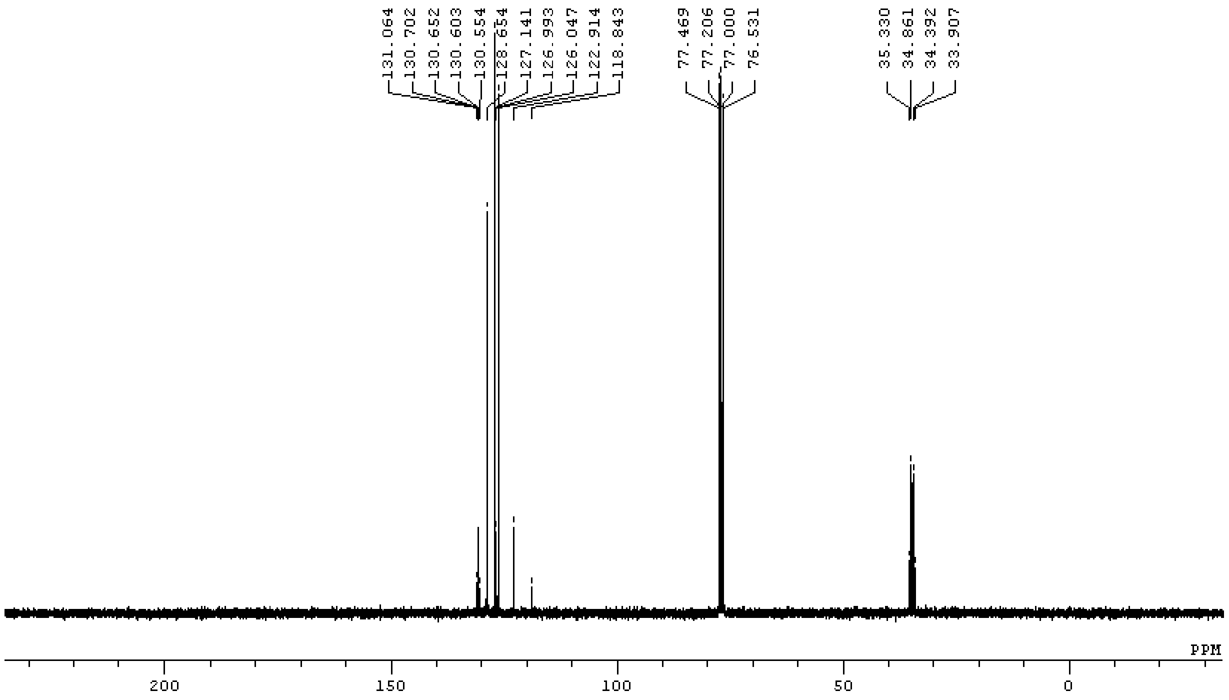

155.826
133.120
132.347
129.542
128.268
127.009
125.924
125.151
124.180
123.440
123.415
123.399
123.374
122.675
120.093
118.341
118.300
118.259
118.218
103.209
77.469
77.000
76.523
55.503
37.024
36.580
36.136
35.692
PPM
200
150
100
50
0

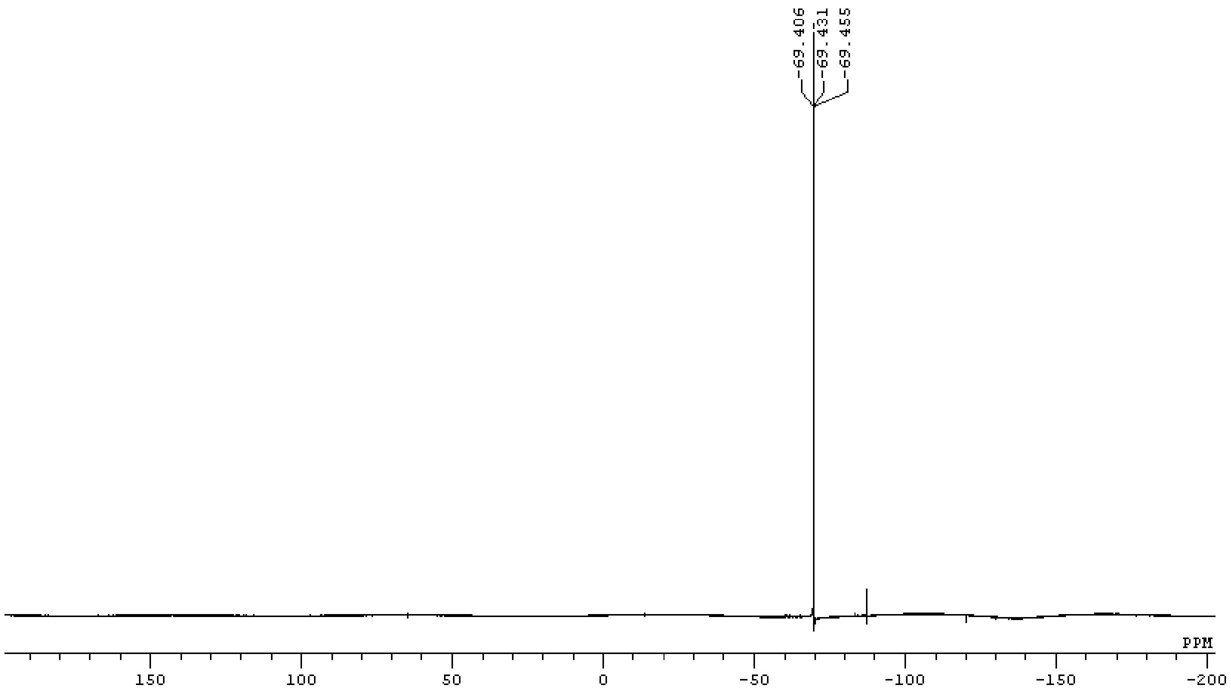

-67.681
-67.706
-67.730
PPM
150
100
50
0
-50
-100
-150
-200

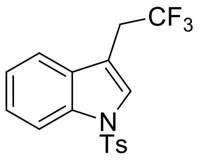

S
CF3

2e

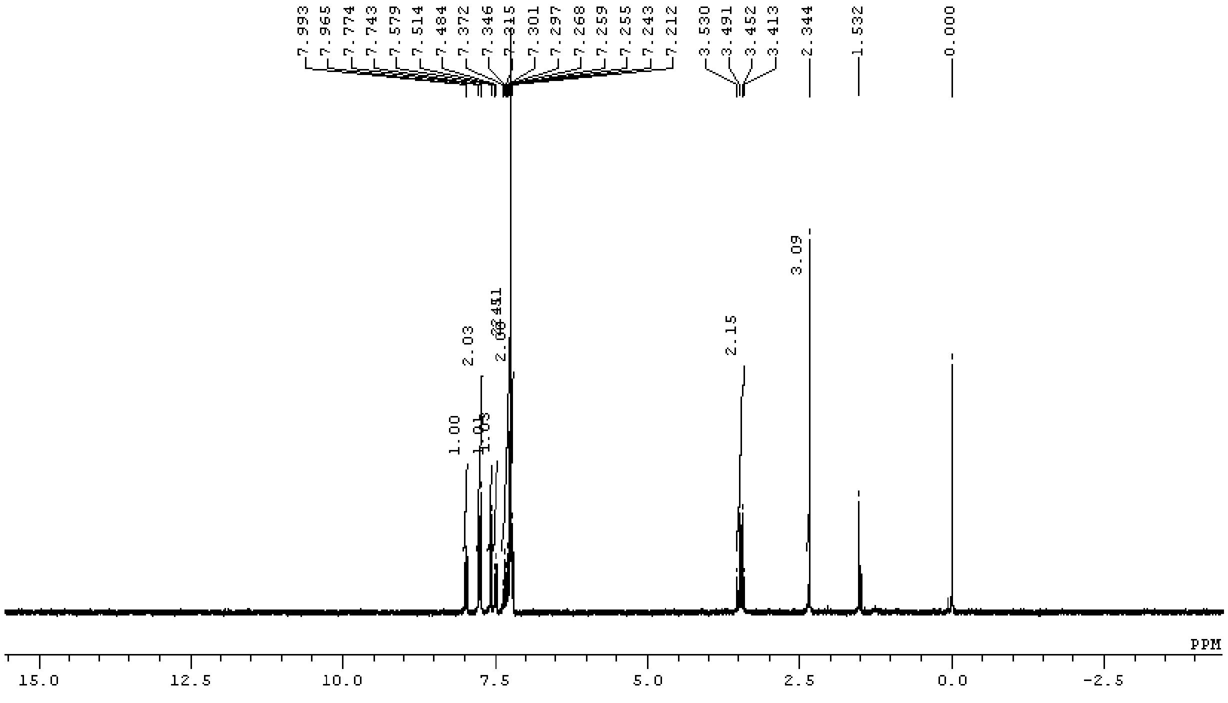

7.298
7.291
7.280
7.274
7.258
7.019
7.001
6.988
3.654
3.616
3.577
3.539
1.535
0.000
0.99
1.91
2.00
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

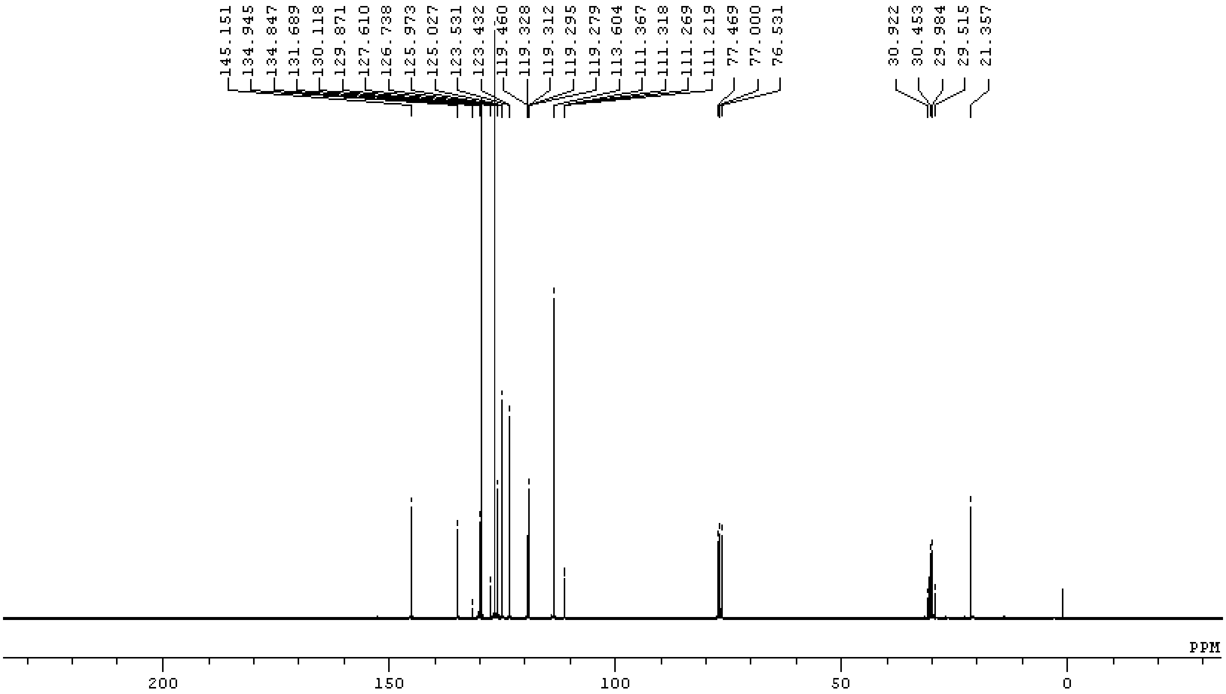

131.064
130.702
130.652
130.603
130.554
128.654
127.141
126.993
126.047
122.914
118.843
77.469
77.206
77.000
76.531
35.330
34.861
34.392
33.907
PPM
200
150
100
50
0

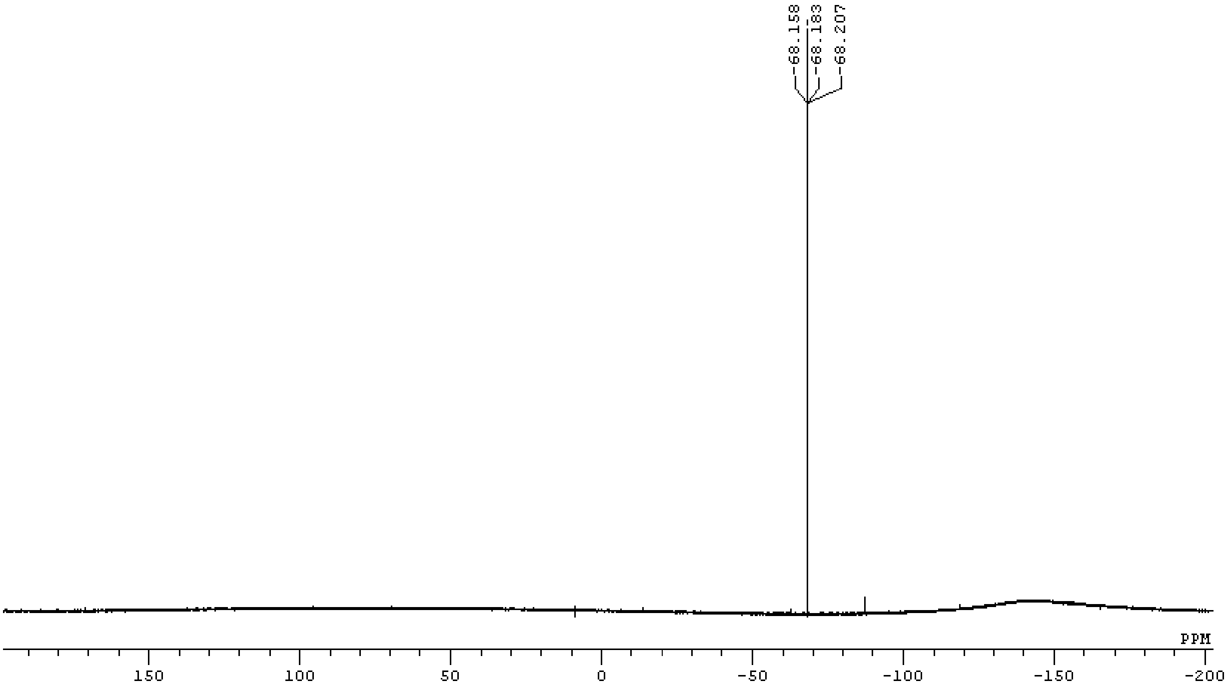

-69.406
-69.431
-69.455
PPM
150
100
50
0
-50
-100
-150
-200

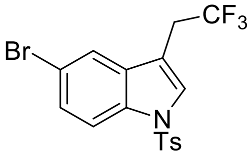

CF3
N
Ts

2f

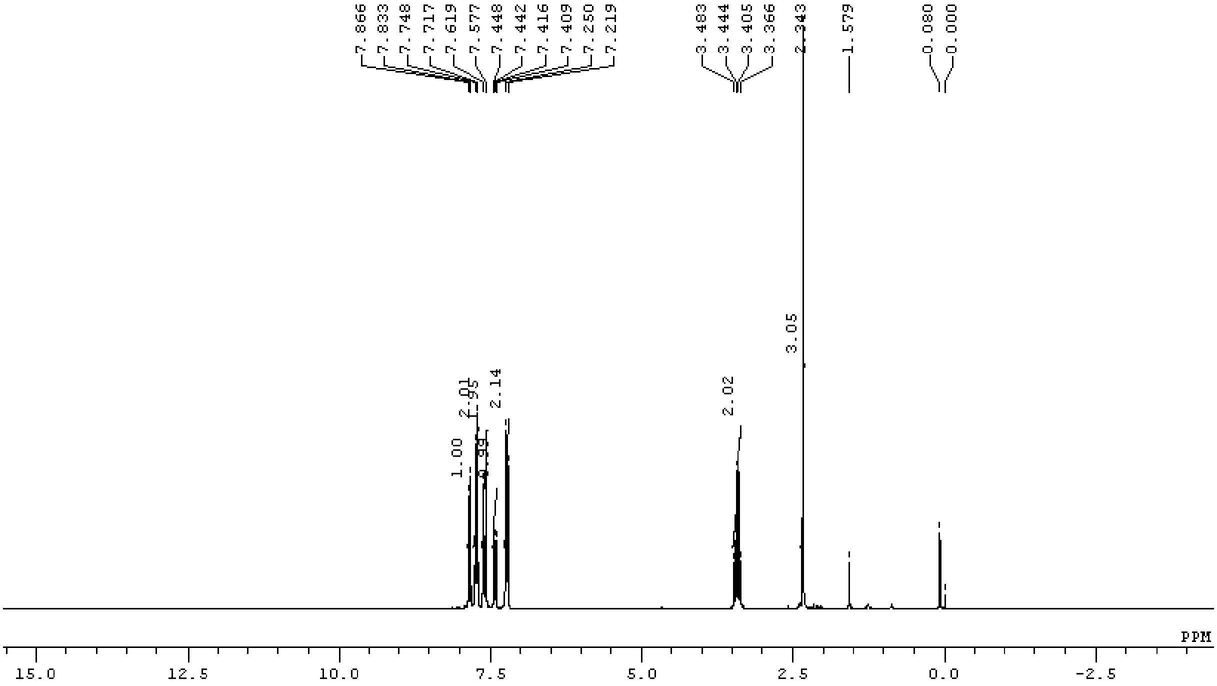

7.993
7.965
7.774
7.743
7.579
7.514
7.484
7.372
7.346
7.315
7.301
7.297
7.268
7.259
7.255
7.243
7.212
3.530
3.491
3.452
3.413
2.344
1.532
0.000
1.00
1.01
1.05
2.03
2.15
3.09
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

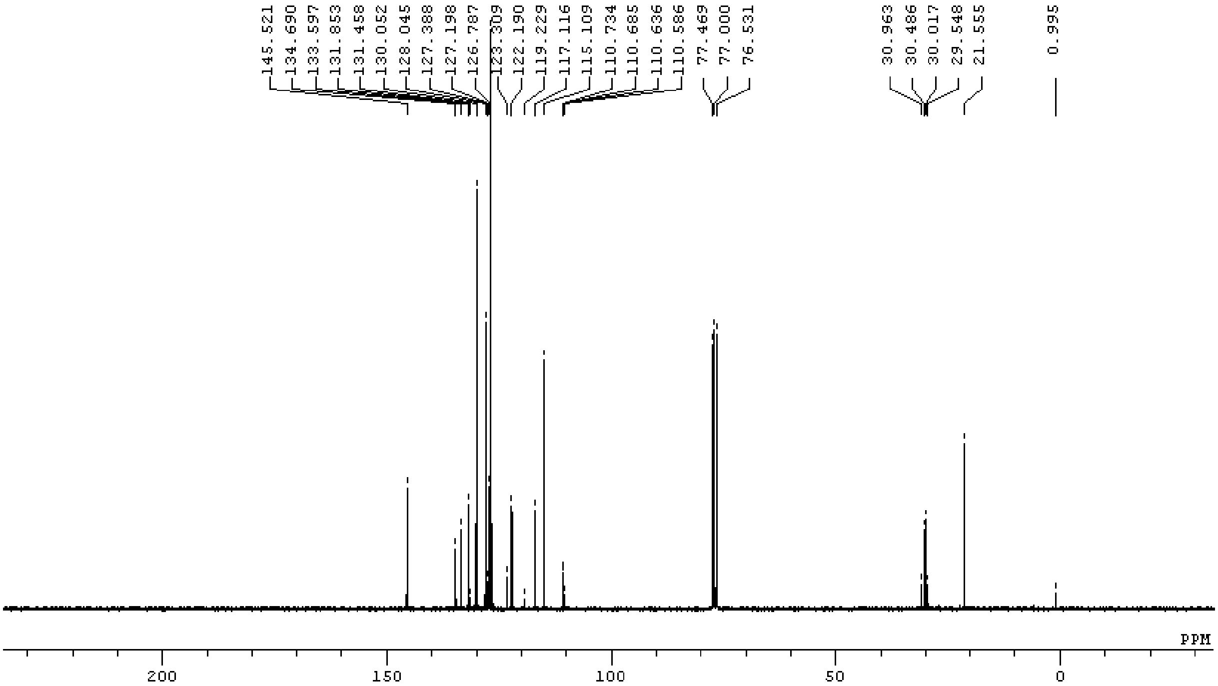

145.151
134.945
134.847
131.689
130.118
129.871
127.610
126.738
125.973
125.027
123.531
123.432
119.460
119.328
119.312
119.295
119.279
113.604
111.367
111.318
111.269
111.219
77.469
77.000
76.531
30.922
30.453
29.984
29.515
21.357
PPM
200
150
100
50
0

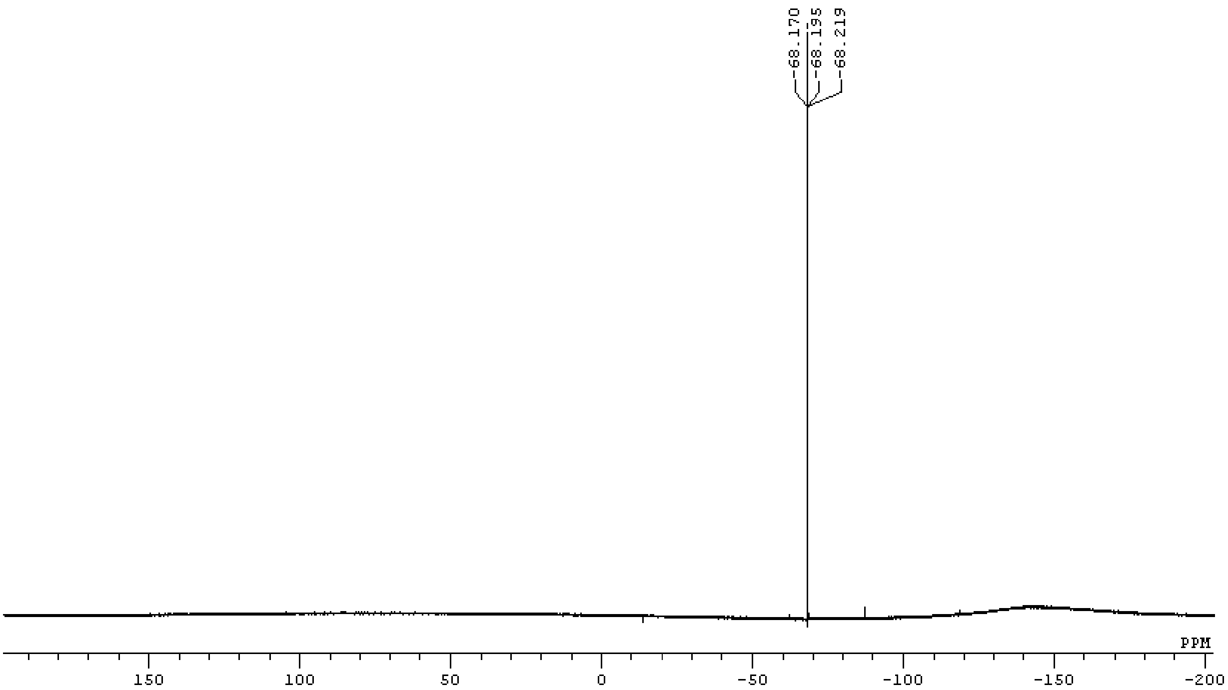

-68.158
-68.183
-68.207
PPM
150
100
50
0
-50
-100
-150
-200

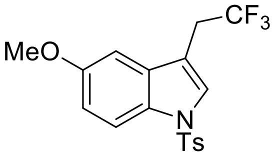

Br
CF3
N
Ts

2g

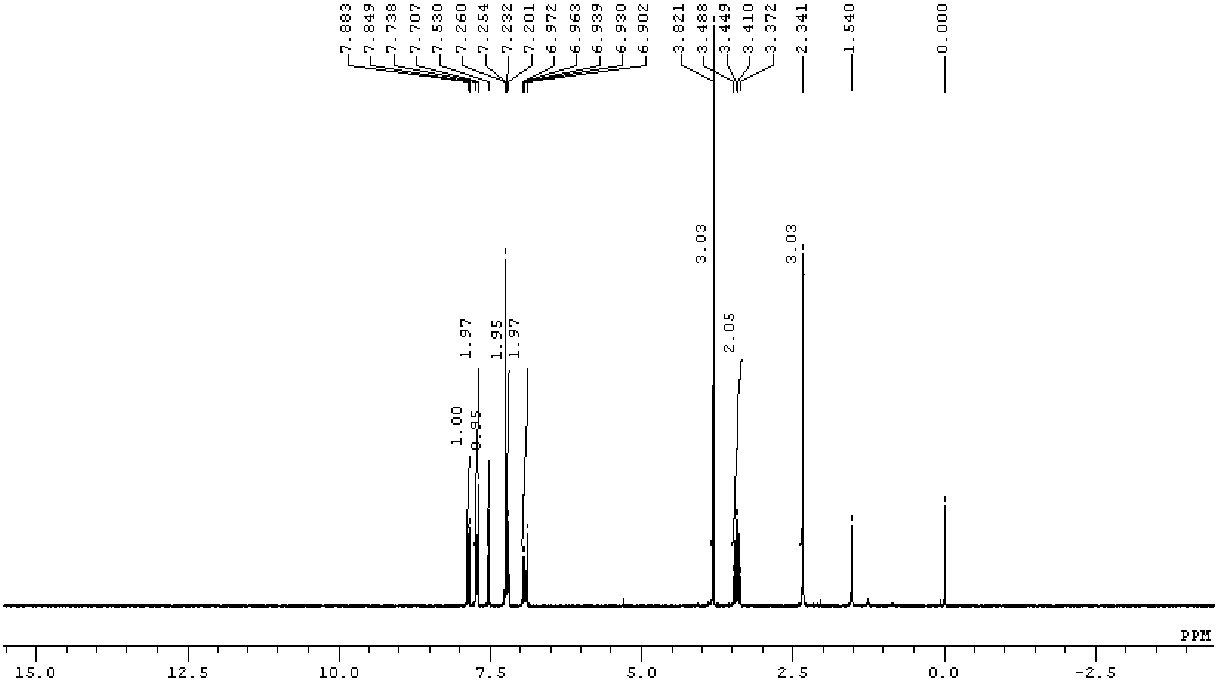

7.866
7.833
7.748
7.717
7.619
7.577
7.448
7.442
7.416
7.409
7.250
7.219
3.483
3.444
3.405
3.366
2.343
1.579
0.080
0.000
1.00
2.01
1.95
0.99
2.14
2.02
3.05
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

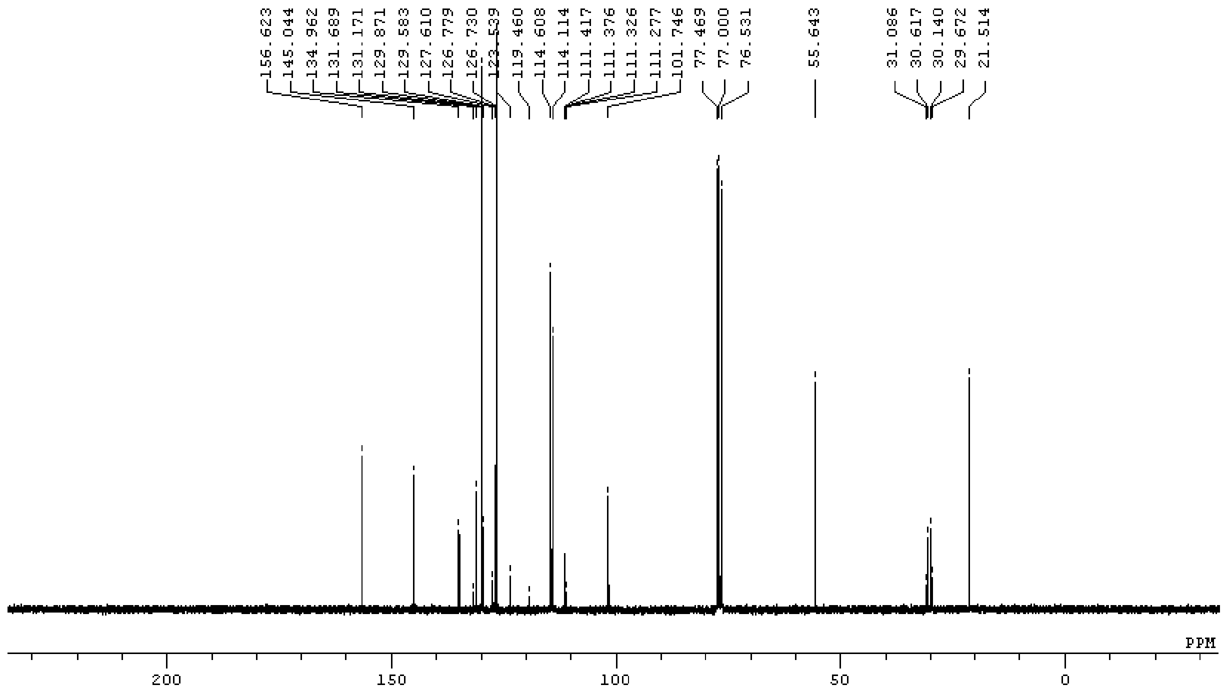

145.521
134.690
133.597
131.853
131.458
130.052
128.045
127.388
127.198
126.787
123.309
122.190
119.229
117.116
115.109
110.734
110.685
110.636
110.586
77.469
77.000
76.531
30.963
30.486
30.017
29.548
21.555
0.995
PPM
200
150
100
50
0

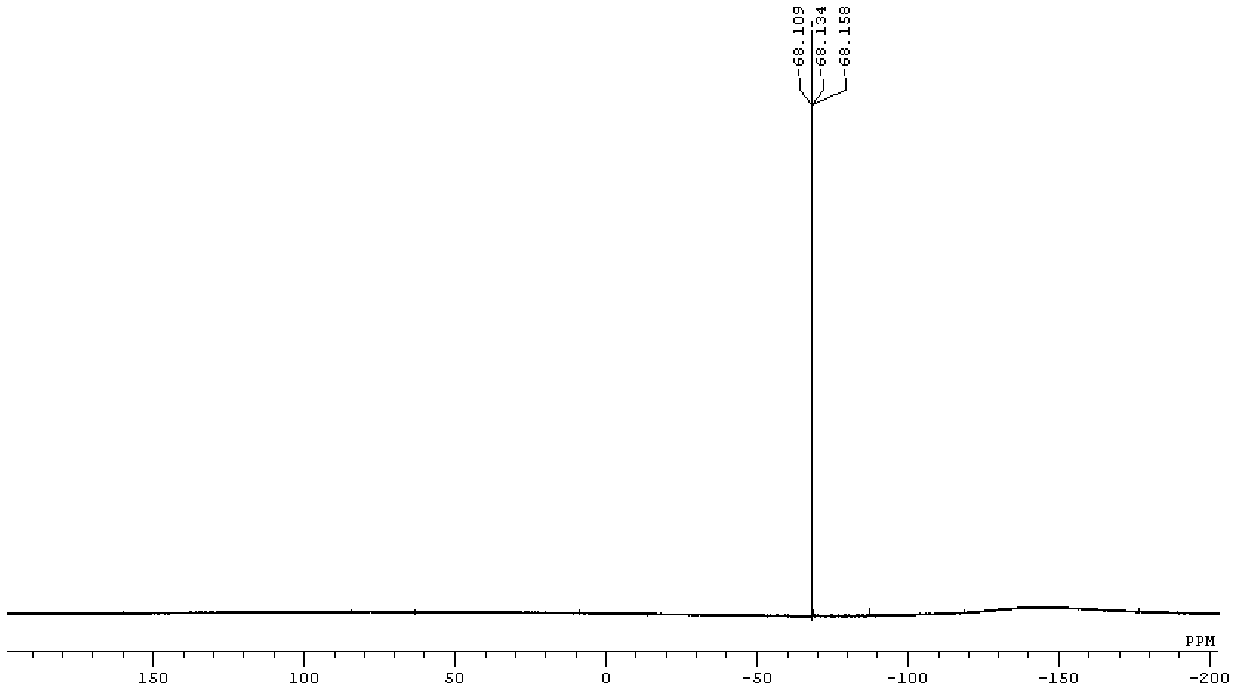

-68.170
-68.195
-68.219
PPM
150
100
50
0
-50
-100
-150
-200

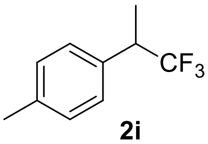

CF3
MeO
N
Ts

2h

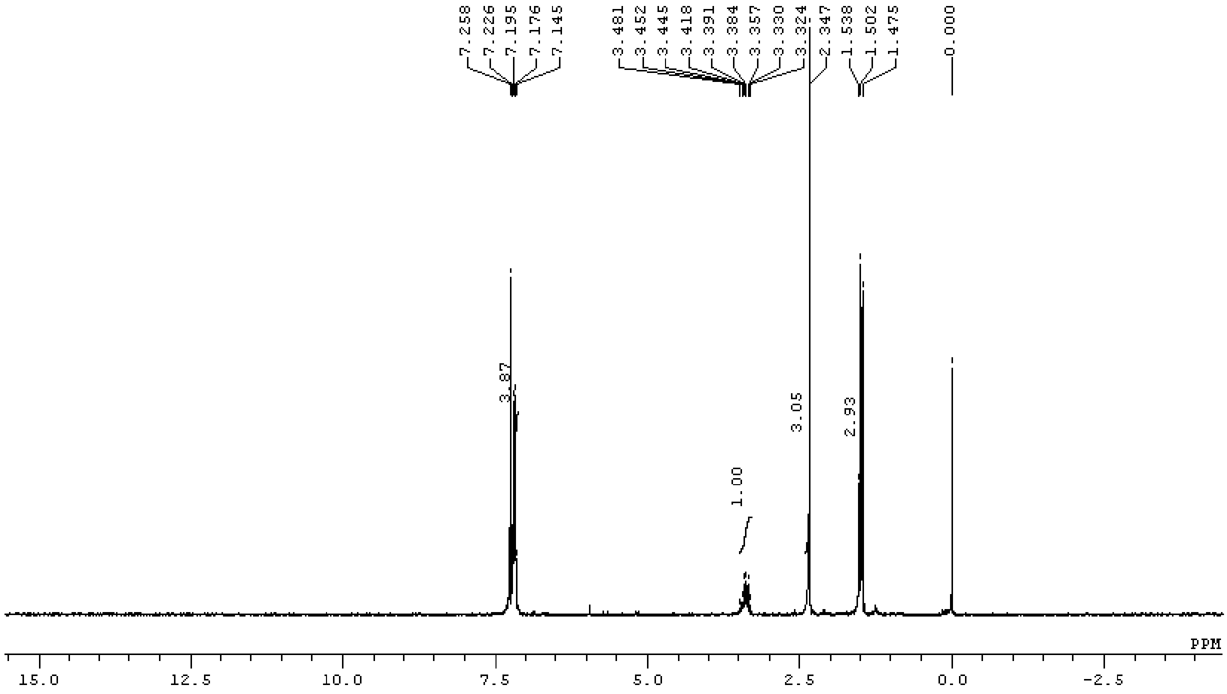

7.883
7.849
7.738
7.707
7.530
7.260
7.254
7.232
7.201
6.972
6.963
6.939
6.930
6.902
3.821
3.488
3.449
3.410
3.372
2.341
1.540
0.000
1.00
0.95
1.97
1.95
1.97
3.03
2.05
3.03
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

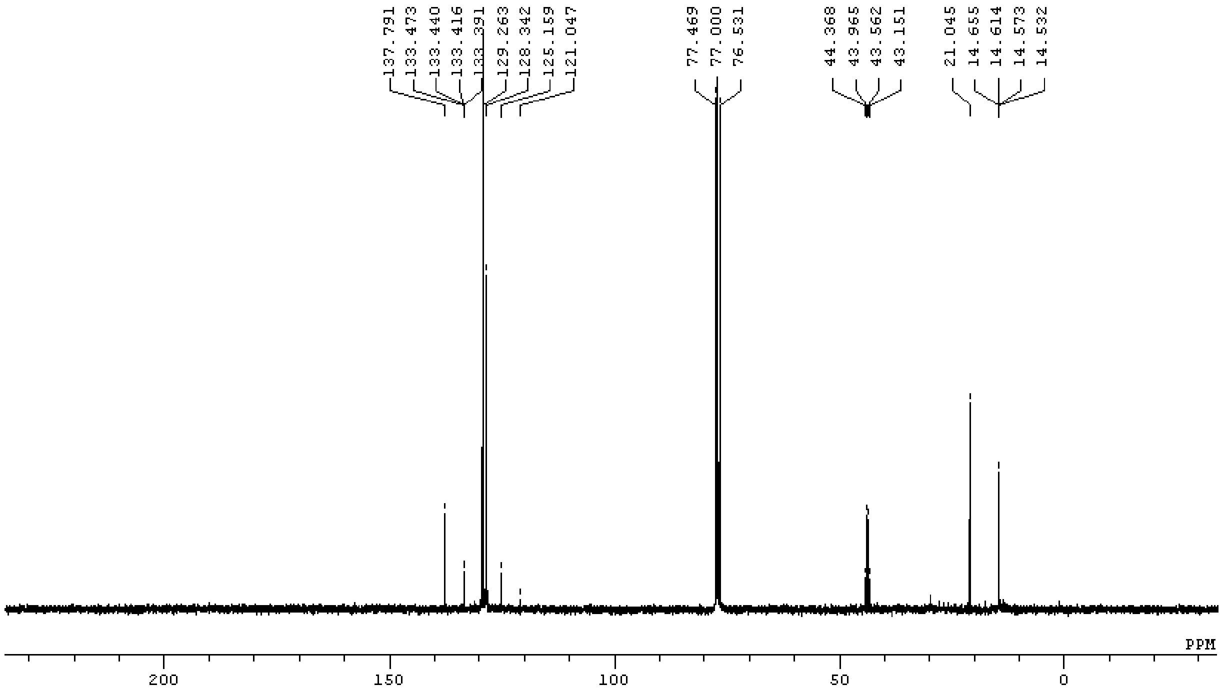

156.623
145.044
134.962
131.689
131.171
129.871
129.583
127.610
126.779
126.730
123.539
119.460
114.608
114.114
111.417
111.376
111.326
111.277
101.746
77.469
77.000
76.531
55.643
31.086
30.617
30.140
29.672
21.514
PPM
200
150
100
50
0

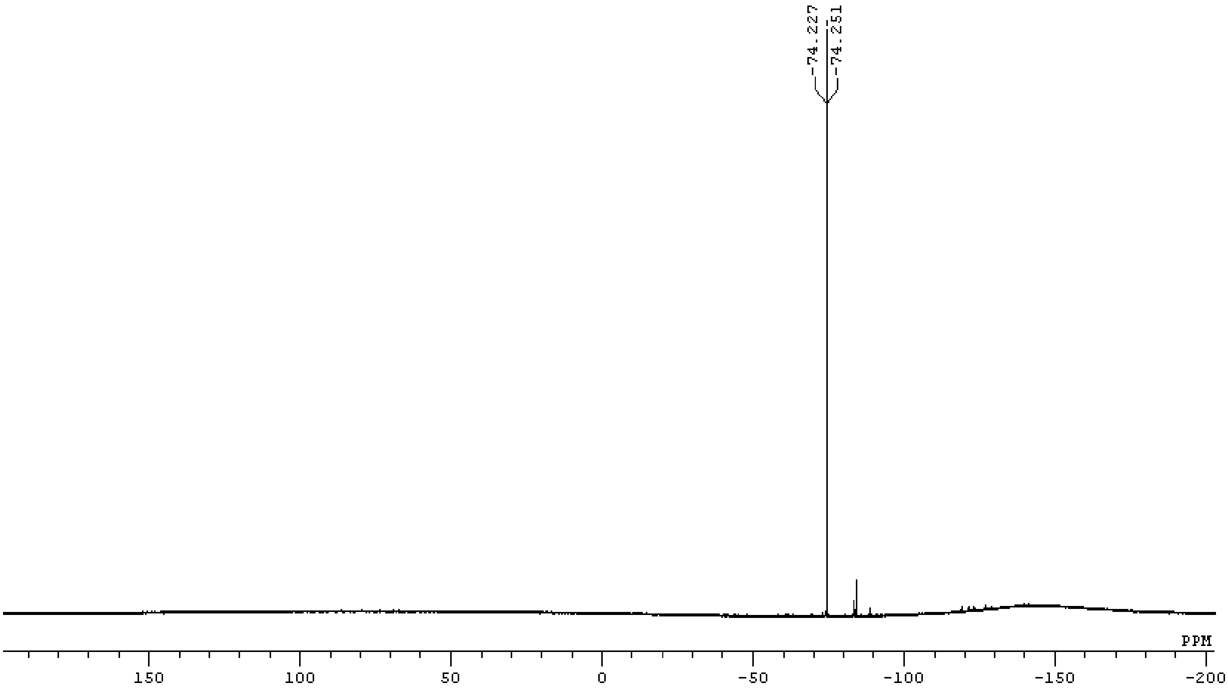

-68.109
-68.134
-68.158
PPM
150
100
50
0
-50
-100
-150
-200

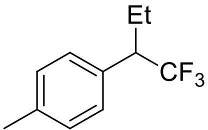

CF3

2i

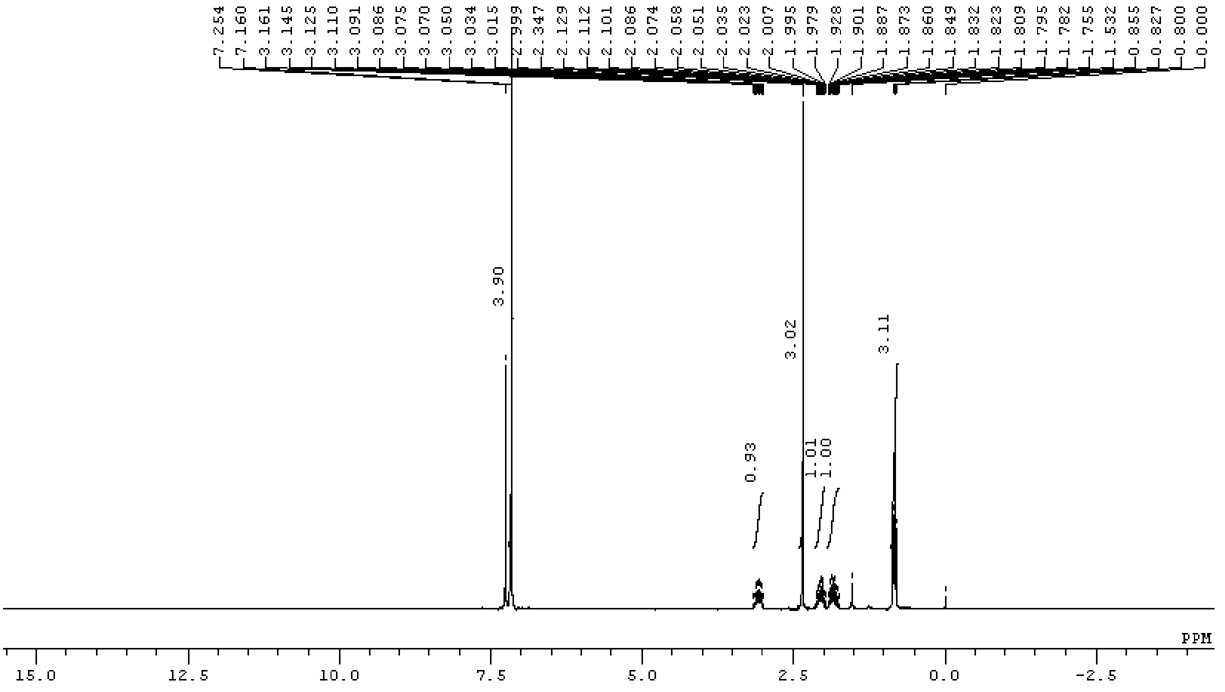

7.258
7.226
7.195
7.176
7.145
3.481
3.452
3.445
3.418
3.391
3.384
3.357
3.330
3.324
2.347
1.538
1.502
1.475
0.000
3.87
1.00
3.05
2.93
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5

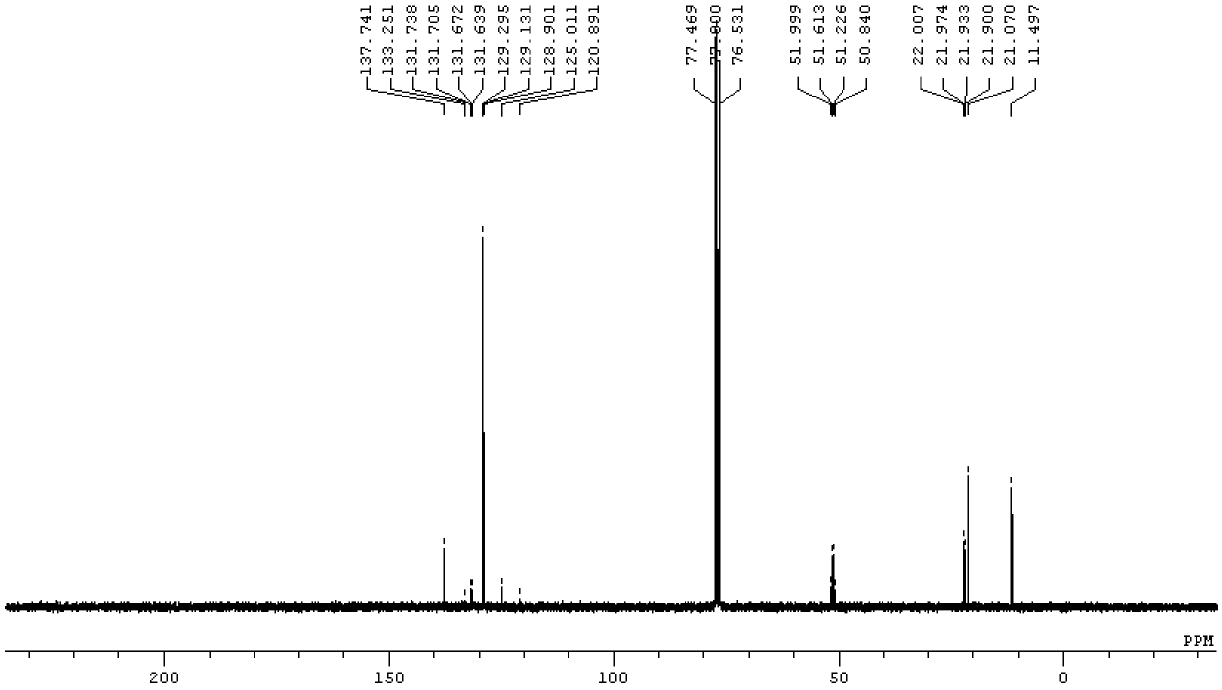

137.791
133.473
133.440
133.416
133.391
129.263
128.342
125.159
121.047
77.469
77.000
76.531
44.368
43.965
43.562
43.151
21.045
14.655
14.614
14.573
14.532
PPM
200
150
100
50
0

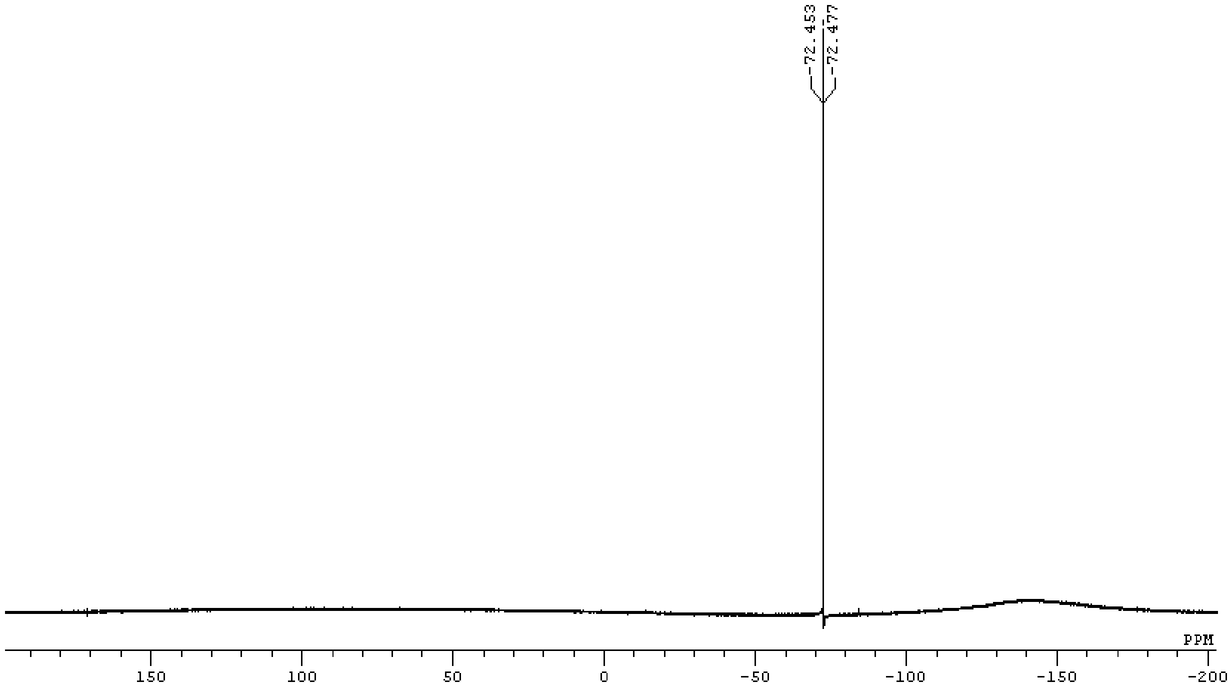

-74.227
-74.251
PPM
150
100
50
0
-50
-100
-150
-200


Et
CF$_3$

2j


7.254
7.160
3.161
3.145
3.125
3.110
3.091
3.086
3.075
3.070
3.050
3.034
3.015
2.999
2.347
2.129
2.112
2.101
2.086
2.074
2.058
2.051
2.035
2.023
2.007
1.995
1.979
1.928
1.901
1.887
1.873
1.860
1.849
1.832
1.823
1.809
1.795
1.782
1.755
1.532
0.855
0.827
0.800
0.000
3.90
3.02
3.11
0.93
1.01
1.00
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5


137.741
133.251
131.738
131.705
131.672
131.639
129.295
129.131
128.901
125.011
120.891
77.469
77.000
76.531
51.999
51.613
51.226
50.840
22.007
21.974
21.933
21.900
21.070
11.497
PPM
200
150
100
50
0


-72.453
-72.477
PPM
150
100
50
0
-50
-100
-150
-200