Supporting Information Section

Exploring Catalyst and Solvent Effects in the Multi-component Synthesis of Pyridine-3,5-Dicarbonitriles

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Preparation of 1-Butyl-3-Methylimidazolium Hydroxide [bmIm]OH

Method A. [bmIm]OH was prepared by modification of a reported procedure.[11] Solid potassium hydroxide (2.3 g, 40 mmol) was added to a solution of [bmIm]Br (8.8 g, 40 mmol) in dry DCM (20 mL), and the mixture was stirred vigorously at rt for 10 h. The precipitated KBr was filtered off and the filtrate was evaporated to obtain the crude [bmIm]OH, which was washed with ether (2 × 20 mL) and dried at 90 ºC for 10 h in an attempt to prepare the purified product. However, no pure product was obtained in our laboratory by this protocol. Interestingly, a isolation of a pure sample of [bmIm]OH was achieved when a small amount of water content was maintained (i.e. not dried completely in the final step).

Method B. Meanwhile, an improved preparation method was developed during our studies: a solution of 1-butyl-3-methylimidazolium bromide [bmIm]Br (1.33 g, 6.0 mmol) in water (30 mL) was loaded onto a column of Dowex 1X2 100–200 ion-exchange resin, hydroxide form (80 g). The resin was washed with water and fractions with pH > 7 were collected and pooled. Water was removed (by lyophilization; but not to complete dryness) to afford the clean [bmIm]OH product.

d_H/ppm (250 MHz, D_2O); 0.77 (3H, t, J = 7.0), 1.09–1.28 (2H, m), 1.61–1.78 (2H, m), 3.72 (3H, s), 4.07 (2H, t, J = 7.0), 7.26–7.36 (2H, d, J = 1.5); m/z (ES^+) 139 ($[M–OH]^+$), 295 ($[2M–OH]^+$); HRMS, found 139.1242 ($C_8H_{15}N_2$ $[M–OH]^+$ requires 139.1235).

Representative NMR spectra illustrating the purity of material obtained from the above procedures are shown below. All ^1H NMR spectra were recorded in D_2O at 400 MHz.

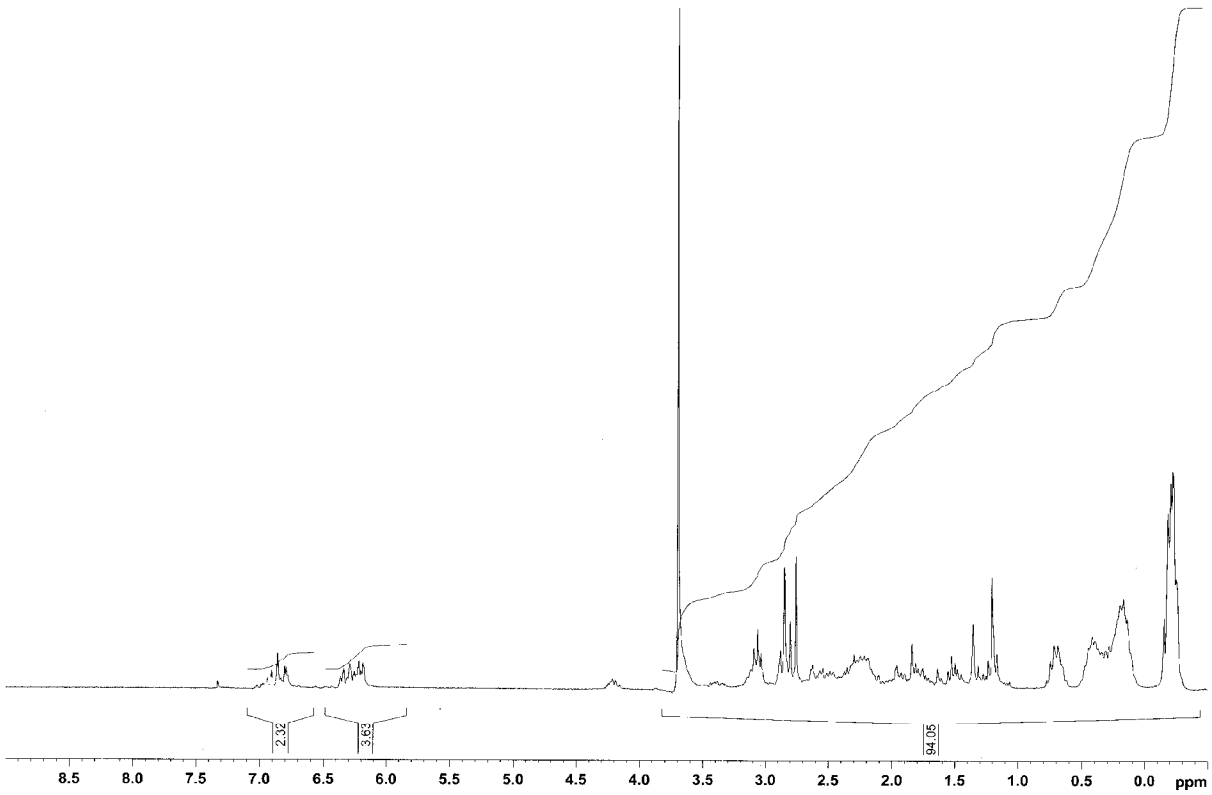


Figure S1. [bmIm]OH prepared following the literature protocol (Ref. 11a).

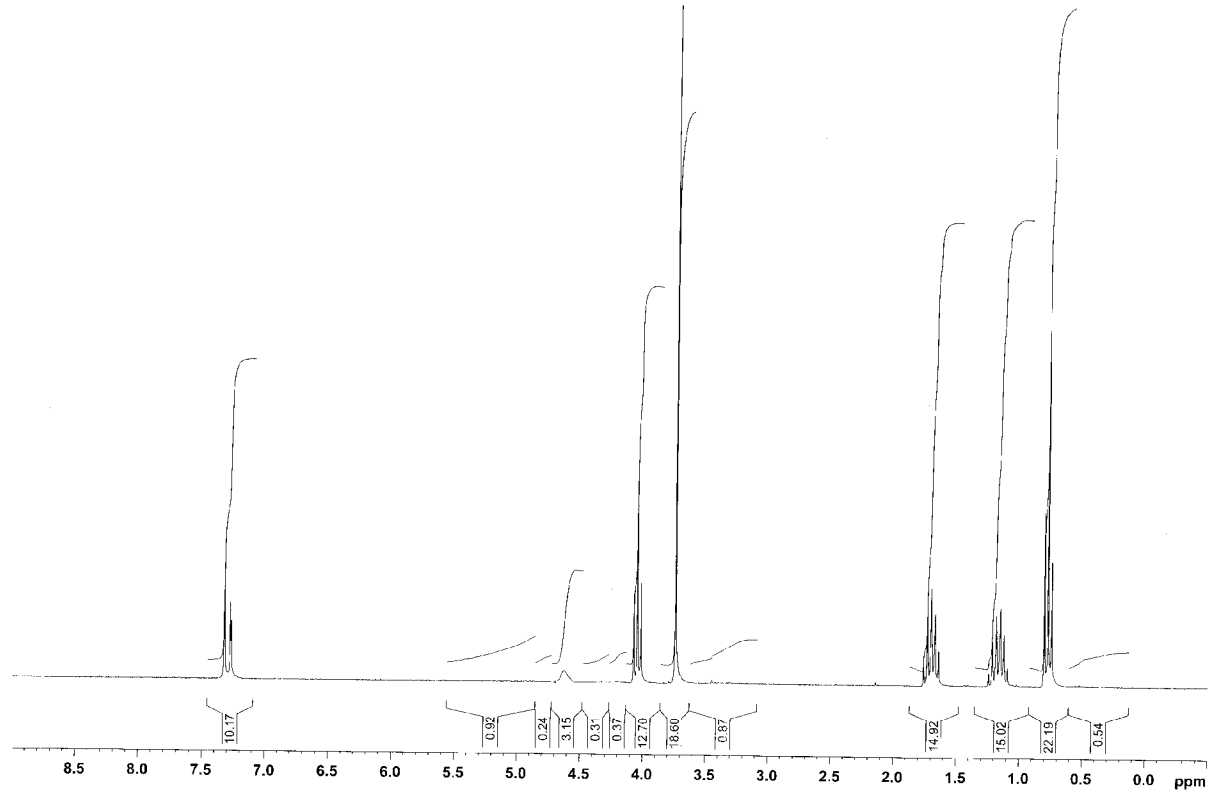


Figure S2. [bmIm]OH prepared following Ref. 11a—but <u>with the final drying step omitted</u> (i.e. no drying at 90 °C for 10 h)—as detailed above in Method A, page 2.

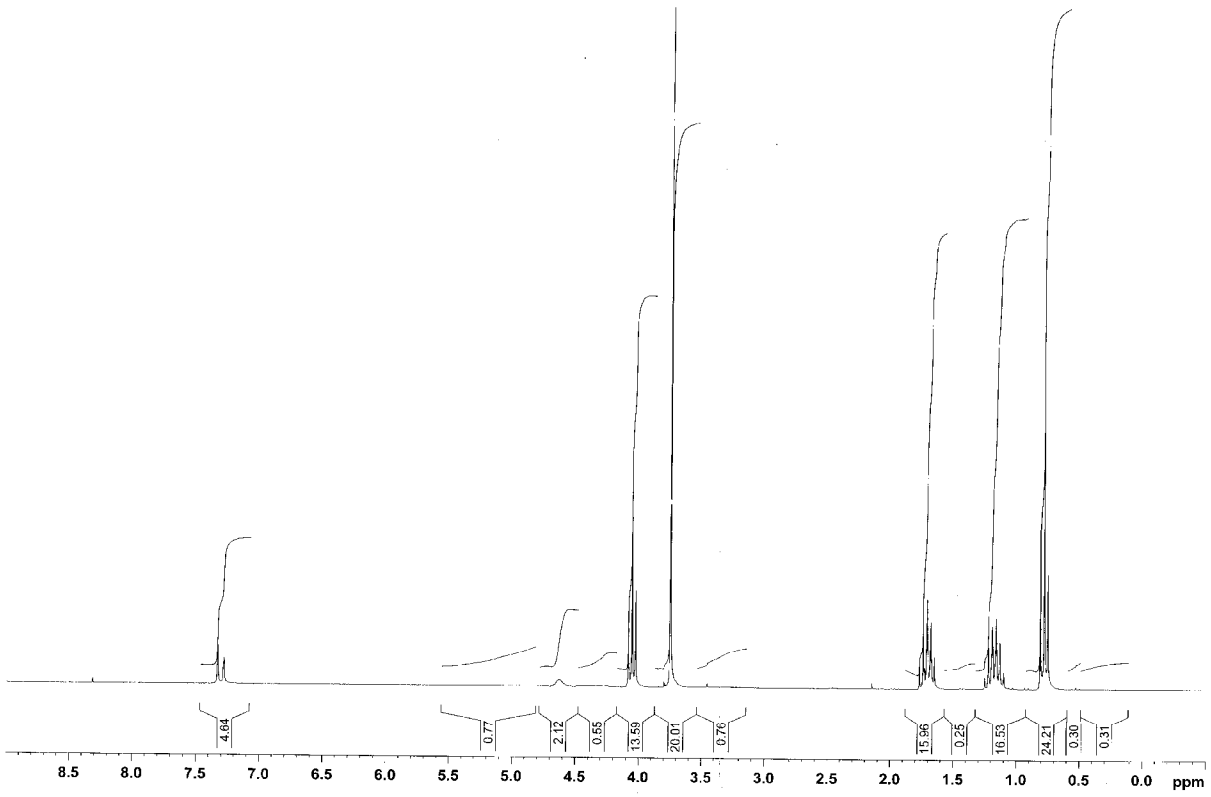


Figure S3. [bmIm]OH prepared by the ion-exchange protocol (Method B, page 2).

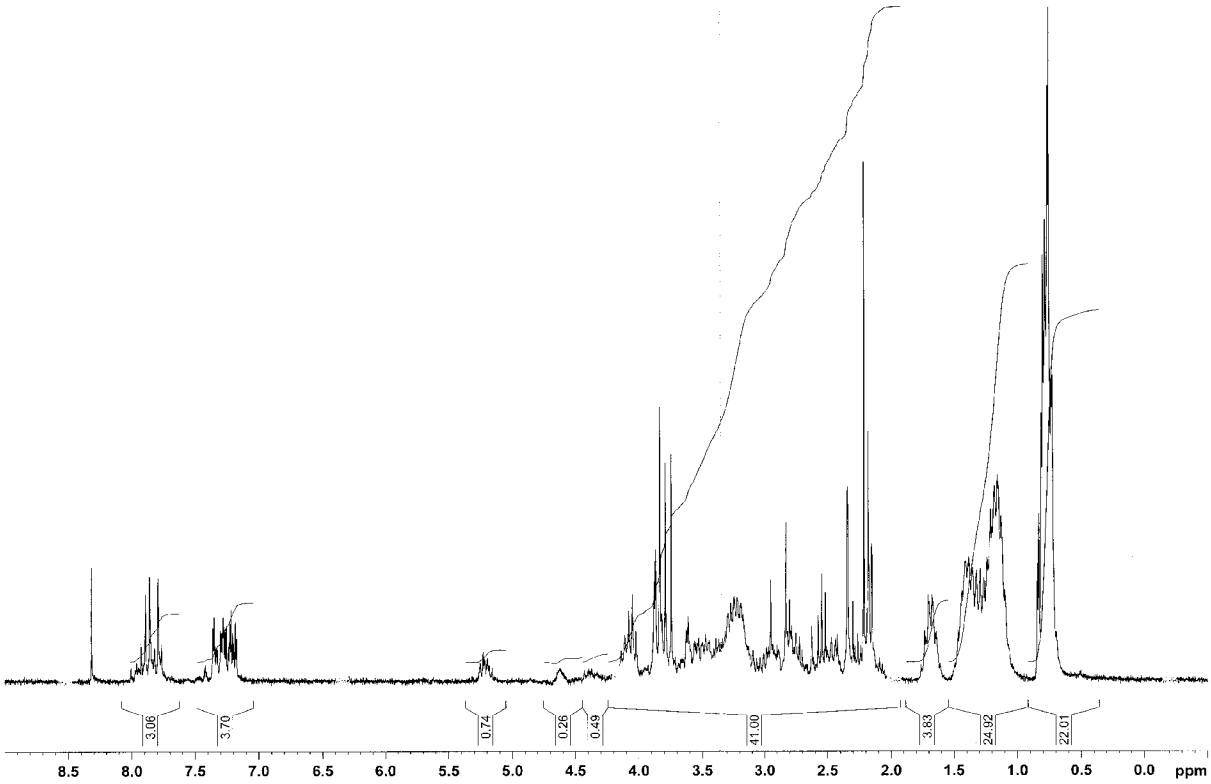


Figure S4. After a clean sample of [bmIm]OH had been left to stand at rt overnight, significant decomposition had occurred, as illustrated by the above NMR spectrum.

Preparation of Additional Compounds

2-Amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile 1. To a stirred solution of benzaldehyde (20 mmol) in ethanol (30 mL) containing piperidine (1 mmol), were added malononitrile (20 mmol) and thiophenol (10 mmol). The reaction mixture was heated at reflux for 3 h, after which it was cooled down to rt. The crystalline precipitate formed was collected by suction filtration, washed with *n*-hexane / ethanol (1:1), and then dried under high vacuum. Yield 2.89 g, 88%; yellow powder. mp 227–228 °C; n_{max} (Solid)/cm^{-1} 3483, 3358, 2208, 1614, 1542, 1513, 1494, 1462, 1440, 1254, 1019, 999, 752, 703, 680; d_H/ppm (250 MHz, $CDCl_3$); 7.40–7.62 (10H, m), 5.49 (2H, br s); d_C/ppm (62.8 MHz, $CDCl_3$), 87.4, 96.0, 114.8, 115.2, 127.2, 128.5, 129.1, 129.3, 130.0, 131.0, 133.2, 135.8, 158.4, 159.3, 169.1; *m*/*z* (ES) 329 ($[M+H]^+$); HRMS, found 329.0845 ($C_{19}H_{13}N_4S$ $[M+H]^+$ requires 329.0861).

2-Benzylidenemalononitrile 7. Malononitrile (10.0 mmol) was added to a stitrred solution of benzaldehyde (10.0 mmol) in ethanol (10 mL) containing piperidine (1.0 mmol). The reaction mixture was stirred at rt for 5 h. A precipitate was formed and collected by suction filtration, washed with *n*-hexane / ethanol (10:1), and then dried under high vacuum. Yield: 1.22 g, 79%; yellow powder. mp 80–81 ºC; n_{max} (Solid)/cm^{-1} 2218.6, 2161.9, 2032.0, 1969.9, 1588.1, 1566.7, 1449.5, 1294.6, 1215.7, 1185.9, 1100.5, 1037.9, 999.8, 958.0; d_H/ppm (250 MHz, CD_3CN), 7.53–7.96 (5H, m), 8.12 (1H, s); d_C/ppm (62.8 MHz, CD_3CN), 113.7, 116.9, 128.2, 128.4, 129.2, 130.2, 131.0, 134.0, 160.6; *m*/*z* (EI), 154 (M^+); HRMS, found 154.0525 ($C_{10}H_6N_2$ $[M]^+$ requires 154.0531).

2-Benzylmalononitrile 8. To a stirred mixture of malononitrile (1.59 mL, 25 mmol) and benzyl bromide (1.52 mL, 12.5 mmol) was added tetra-*n*-butylammonium bromide (0.32 g, 0.5 mmol). The reaction mixture was stirred at rt for 30 min before potassium carbonate (1.73 g, 12.5 mmol) was added at 0 ºC. After addition, stirring was continued for 5 hours at rt. The mixture was extracted with DCM (3 × 50 mL). The organic phase was concentrated and FC, eluted with toluene. Yield 0.78 g, 40%; white powder. mp 90–91 °C, decomp.; n_{max} (Solid)/cm^{-1} 1601.6, 1495.1, 1453.4, 1445.9, 1328.5, 1283.8, 1251.1, 1205.9, 1162.0, 1074.6, 1030.9, 1014.6; d_H/ppm (250 MHz, d_6-DMSO), 3.34 (2H, d, J = 3.5), 5.11 (1H, t, J = 7.0), 7.03–7.44 (5H, m); d_C/ppm (62.8 MHz, d_6-DMSO), 24.8, 35.1, 114.5, 128.4, 129.1, 129.8, 135.2; *m*/*z* (ES^-), 155 ($[M–H]^-$); HRMS, found 155.0609 ($C_{10}H_7N_2$ $[M–H]^-$, requires 155.0609).

3-Amino-2-benzyl-3-(phenylthio)acrylonitrile 9. To a stirred solution of benzaldehyde (3.0 mmol) in ethanol (15.0 mL) containing piperidine (0.9 mmol), were added malononitrile (6.0 mmol) and thiophenol (3.00 mmol). The reaction mixture was heated at reflux for 3 h, after which it was stirred exposed to air for a further 3 h. The mixture was then filtered and the filtrate evaporated then FC, eluted with ethyl acetate / hexane (1:3). Yield 40 mg, 5%; yellow oil. n_{max} (Oil)/cm^{-1} 1603.8, 1495.7, 1453.7, 1446.0, 1328.5, 1283.7, 1250.9, 1206.0, 1163.0, 1074.7, 1030.9, 1015.9, 937.3; d_H/ppm (250 MHz, $CDCl_3$) 3.57 (s, minor isomer) + 3.69 (s, major isomer); 4.20 (br s, minor isomer) + 4.55 (br s, major isomer); 7.24–7.61 (10H, m); d_C/ppm (62.8 MHz, d_6-DMSO) 83.0, 114.0, 121.9, 126.3, 127.7, 127.8, 127.9, 128.1, 128.4, 128.6, 129.3, 129.4, 129.6, 130.3, 131.8, 132.2, 134.7, 139.0, 150.1; *m*/*z* (ES+), 267 ($[M+H]^+$), 289 ($[M+Na]^+$); HRMS, found 289.0785 ($C_{16}H_{14}N_2SNa$ $[M+Na]^+$, requires 289.0775).

2-Amino-4-(2,6-dichlorophenyl)-6-(phenylthio)-1,4-dihydropyridine-3,5-dicarbonitrile 10. To a solution of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) and malononitrile (1.3 mL, 20 mmol) in ethanol (20 mL), were added thiophenol (1.0 mL) and piperidine (0.3 mL, 0.3 mmol). The reaction mixture was then refluxed for 3 h before being cooled down to rt. The formed precipitate was filtered off and washed with ethanol. The title compound was obtained as a yellow solid (3.77 g, 95%). mp 192– 193 ºC; n_{max} (Solid)/cm^{-1} 3351.0, 2203.3, 2168.7, 1656.7, 1618.0, 1584.8, 1445.9, 1419.1, 1394.0, 1252.4, 1222.1; d_H/ppm (250 MHz, d_6-DMSO), 5.64 (1H, s), 6.01 (2H, br s), 6.90–7.09 (8H, m), 9.19 (1H, s); d_C/ppm (62.8 MHz, d_6-DMSO) 52.2, 88.1, 117.4, 119.7, 128.6, 129.7, 129.8, 130.2, 130.6, 135.2, 142.7, 151.5; *m/z* (ES+), 400 ($[M+H]^+$); HRMS, observed 400.0027 (required for $C_{19}H_{13}SN_4Cl_2$ $[M+H]^+$ 400.0029).

2-(2,6-Dichlorobenzylidene)malononitrile 16. To a stitrred solution of 2,6-dichlorobenzaldehyde (10.0 mmol) in ethanol (10.0 mL) containing piperidine (1.0 mmol) was added malononitrile (10.0 mmol). The reaction mixture was stirred at rt for 5 hours.The precipitate formed was collected by suction filtration, washed with *n*-hexane / ethanol (10:1), and then dried under high vacuum. Yield 1.32 g, 59%; brown solid. mp 88–89 ºC; n_{max} (Solid)/cm^{-1} 1602.0, 1577.8, 1556.3, 1438.4, 1431.2, 1199.4, 1144.8, 1097.3, 902.3, 855.7; d_H/ppm (250 MHz, $CDCl_3$) 7.39–7.50 (3H, m), 7.97 (1H, s); d_C/ppm (62.8 MHz, CD_3CN) 93.6, 110.6, 111.6, 116.9, 128.5, 132.8, 133.2, 157.6; *m*/*z* (EI), 221 (M^+); HRMS, found 221.975038 ($C_{10}H_4N_2Cl_2$ $[M]^+$ requires 221.975154).

Dilution and HPLC Details for Table 1

catalyst	Temp.	Time (h)	MeCN[a] 1:2:1	MeCN[a] 2:3:1	DMSO[a] 1:2:1	DMSO[a] 2:3:1	EtOH[a] 1:2:1	EtOH[a] 2:3:1
TBAH	r.t.	6	1000/C	100/C	40/C	10/C	80/C	70/C
TBAH	Reflux	1	1000/C	200/C	20/C	50/C	200/C	2000/C
TBAH	Reflux	18	20/C	80/C	40/C	80/C	50/C	40/C
[bmIm]OH	r.t.	6	200/C	100/C	600/C	100/C	600/C	350/C
[bmIm]OH	Reflux	1	150/C	500/C	150/C	600/C	500/C	350/C
[bmIm]OH	Reflux	18	150/C	150/C	100/C	250/C	150/C	150/C
Piperidine	Reflux	3	50/C	100/C	400/C	260/C	80/C	2000/C
Piperidine	Reflux	24	150/A	150/A	150/A	150/A	150/A	150/A

[a] dilution ratio / HPLC method used.

HPLC Conditions.

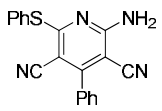
Method A. Ace 3*m* C18 column, 12.5 × 4.6 cm; 40–70 % MeOH in water over 10 min, then 70–90% MeOH in water over 3 min, hold 2 min; flow rate 1.0 mL/min; 5 *m*L injection; uv detection at 254 nm.

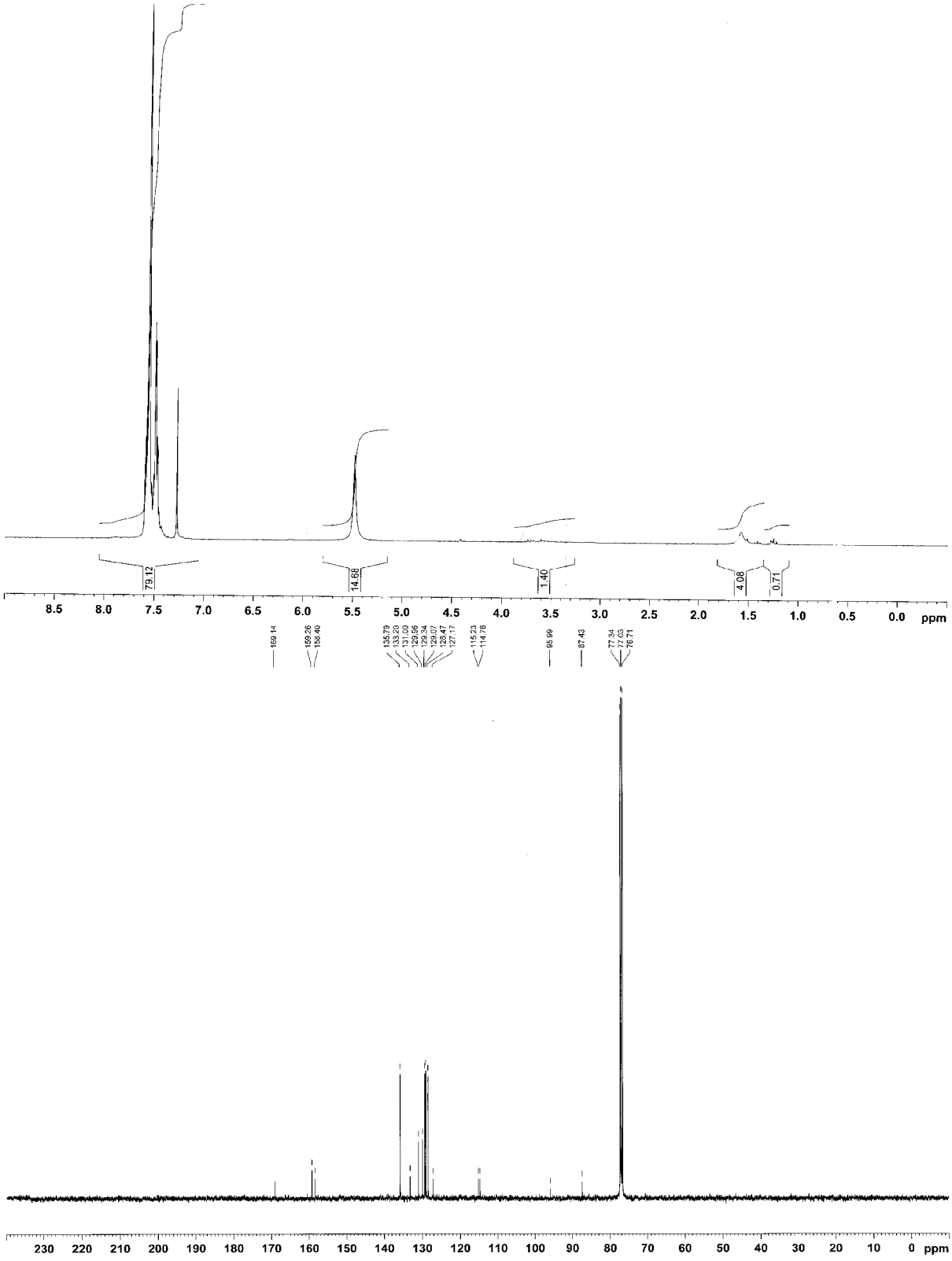
Method B. Ace 3*m* C18 column, 12.5 × 4.6 cm; 70% MeOH in water over 7 min; flow rate 1.0 mL/min; 5 *m*L injection; uv detection at 254 nm.

Method C. Alltima HP C18 3*m* column, 15 × 4.6 cm; 40–70% MeCN in water over 20 min; 70–90% MeCN in water over 5 min; flow rate 1.0 mL/min; 20 *m*L injection; uv detection at 254 nm.

1

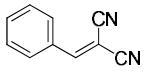
2-Amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile

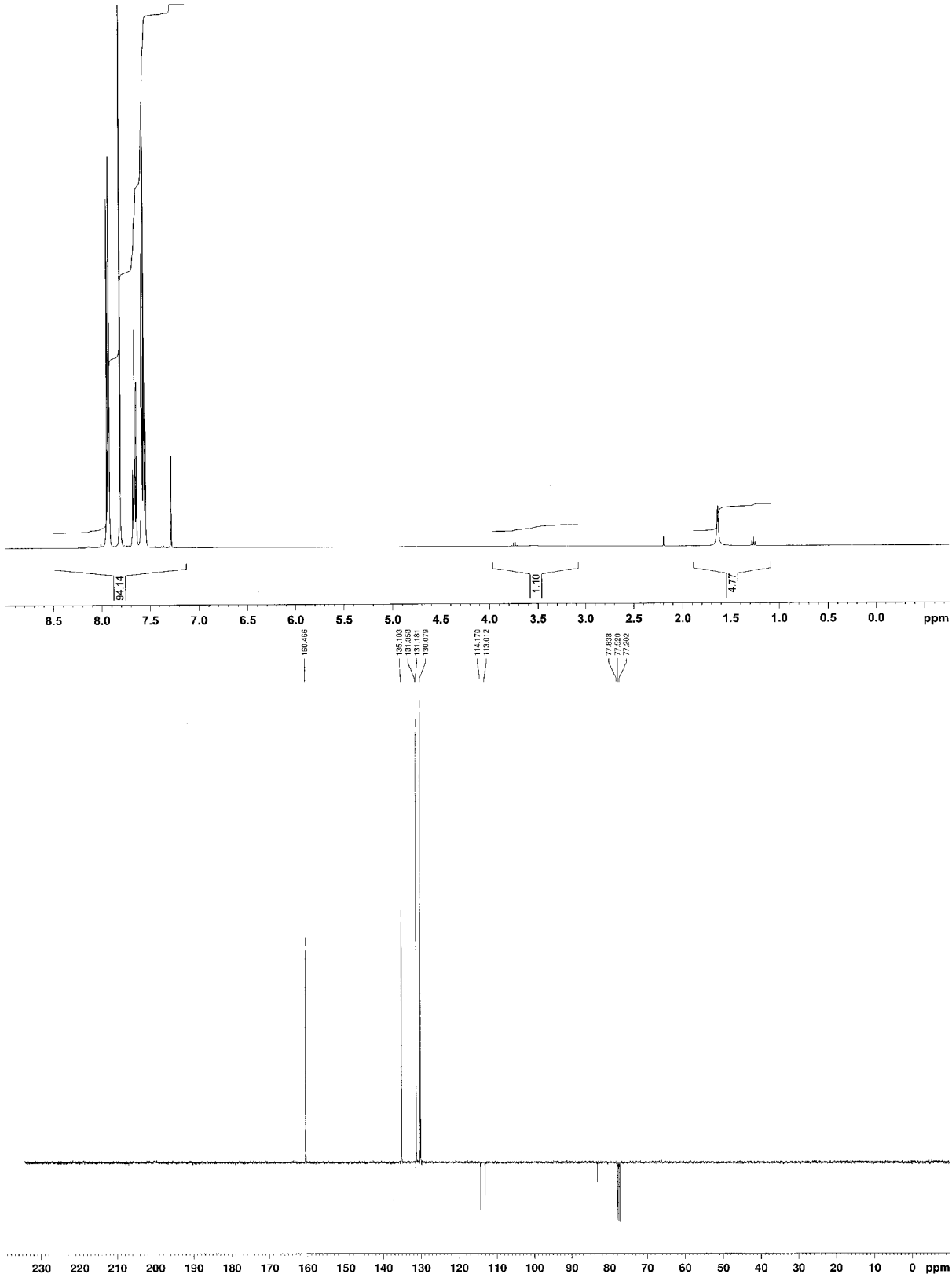




7

2-Benzylidenemalononitrile





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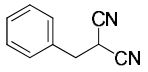
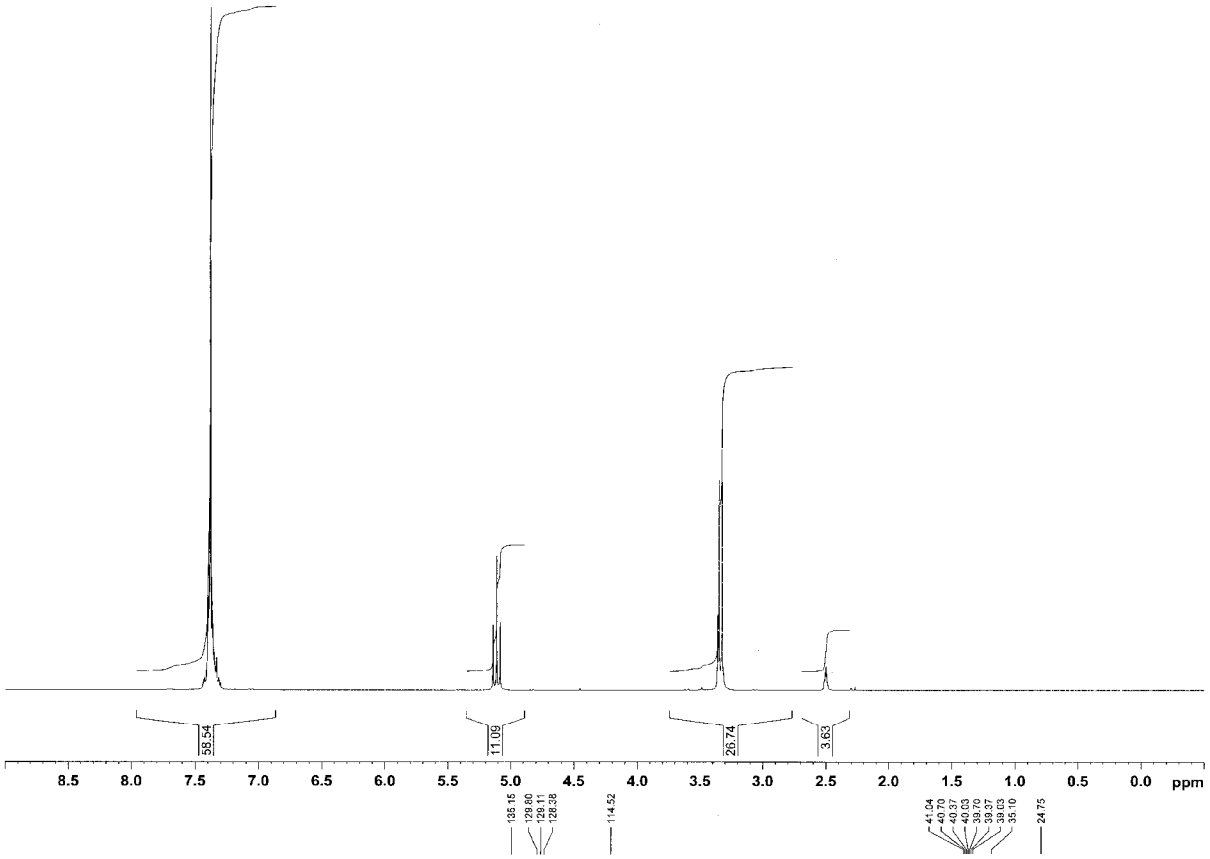
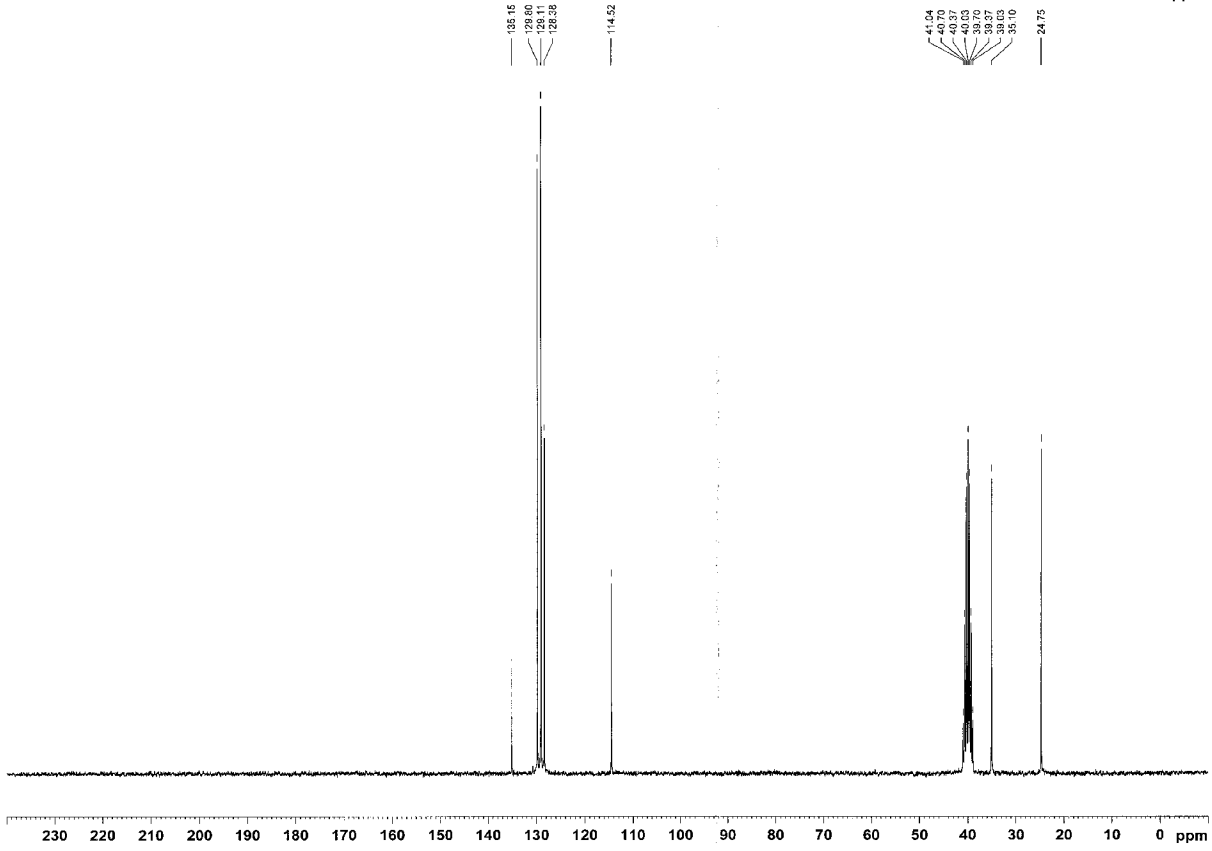
2-Benzylmalononitrile

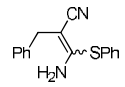


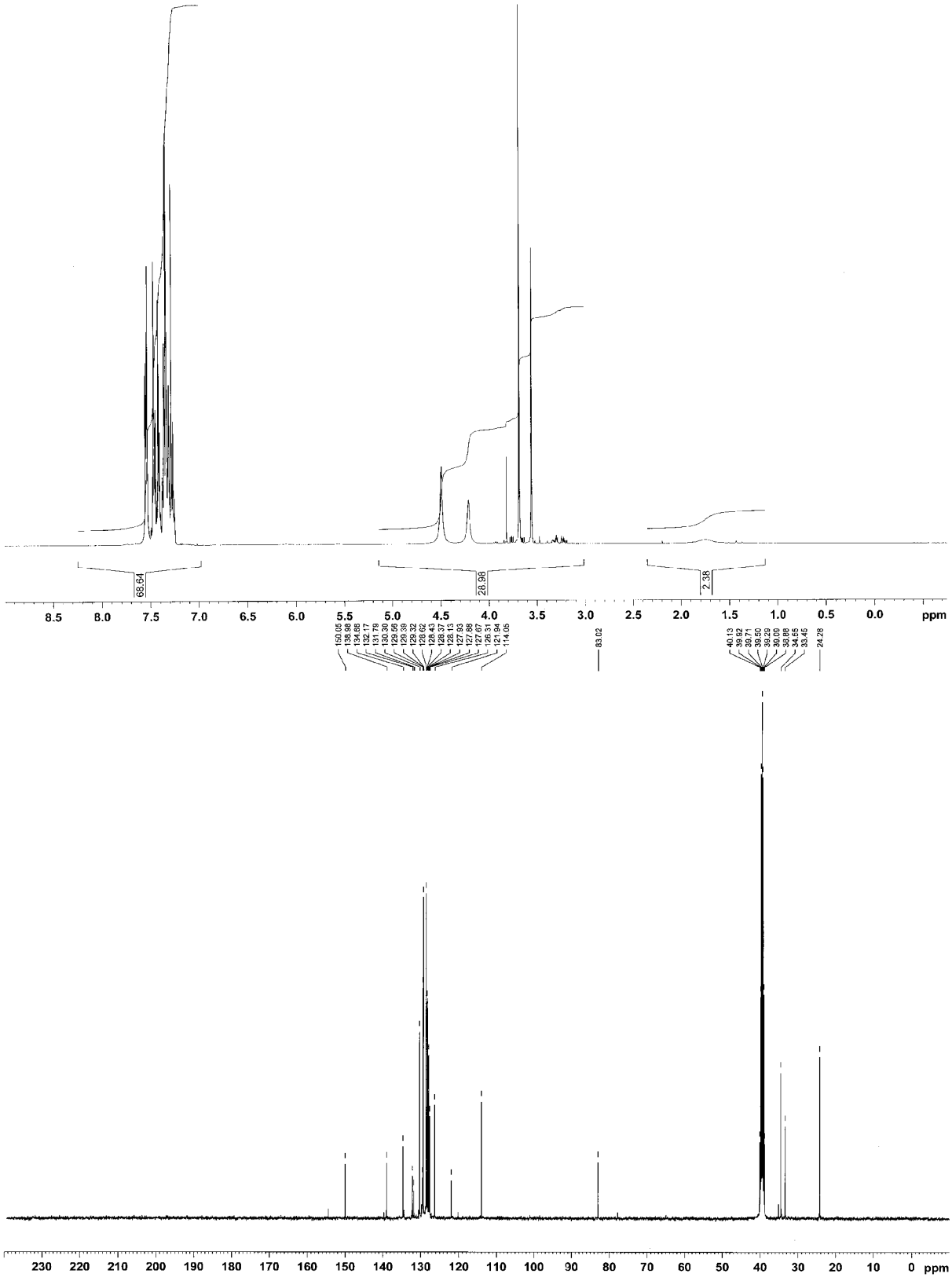




9

3-Amino-2-benzyl-3-(phenylthio)acrylonitrile





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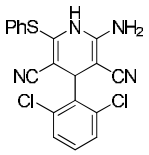
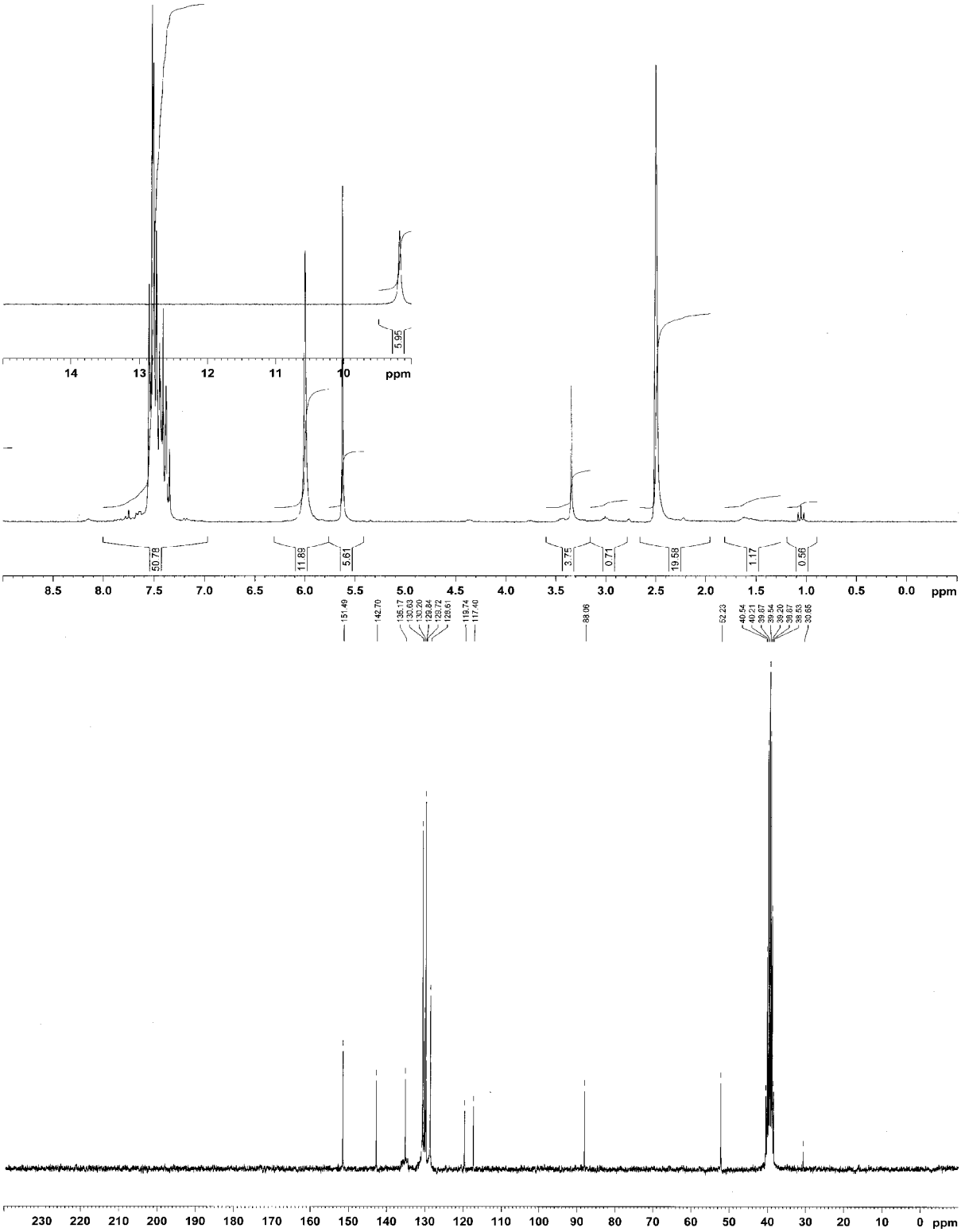
2-Amino-4-(2,6-dichlorophenyl)-6-(phenylthio)-1,4-dihydropyridine-3,5-dicarbonitrile





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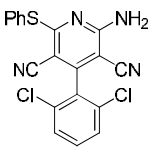
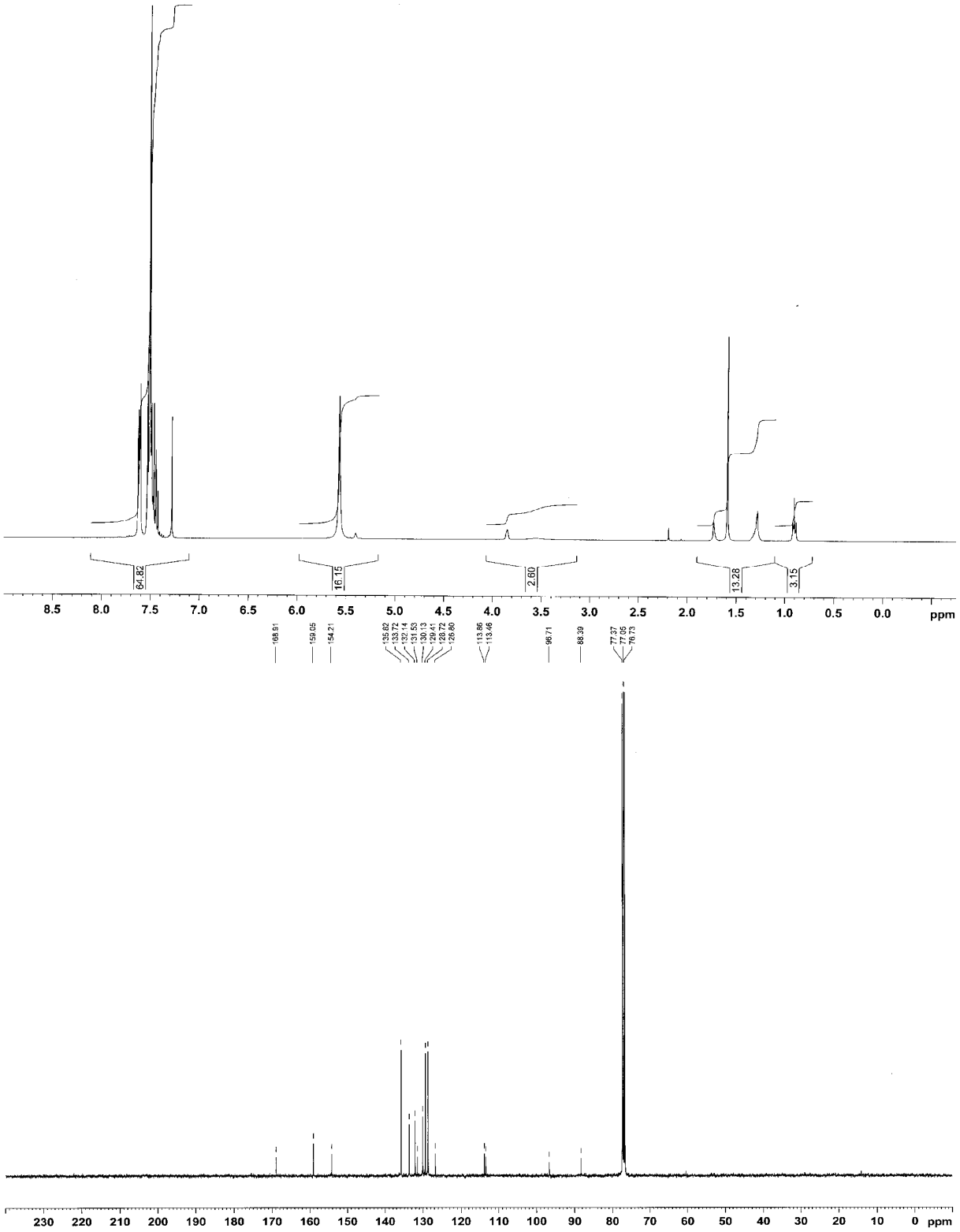
2-Amino-4-(2,6-dichlorophenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile





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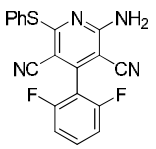
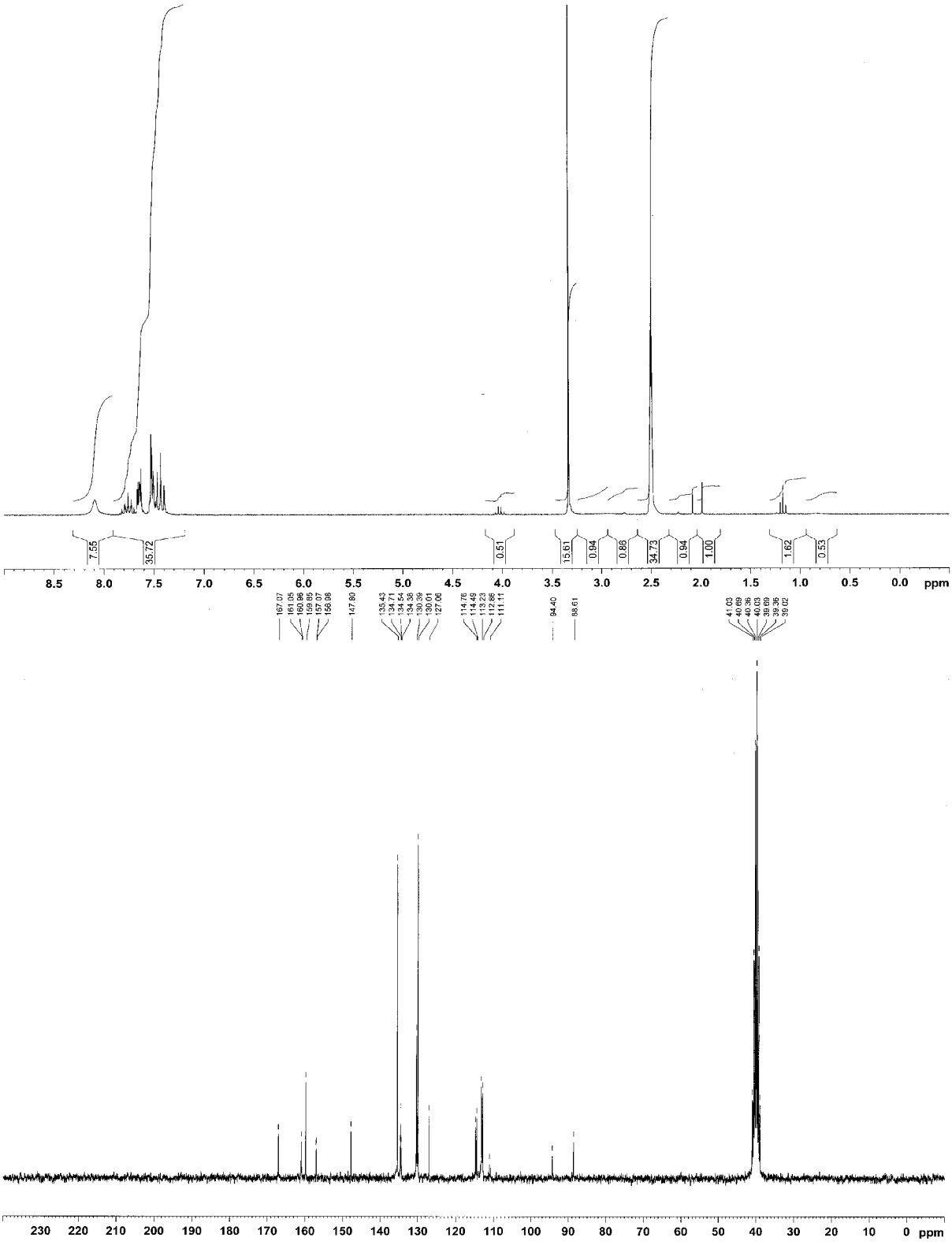
2-Amino-4-(2,6-difluorophenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile





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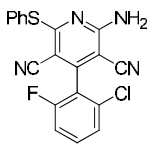
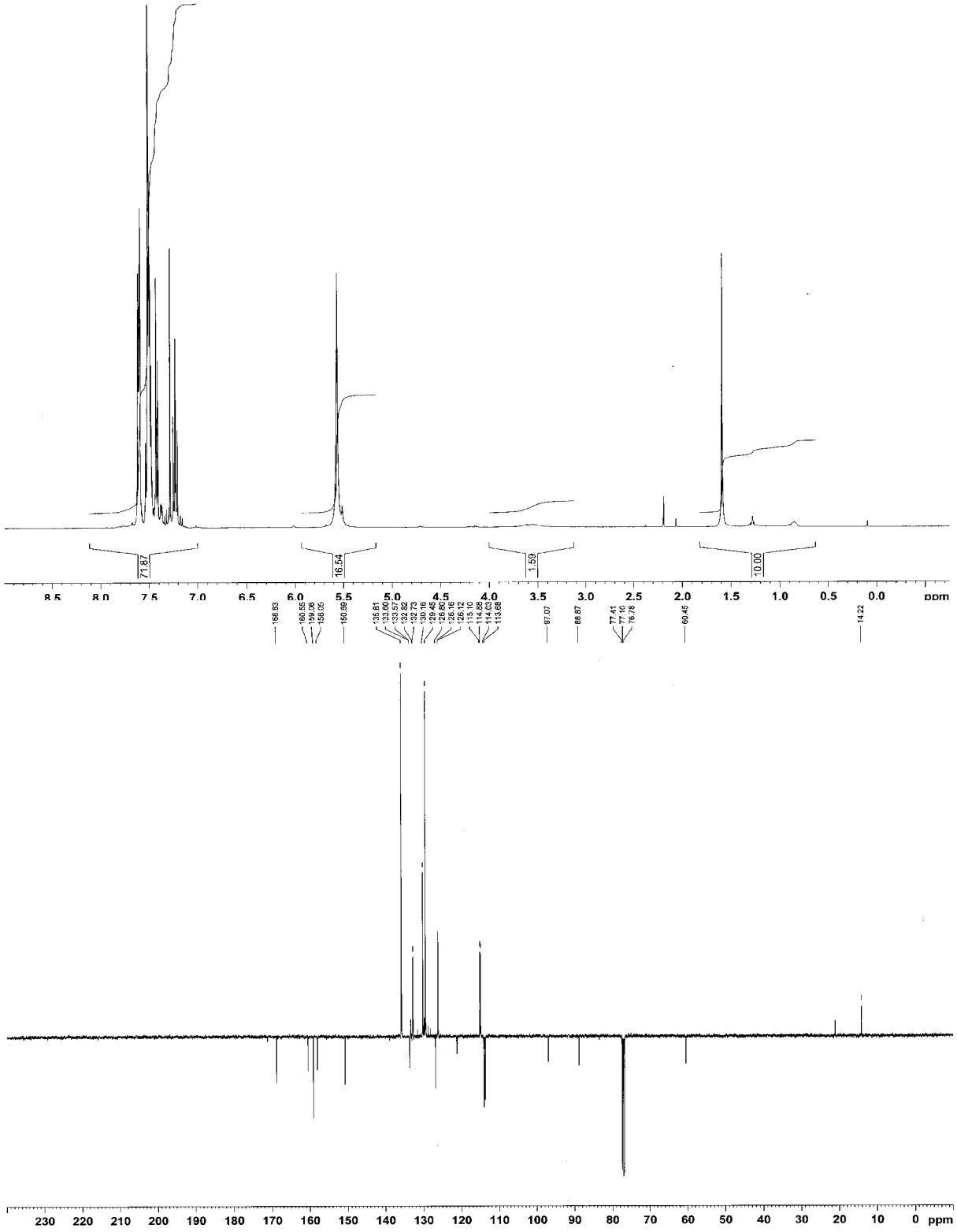
2-Amino-4-(2-chloro-6-fluorophenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile





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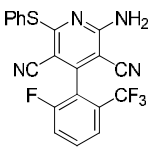
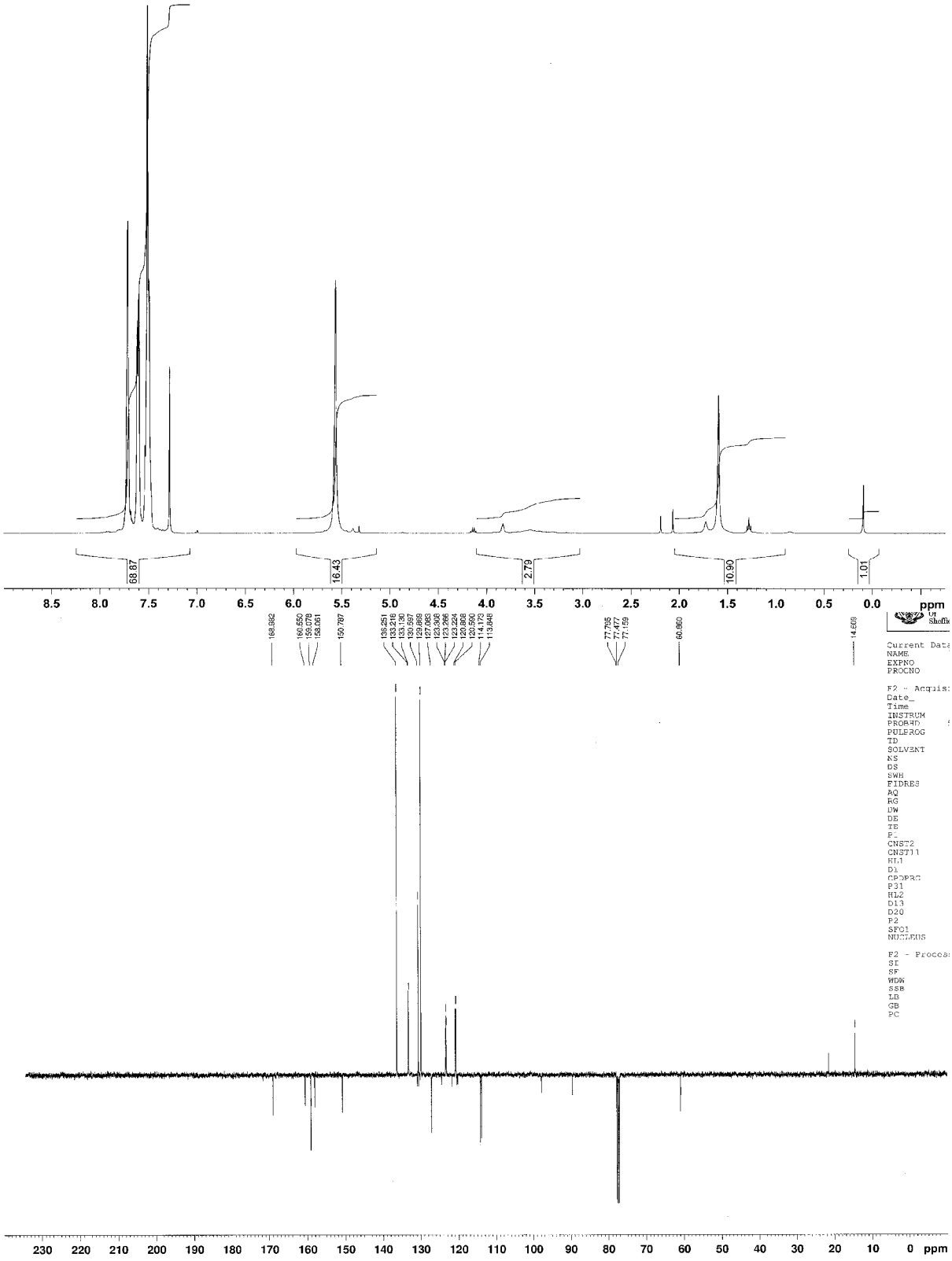
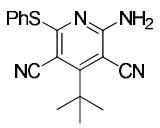
2-Amino-4-(2-fluoro-6-(trifluoromethyl)phenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile

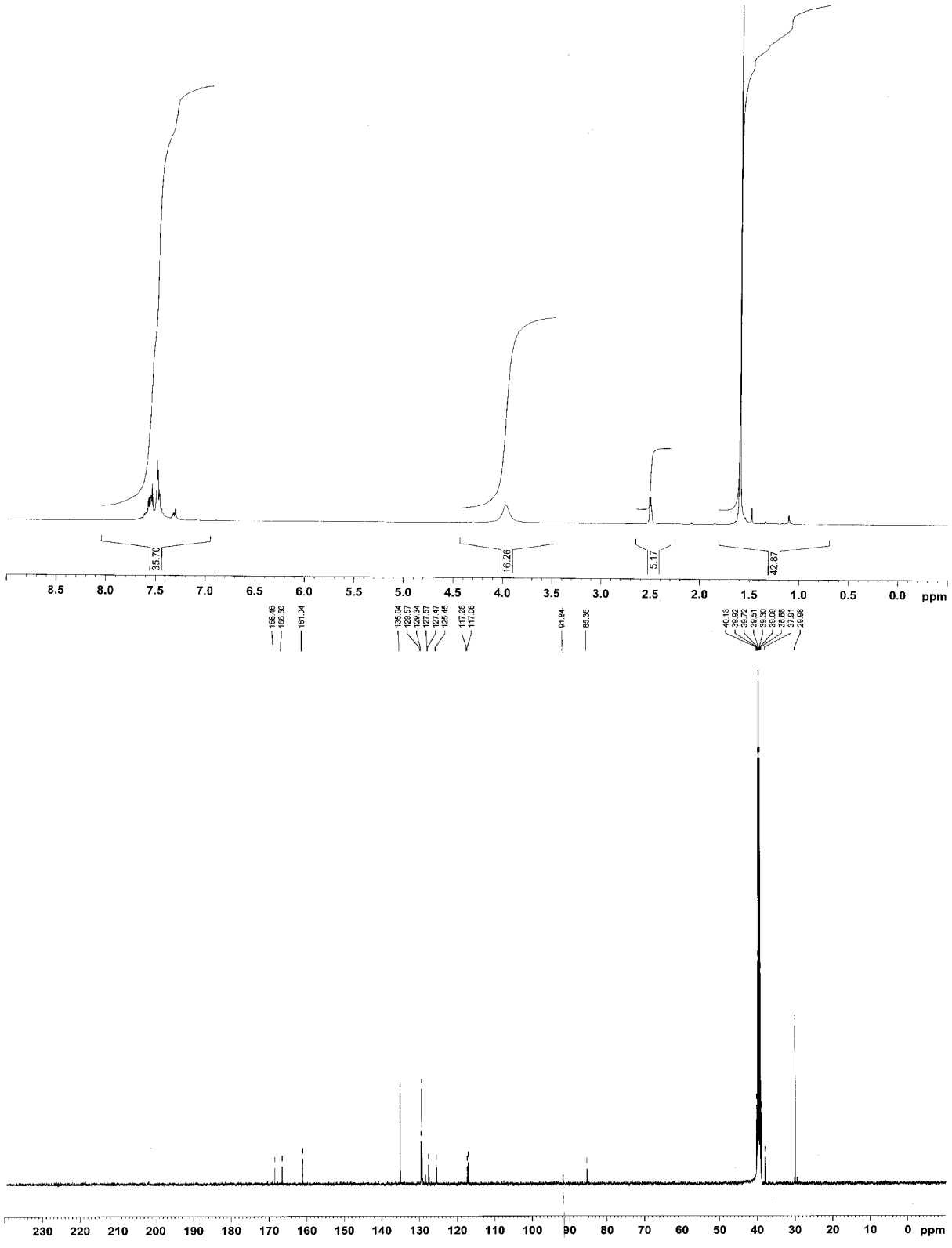




15

2-Amino-4-*tert*-butyl-6-(phenylthio)pyridine-3,5-dicarbonitrile





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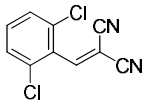
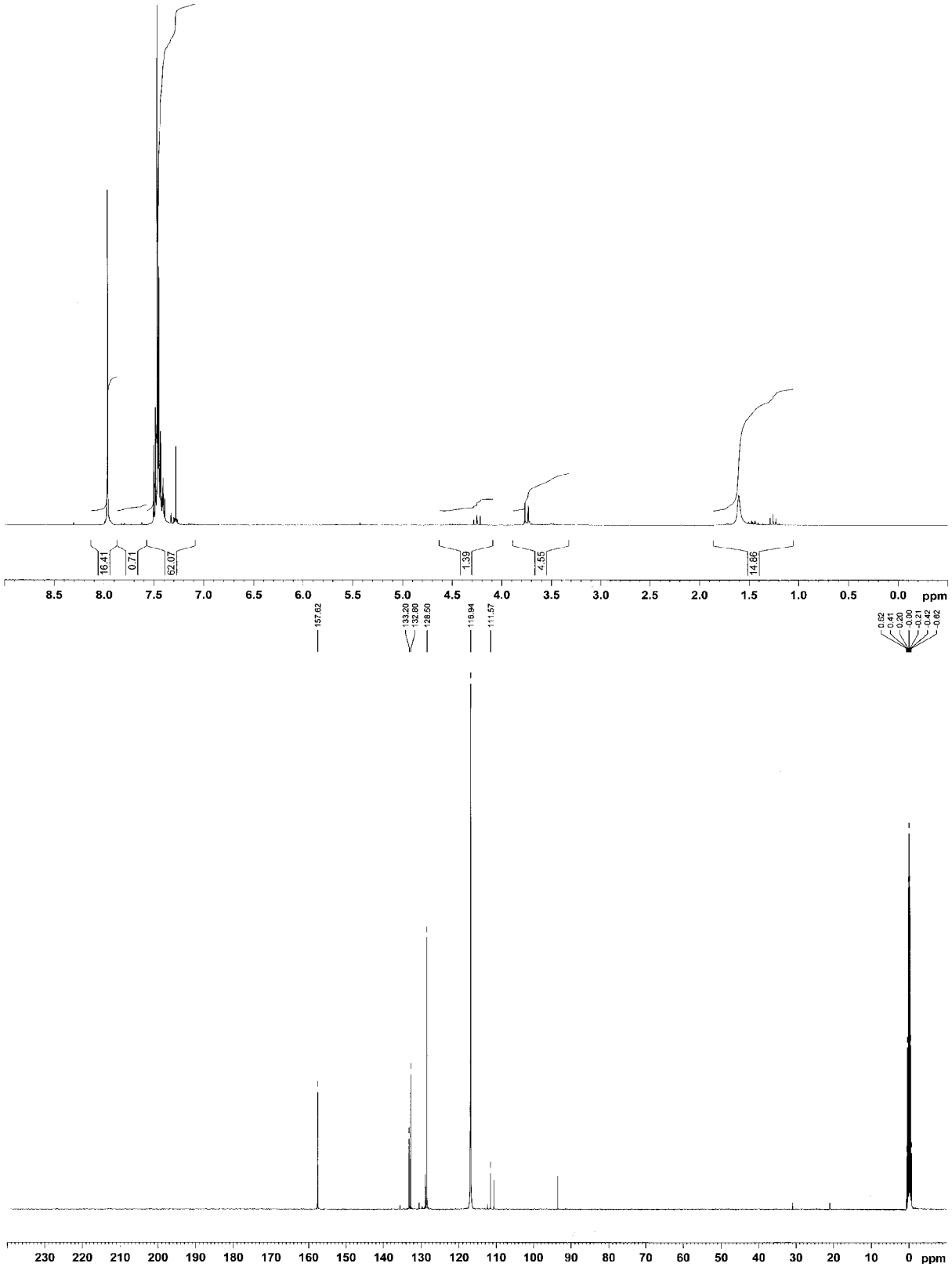
2-(2,6-Dichlorobenzylidene)malononitrile

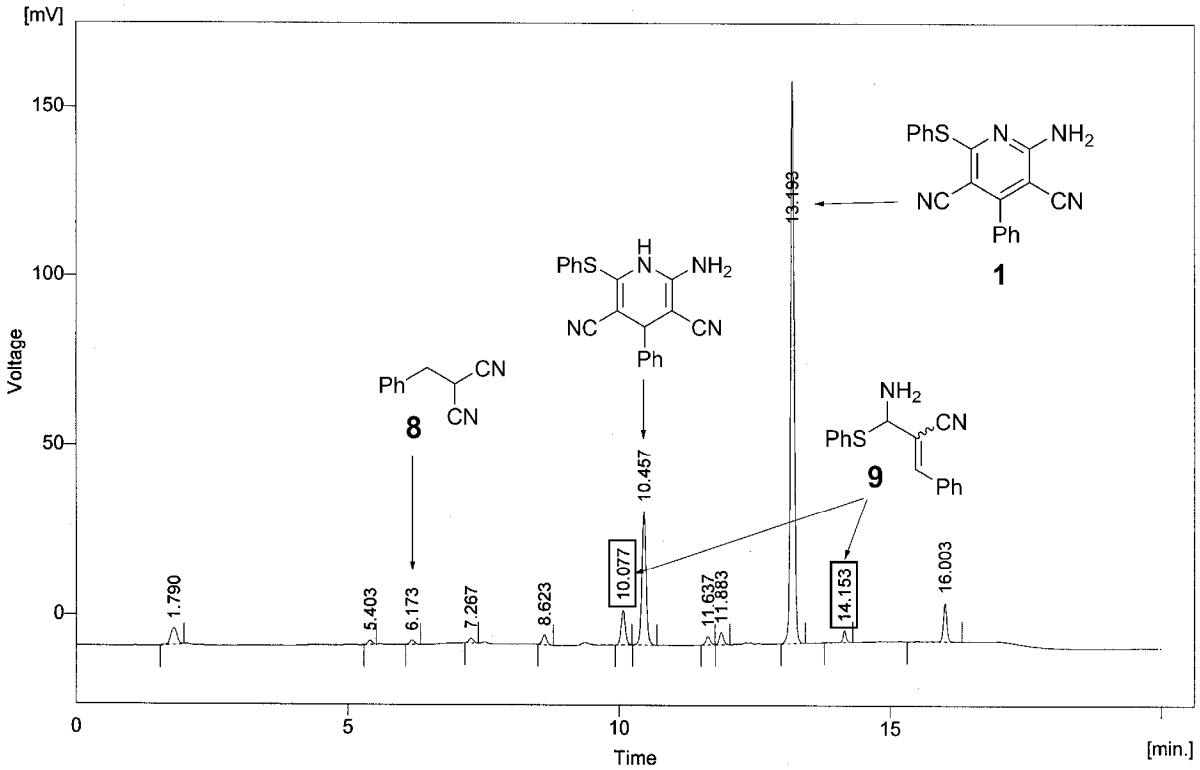




Example HPLC Traces

Example using: Method A

Reaction: Figure 5, Column 1 (Reaction under N_2; 28% yield).

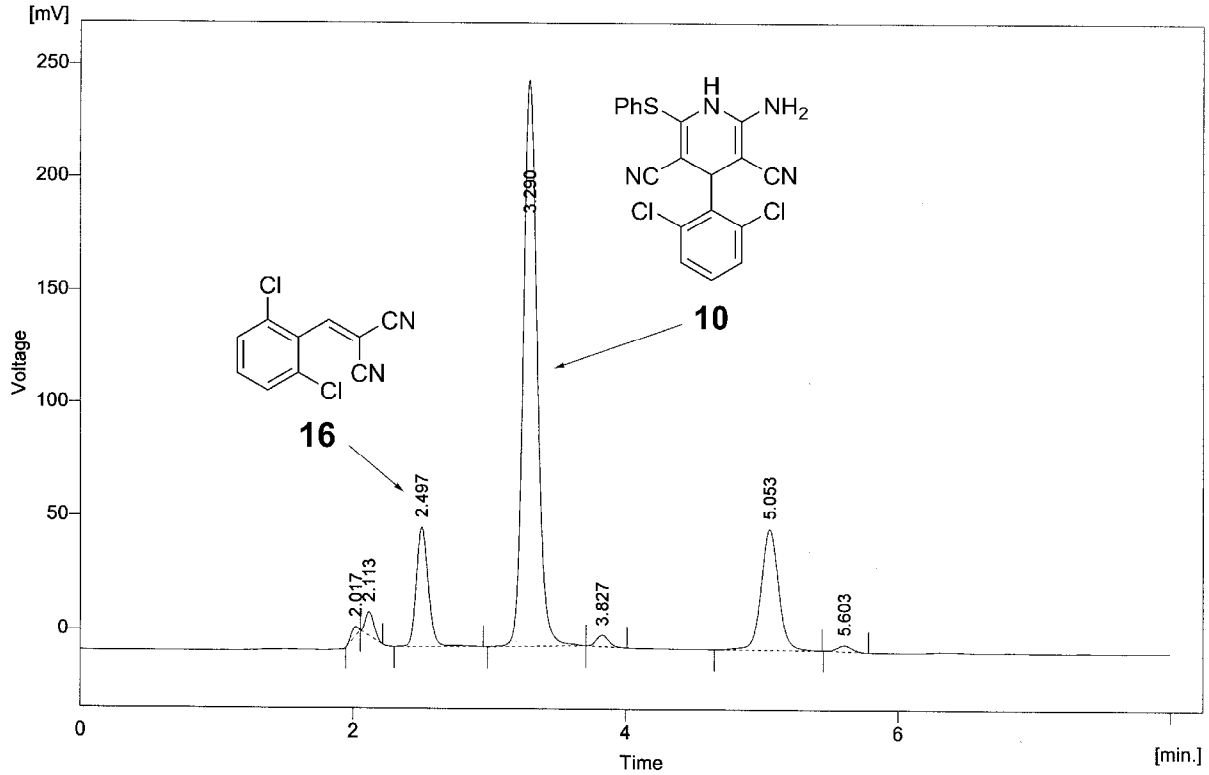


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	1.790	39.781	4.712	3.3	1.9	0.14
2	5.403	6.965	1.239	0.6	0.5	0.09
3	6.173	7.616	1.306	0.6	0.5	0.10
4	7.267	8.296	1.449	0.7	0.6	0.09
5	8.623	16.687	2.934	1.4	1.2	0.09
6	10.077	56.696	10.369	4.7	4.2	0.09
7	10.457	217.457	39.415	17.9	15.9	0.09
8	11.637	13.770	2.466	1.1	1.0	0.09
9	11.883	18.631	3.544	1.5	1.4	0.09
10	13.193	758.849	165.973	62.4	66.8	0.07
11	14.153	14.901	3.481	1.2	1.4	0.06
12	16.003	56.320	11.568	4.6	4.7	0.07
	Total	1215.969	248.456	100.0	100.0	

Example using: Method B

Reaction: Figure 3, Final Column.

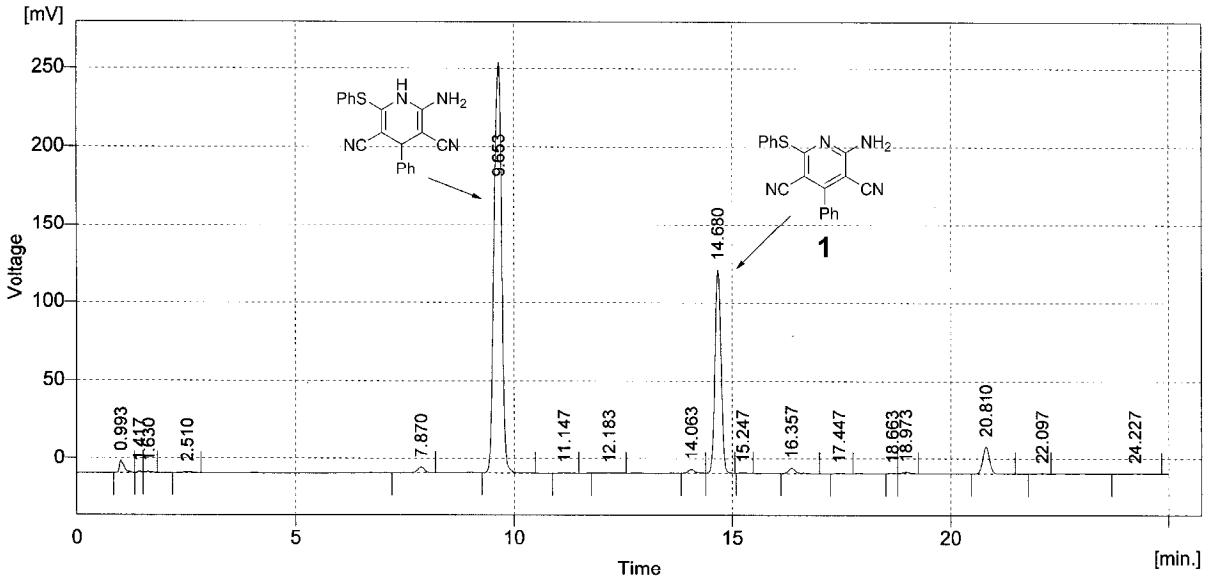


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	2.017	14.393	4.290	0.5	1.1	0.06
2	2.113	46.480	10.467	1.7	2.8	0.07
3	2.497	323.068	52.488	12.0	13.9	0.10
4	3.290	1784.008	250.431	66.0	66.1	0.11
5	3.827	32.595	5.163	1.2	1.4	0.10
6	5.053	479.392	53.128	17.7	14.0	0.14
7	5.603	21.360	2.734	0.8	0.7	0.13
	Total	2701.297	378.700	100.0	100.0	

Example using: Method C

Reaction: Table 1, Row 5, Column E (28% yield; reflux with [bmIm]OH in EtOH for 1 h).



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	0.993	56.618	7.636	1.2	1.8	0.12	0.0
2	1.417	3.336	0.704	0.1	0.2	0.08	0.0
3	1.630	4.520	0.456	0.1	0.1	0.16	0.0
4	2.510	10.398	0.712	0.2	0.2	0.21	0.0
5	7.870	37.821	3.409	0.8	0.8	0.17	0.0
6	9.653	3169.675	262.535	65.8	60.8	0.20	0.0
7	11.147	3.611	0.282	0.1	0.1	0.19	0.0
8	12.183	5.684	0.271	0.1	0.1	0.22	0.0
9	14.063	25.100	2.290	0.5	0.5	0.16	0.0
10	14.680	1254.799	130.415	26.0	30.2	0.15	0.0
11	15.247	3.013	0.315	0.1	0.1	0.15	0.0
12	16.357	37.379	3.228	0.8	0.7	0.17	0.0
13	17.447	3.323	0.321	0.1	0.1	0.16	0.0
14	18.663	1.296	0.150	2.7e-02	3.5e-02	0.17	0.0
15	18.973	9.940	0.906	0.2	0.2	0.16	0.0
16	20.810	184.976	17.311	3.8	4.0	0.17	0.0
17	22.097	3.361	0.313	0.1	0.1	0.15	0.0
18	24.227	5.161	0.365	0.1	0.1	0.12	0.0
	Total	4820.010	431.616	100.0	100.0		-