Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

A highly active and easily recoverable chitosan@copper catalyst for the C-S coupling and its application in the synthesis of Zolimidine

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1. General Information

a. Materials

Chitosan powder (MW: 10,000-50,000, deacetylation degree 95%, purchased from Aladdin reagent (Shanghai) Co., Ltd.) was used without further purification. Aryl halides and sulfinic acid salts were purchased from Alfa Aesar. Other chemicals were obtained commercially and used without any prior purification. ^{1}H NMR spectra were recorded on a Bruker AvanceII 400 spectrometer using TMS as the internal standard. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60-90 °C), unless otherwise noted. All compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, which are consistent with those reported in the literature[1-6].

b. Methods

Melting points were determined on an X-5 Data microscopic melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature with $CDCl_3$ or DMSO-d_6 as solvent unless otherwise noted and tetramethylsilane (TMS) as the internal standard. Mass spectra (GC-MS) were acquired on an Agilent 5975 spectrometer. IR spectra were recorded on a Nicolet 380 FT-IR spectrophotometer using KBr discs. Transmission electron microscopy (TEM) images were taken on FEI T20 microscope. ICP-AES metal determinations were carried out on a Perkin-Elmer Optima 3100 XL inductively coupled plasma atomic emission spectrometer equipped with an axial torch,segmented array charge-coupled device detector, and Babington-type nebulizer with cyclonic spray chamber for sample introduction. The small-angle X-ray diffraction (SAXRD) data were taken on a German Bruker D4 X-ray diffractometer with Niltered Cu Ka radiation (40 kV, 40 mA). Thermogravimetric analyses were performed with a SII Nano Technology EXTAR TG/DTA7220 thermal analyzer at 10 °C/min in nitrogen atmosphere (10 ml/min). 5 mg of each sample in an alumina pan was analyzed in the 40-900 °C temperature range. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates.

2. Experimental

Experimental procedure for synthesis of chitosan@copper catalyst.

Chitosan (5 g) was suspended in 100 mL of water. To this suspension, 1 g of copper salt was added and stirring was continued for 3 h. The catalyst was separated using centrifuge (5000 rpm/5 min), dried under vacuum at 50 °C. The catalyst was characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM) Infrared Spectroscopy (IR) and plasma-atomic emission spectrometry (ICP-AES),. The signals pertaining to copper metal were not detected in XRD; it may be due to complexation with chitosan or low percentage. The copper loading levels of catalysts, which was measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES), were 1.95, 1.50, and 1.46 mmol/g, respectively

General procedure for CS@$Cu(OAc)_2$-catalyzed coupling of aryl halides and sodium benzenesulfonate.

A mixture of aryl halide (1 mmol), sodium benzenesulfonate (1.2 mmol), CS@$Cu(OAc)_2$ (120 mg, loading 10 mol%), KOAc (2 mmol), 3 mL of DMSO-H_2O (1:1) in a sealed tube was heated to 120 °C under air. The reaction was monitored using thin layer chromatographic technique. After complete disappearance of aryl halide, the reaction was cooled and the catalyst was filtered off, then the solvent was evaporated and further purification has done by column chromatography on neutral alumina using ethyl acetate/hexanes as the eluent to afford the product.

The catalyst recycling experiment.

. To check if the CS@$Cu(OAc)_2$ is recyclable, the C-S coupling reaction was repeated five times with the same catalyst sample, which was recovered after each reaction. The initial amount of catalyst was 120 mg. Reactions were carried out for 24 h. After the reaction, the catalyst was filtered off, washed with ethyl acetate and water twice, then dried for 3 h at 60 °C. It was then stored at ambient conditions over night and used again.

The leaching study of CS@Cu(OAc)$_2$ catalyst.

To verify whether the observed catalysis is derived from CS@Cu(OAc)$_2$ catalyst or leached copper species, the reaction of 4-iodoanisole (1.0 mmol) with benzenesulfinic acid sodium salt (1.2 mmol), CS@Cu(OAc)$_2$ (120 mg, loading 10 mol%), KOAc (2 mmol), in DMSO : H_2O (3 ml 1:1) at 120 °C under air. The catalyst was removed from the reaction mixture by hot filtration after 6 hours (at this time, approximately 50% conversion). The catalyst was isolated by filtration and dried for several hours under vacuum to provide the recovered catalyst. After removal of the catalyst, the reaction was carried out again and no more product conversion was further observed even during extended time.

ICP-AES metal determinations were carried out on a Perkin-Elmer Optima 3100 XL inductively coupled plasma atomic emission spectrometer. The ICP-AES analysis was preformed using bomb digestion for CS@Cu(OAc)$_2$ catalyst (approximately 120 mg of per sample was employed) and an argon gas nebulizer for aqueous filtrate. An appropriate amount of nitric acid (30 wt%) was added to the samples, and the resulting sample adjusted to 5 wt% nitric acid was applied for ICP-AES to characterize the Cu leaching. Samples were run in duplicate, and average values are reported. The recovered catalyst from hot filtration was measured to be 5.83 (±0.05) wt % Cu and the filtrate was <0.0001 wt % Cu. After the catalyst recycling experiment, the copper content was measured to be 5.80% (±0.04) after the five reactions. Since the original catalyst was 5.83 (±0.02) wt % Cu, this experiment indicates that essentially no copper was leached from the CS@Cu(OAc)$_2$ catalyst under the C-S cross-coupling reaction conditions.

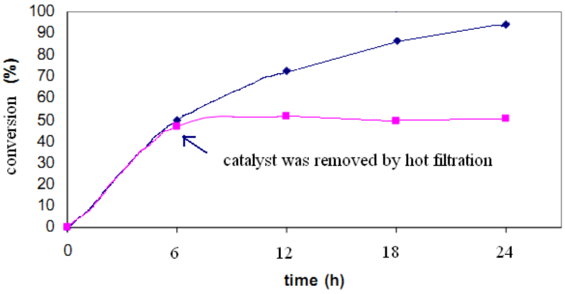


Figure S0. Hot filtration test

General procedure for one-pot synthesis of Zolimidine.

A mixture of 2-aminopyridine (113 mg, 1.2 mmol), *p*-iodoacetophenone (246 mg, 1 mmol), CS@$Cu(OAc)_2$ (120 mg, loading 10 mol%), and ZnI_2 (0.1 mmol) in DMSO (3 mL) was stirred at 120 °C for 24 hours under ambient air. Then sodium methanesulfinate (122 mg, 1.2 mmol) and KOAc (196 mg, 2 mmol) were added. The reaction was stirred at 120 °C for another 24 hours under air. After cooling the reaction mixture, the catalyst was filtered and washed with with ethyl acetate and water. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent. Yellowish white solid (166 mg, 61% yield). It is characterized by ^1H NMR, ^{13}C NMR which is consistent with those reported in the literature.[5-6]

3. Characterization of the Products

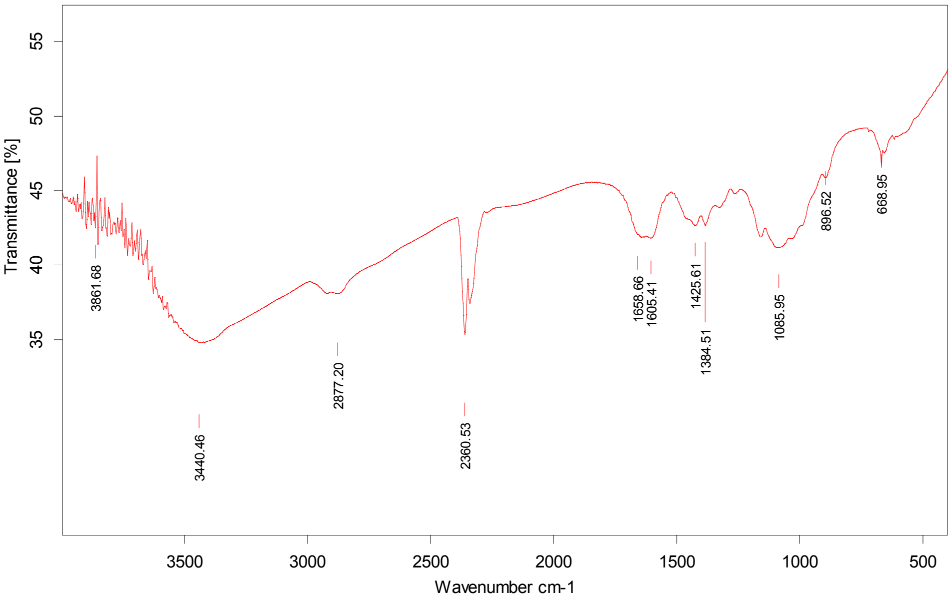


Figure S1. Infrared spectra of chitosan

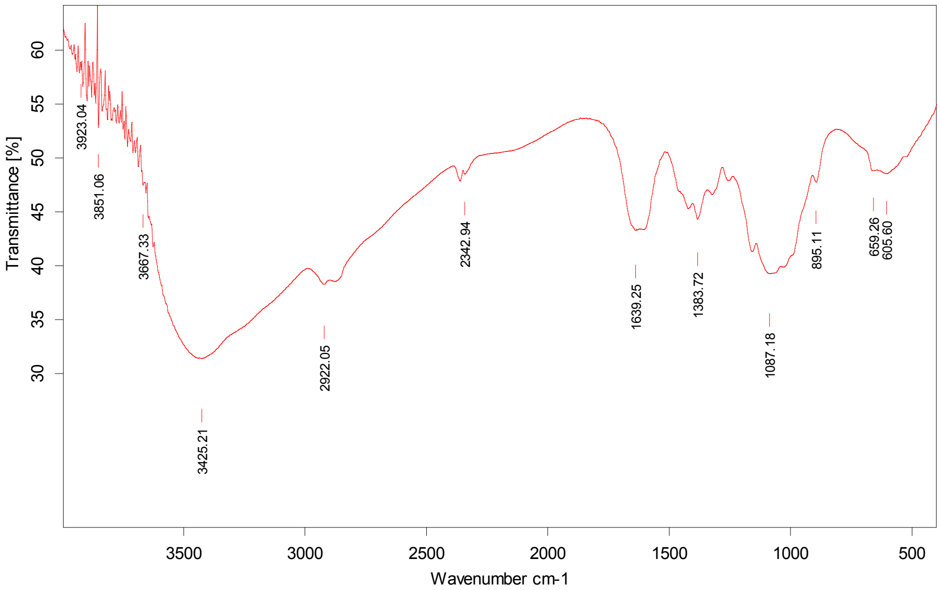


Figure S2. Infrared spectra of CS@CuI

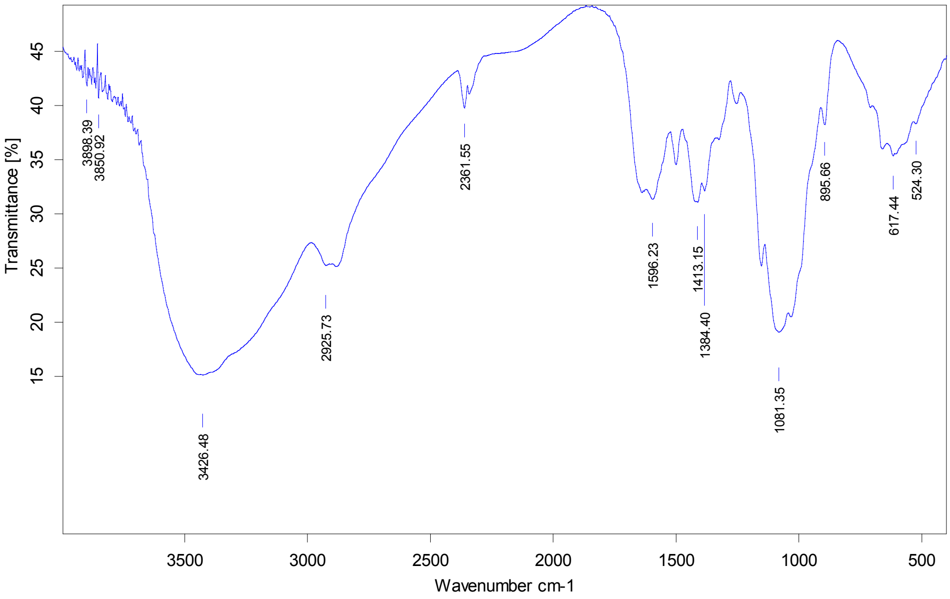


Figure S3. Infrared spectra of CS@Cu(OAc)$_2$

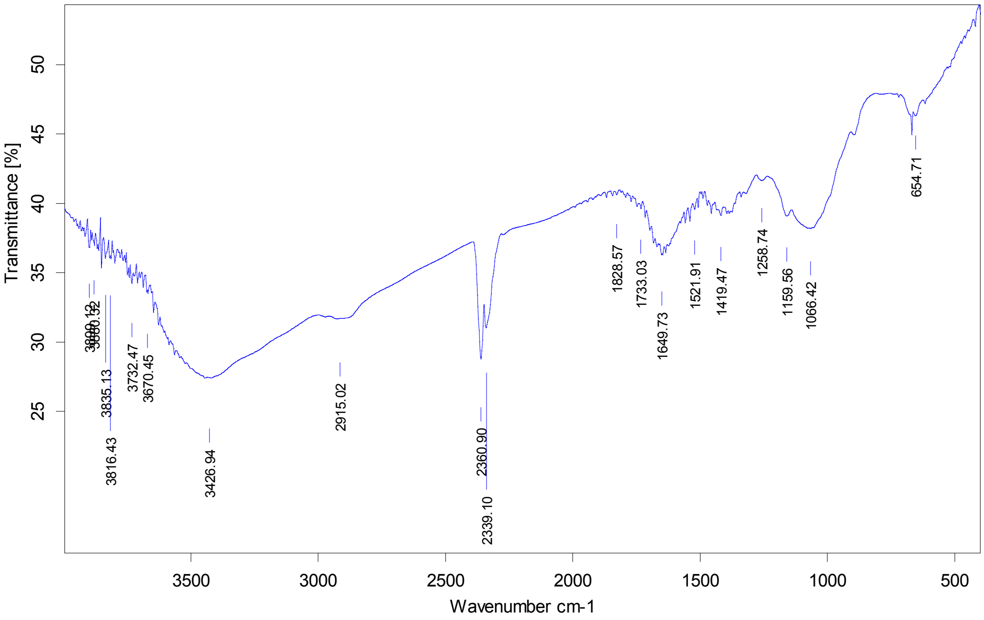
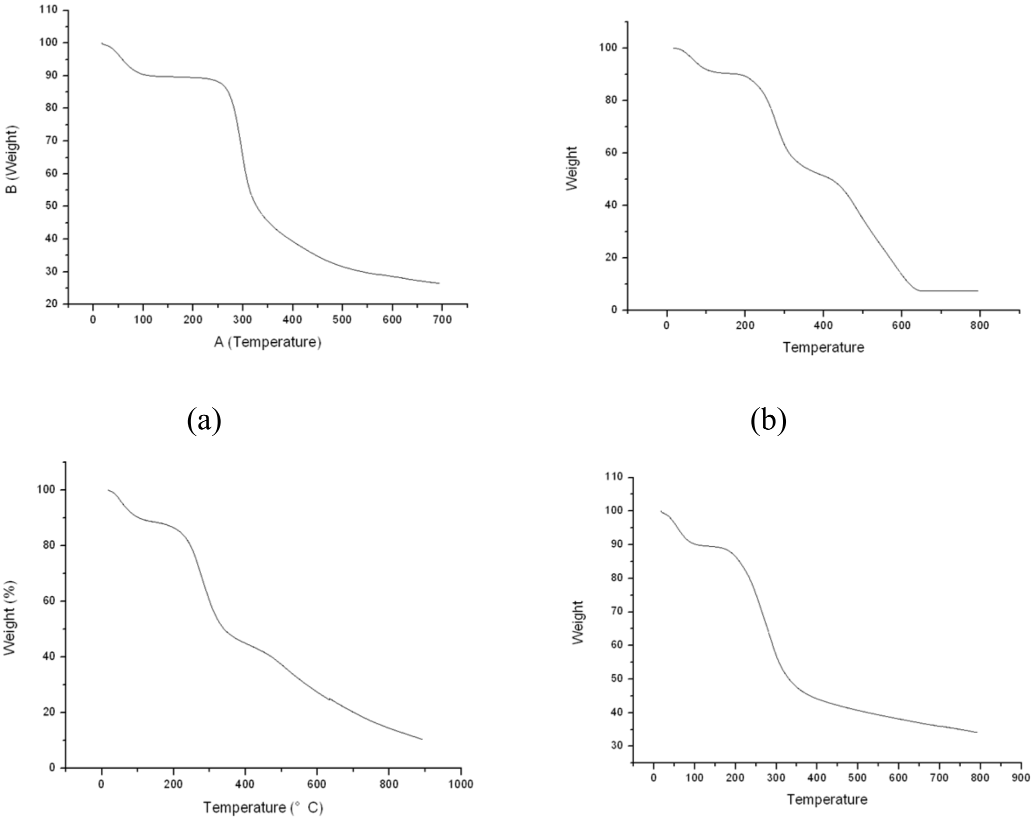


Figure S4. Infrared spectra of CS@CuSO$_4$



(a) (b)

(c) (d)

Figure S5. Thermogravimetric plots of (a) Chitosan, (b) CS@CuI, (c) CS@CS@$CuSO_4$ and (d) CS@CS@$Cu(OAc)_2$.

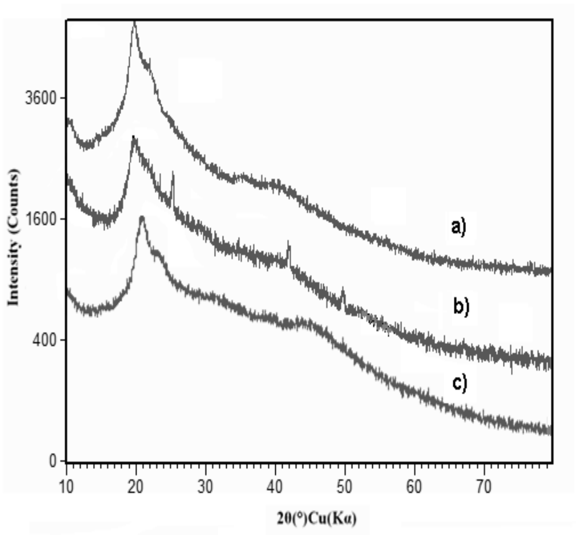


Figure S6. X-ray diffraction of a) CS@$CuSO_4$ b) CS@CuI and c) CS@$Cu(OAc)_2$

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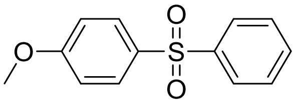
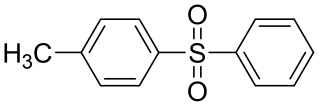
3. Characterization of the Products

1-(4-Methoxyphenylsulfonyl)benzene 3a[1]:



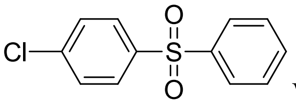
White solid; m.p.: 90-91 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.85-7.79 (m, 4H) ,7.46-7.41 (m, 3H), 6.90-6.88 (m, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 162.4, 141.3, 131.8, 128.9, 128.2, 126.3, 113.5, 54.6. GC-MS (EI) [M]+: m/z calcd. for C$_{13}$H$_{12}$O$_3$S: 248.0, found: 248.

1-(*p*-Tolylsulfonyl)benzene 3b[1]:



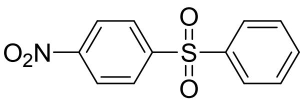
White solid; m.p.: 125-127 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87-7.85 (m, 2H), 7.77-7.75 (m, 2H), 7.48-7.40 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 143.1, 140.9, 137.5, 131.9, 128.9, 128.2, 126.6, 126.4, 20.5. GC-MS (EI) [M]+: m/z calcd. for C$_{13}$H$_{12}$O$_2$S: 232.0, found: 232.

1-(4-Chlorophenylsulfonyl)benzene 3c[2]:



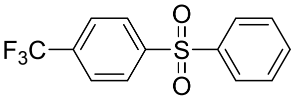
White solid; m.p.: 96-97 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95-7.88 (m, 4H), 7.60-7.46 (m, 5H).^{13}C NMR (100 MHz, CDCl$_3$): δ 141.1, 140.0, 139.8, 133.4, 129.6, 129.4, 129.1, 127.6. GC-MS (EI) [M]+: m/z calcd. for C$_{12}$H$_9$ClO$_2$S: 252.0, found: 252.

1-(4-Nitrophenylsulfonyl)benzene 3d[1,2]:



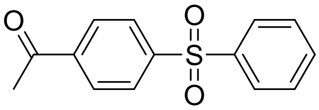
Yellow solid; m.p.:143-145 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36-8.34 (m, 2H), 8.15-8.13 (m, 2H), 7.99-7.97 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.55 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 150.3, 147.3, 140.0, 134.1, 129.7, 128.9, 128.0, 124.5. GC-MS (EI) [M]+: m/z calcd. for C$_{12}$H$_9$NO$_4$S: 263.0, found: 263.

1-(Trifluoromethyl)-4-(phenylsulfonyl)benzene 3e[3]:



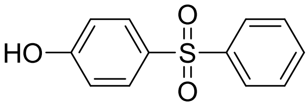
White solid; m.p.: 90-91 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.07 (d, J = 6.8 Hz, 2H), 8.99-7.98 (m, 2H), 7.78 (d, J = 6.8 Hz, 2H), 7.64-7.54 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 145.3, 140.6, 133.7, 129.5, 128.2, 127.9, 126.4, 126.4, 126.3. GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_9F_3O_2S$: 286.0, found: 286.

1-(4-(Phenylsulfonyl)phenyl)ethanone 3f[1]:



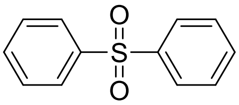
White solid; m.p.: 138-140 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08-8.06 (m, 4H), 7.99-7.97 (m, 2H), 7.62-7.60 (m, 1H), 7.56-7.53 (m, 2H), 2.64 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 196.7, 145.4, 140.7, 140.3, 133.6, 130.9, 129.4, 129.0, 128.0, 127.8, 115.3, 26.8. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}O_3S$: 260.0, found: 260.

4-(Benzenesulfonyl)phenol 3g[4]:



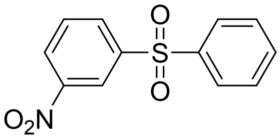
Brown solid; m.p.: 135-137 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.51 (br s, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.56-7.47 (m, 3H), 7.82 (d, J = 8.0 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 131.8, 129.1, 128.1, 126.2, 115.0. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_3S$: 234.0, found: 234.

1-(Phenylsulfonyl)benzene 3h[1-4]:



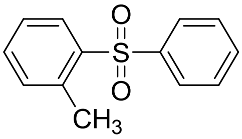
White solid; m.p.:122-124 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.97-7.96 (m, 4H), 7.59-7.50 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.7, 133.1, 129.2, 127.6. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_2S$: 218.0, found: 218.

3-Nitrol-(phenylsulfonyl)benzene 3i[1]:



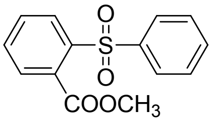
Yellow solid; m.p.:163-165 ^{o}C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36-8.24 (m, 2H), 8.15-8.13 (m, 2H), 7.99-7.97 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.55 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 147.3, 142.9, 139.0, 133.0, 132.0, 129.7, 128.7, 126.9, 126.6, 121.9. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9NO_4S$: 263.0, found: 263.

1-Methyl-2-(phenylsulfonyl)benzene 3j[1, 2]:



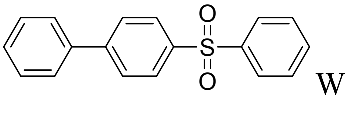
White solid; m.p.: 73-75 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24 (dd, *J* = 0.8, 0.8 Hz, 1H), 7.91-7.90 (m, 2H), 7.61-7.49 (m, 4H), 7.44 -7.41(m, 1H), 7.25 (d, *J* = 6 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.4, 138.9, 138.0, 133.5, 132.9, 132.6, 129.4, 129.0, 127.6, 126.4, 20.1. GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}O_2S$: 232.0, found: 232.

Methyl 2-(phenylsulfonyl)benzoate 3k[2]:



White solid; m.p.: 94-96 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.18-8.16 (m, 1H), 7.99-7.97 (m, 2H), 7.65-7.52 (m, 6H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.7, 141.4, 138.9, 133.4, 133.3, 133.2, 130.9, 130.2, 129.2, 129.0, 127.8, 53.1. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}O_4S$: 276.0, found: 276.

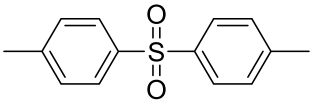
4-(phenylsulfonyl)-1,1'-biphenyl 3l[4]:



White solid; m.p.: 112-114 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.05-8.02 (m, 4H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.59-7.43 (m, 8H). ^{13}C NMR (100 MHz,

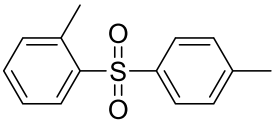
$CDCl_3$): δ 141.6, 133.2, 120.3, 127.6. GC-MS (EI) [M]+: m/z calcd. for $C_{18}H_{14}O_2S$: 294.0, found: 294.

4,4'-Sulfonylbis(methylbenzene) 3m[1]:



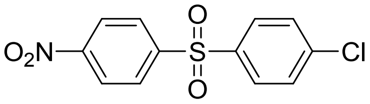
White solid; m.p.: 97-99 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8 Hz, 4H), 7.29 (d, *J* = 8 Hz, 4H), 2.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 139.0, 129.8, 127.5, 21.5. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{14}O_2S$: 246.0, found: 246.

1-Methyl-2-tosylbenzene 3n[2]:



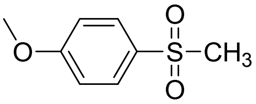
White solid; m.p.: 87-88 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8 Hz, 1H), 7.75 (d, *J* = 8 Hz, 2H), 7.46-7.45 (m, 1H), 7.40-7.38 (m, 1H), 7.30-7.26 (m, 2H), 7.23-7.21 (m, 1H), 2.44 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 139.2, 138.2, 137.9, 133.4, 132.6, 129.6, 129.3, 127.6, 127.7, 126.4, 21.6, 20.2. GC-MS (EI) [M]+: m/z calcd. For $C_{14}H_{14}O_2S$: 246.0, found: 246.

1-Chloro-4-((4-nitrophenyl)sulfonyl)benzene 3o[2]:

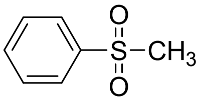


Yellow solid; m.p.: 112-114 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.37-8.35 (m, 2H), 8.14-8.12 (d, *J* = 6.4 Hz, 2H), 7.93-7.91 (d, *J* = 6.4 Hz, 2H), 7.55-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 146.9, 144.9, 141.0, 138.5, 130.2, 129.8, 129.00, 124.6. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_8ClNO_4S$: 296.9, found: 297.

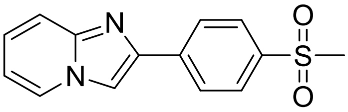
1-Methoxy-4-(methylsulfonyl)benzene 3p[4]:


White solid; m.p.: 120-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (d, *J* = 6.8 Hz, 2H), 7.05-7.03 (d, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 132.2, 129.6, 114.5, 55.8, 44.9. GC-MS (EI) [M]+: m/z calcd. for $C_8H_{10}O_3S$: 186.0, found: 186.

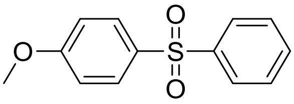
4-(Methanesulfonyl)benzene 3q[4]:


White solid; m.p.: 90-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.64-7.62 (m, 1H), 7.57-7.54 (m, 2H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 133.6, 129.3, 127.2, 44.4. GC-MS (EI) [M]+: m/z calcd. for $C_7H_8O_2S$: 156.0, found: 156.

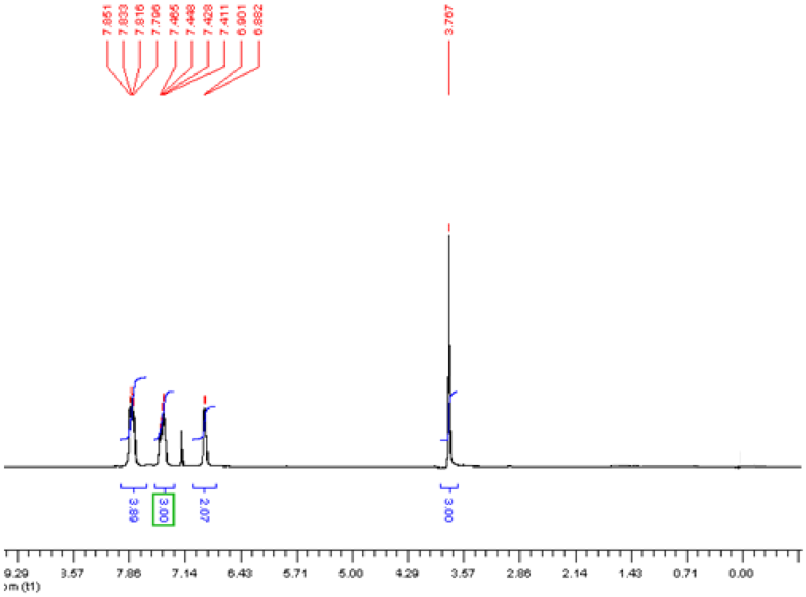
Zolimidine[5,6]


Yellowish white solid ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.15 (m, 3H), 8.03-7.97 (m, 3H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.31-7.29 (m, 1H), 6.89 (t, *J* = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 142.6, 139.6, 127.9, 126.7, 126.3, 126.0, 117.4, 113.5, 109.8, 44.5. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}N_2O_2S$: 272.0, found: 272.

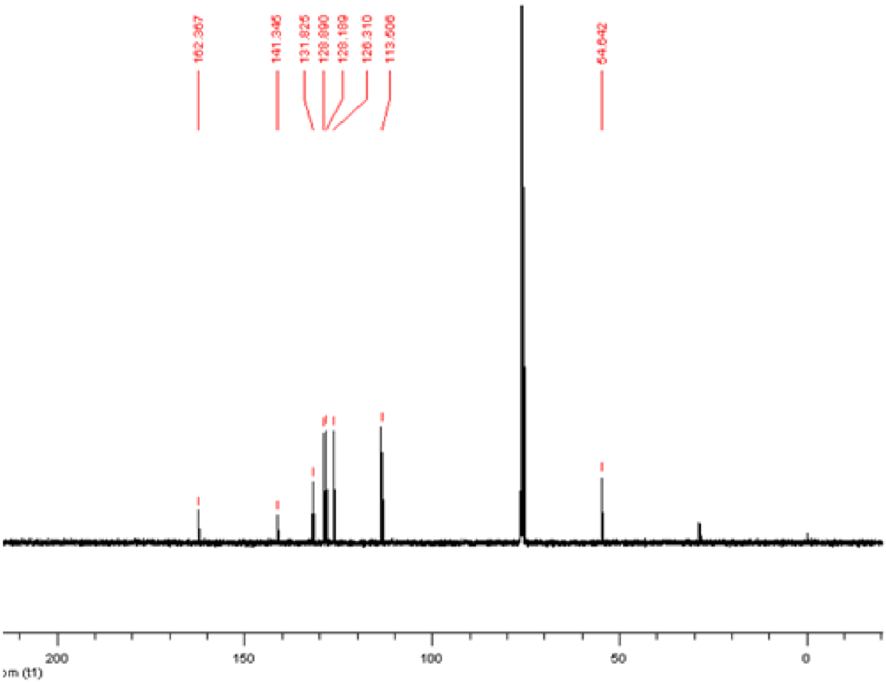
1-(4-Methoxyphenylsulfonyl)benzene 3a:



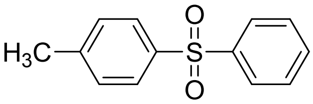
^{1}H NMR:



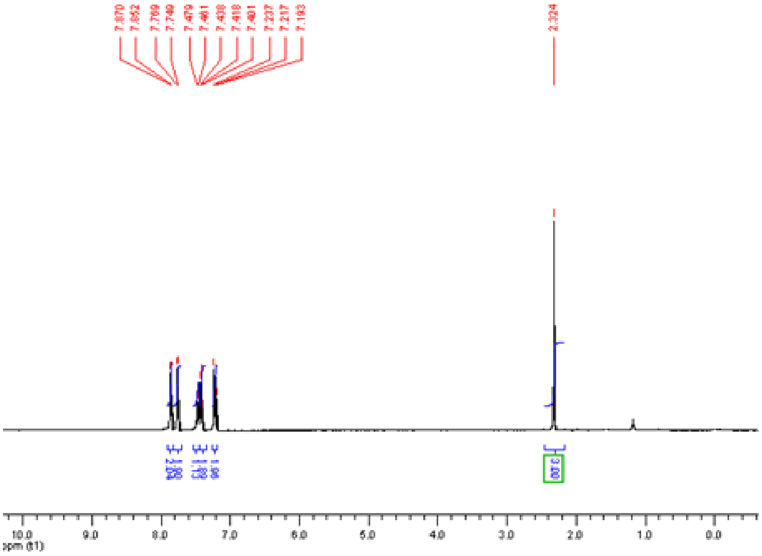
^{13}C NMR:



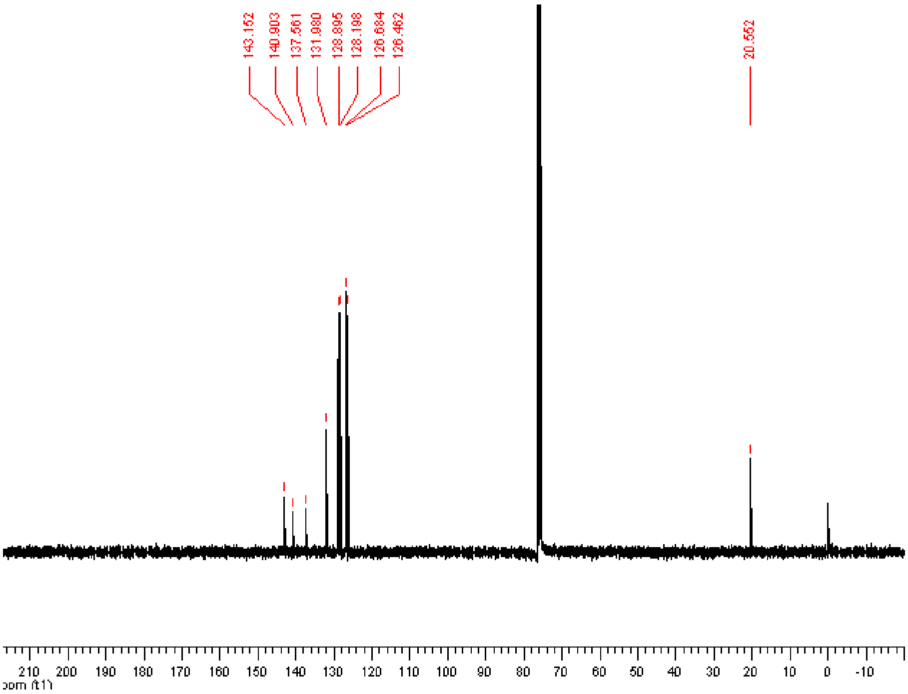
1-(*p*-Tolylsulfonyl)benzene 3b:



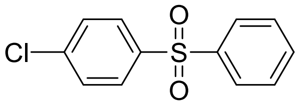
^{1}HNMR:



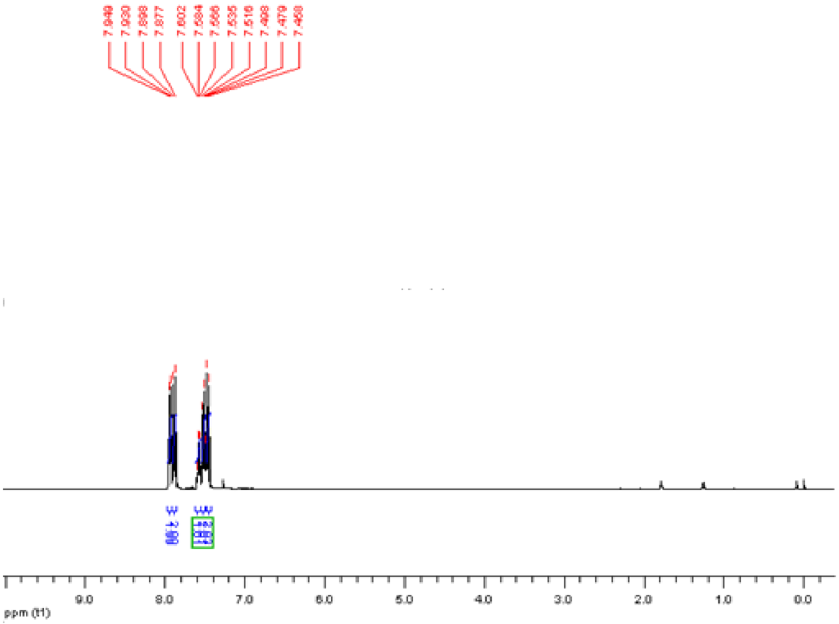
^{13}C NMR:



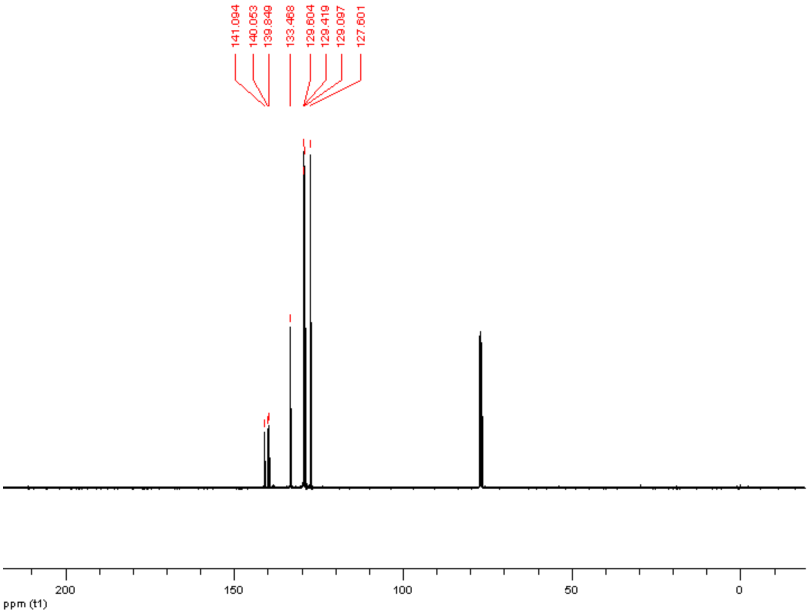
1-(4-Chlorophenylsulfonyl)benzene 3c:



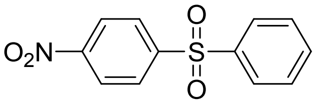
^{1}H NMR



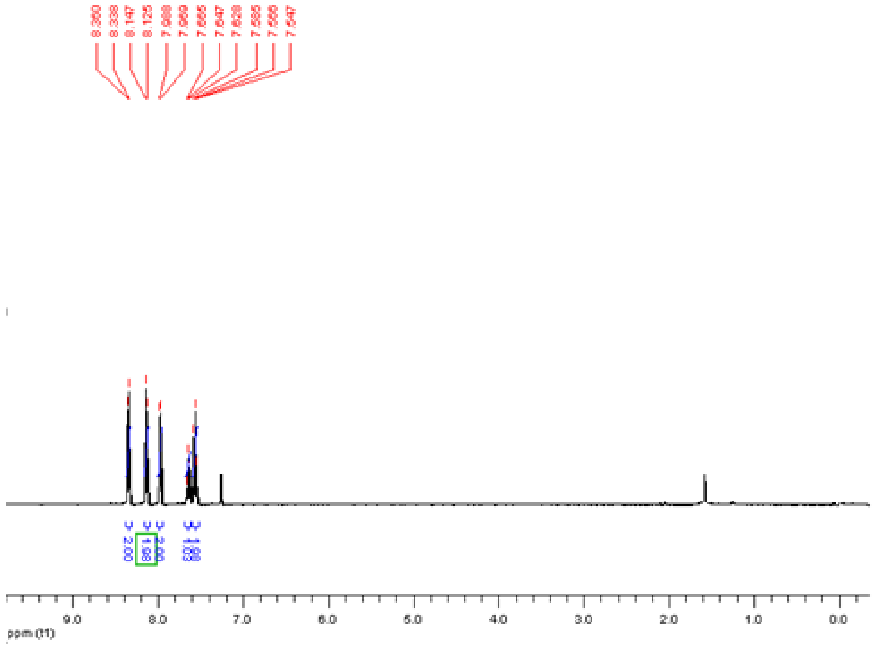
^{13}C NMR



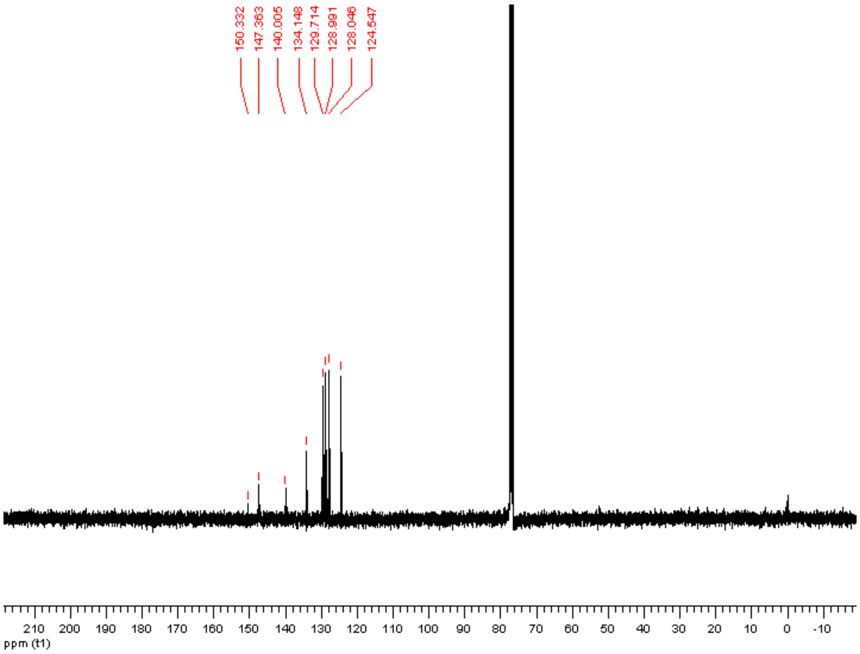
1-(4-Nitrophenylsulfonyl)benzene 3d:



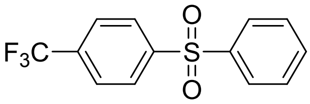
^{1}H NMR



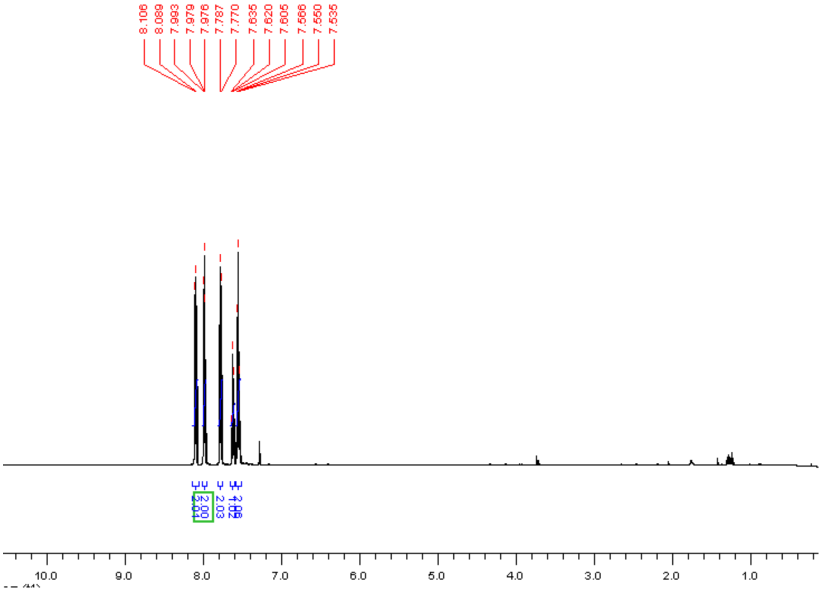
^{13}C NMR



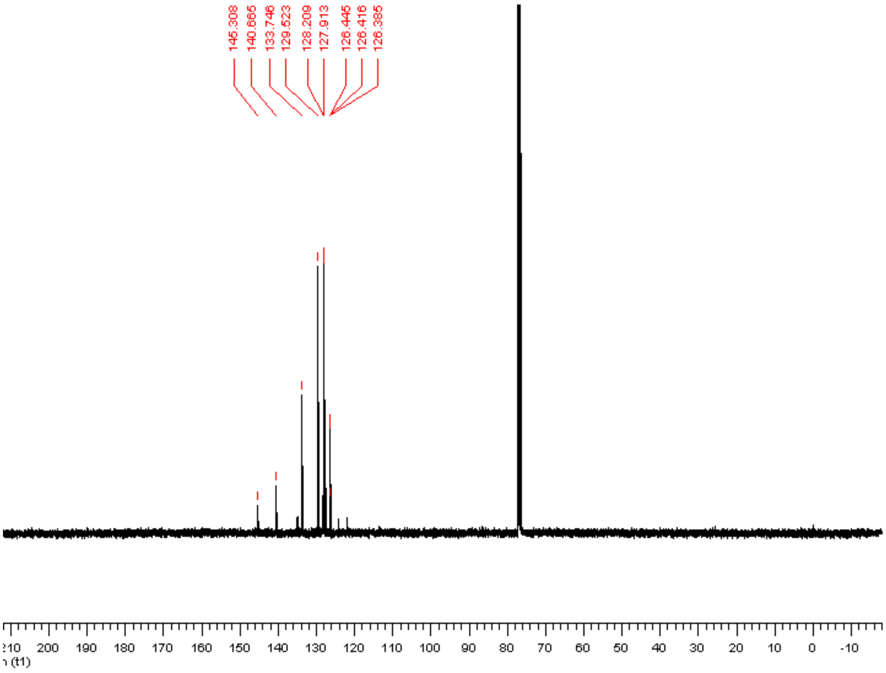
1-(Trifluoromethyl)-4-(phenylsulfonyl)benzene 3e:



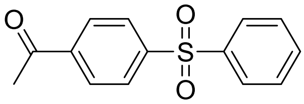
^{1}H NMR



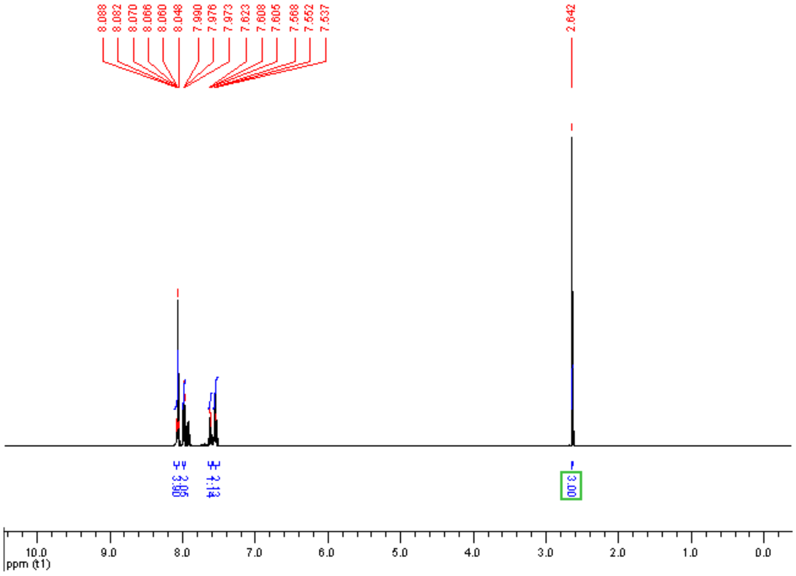
^{13}C NMR



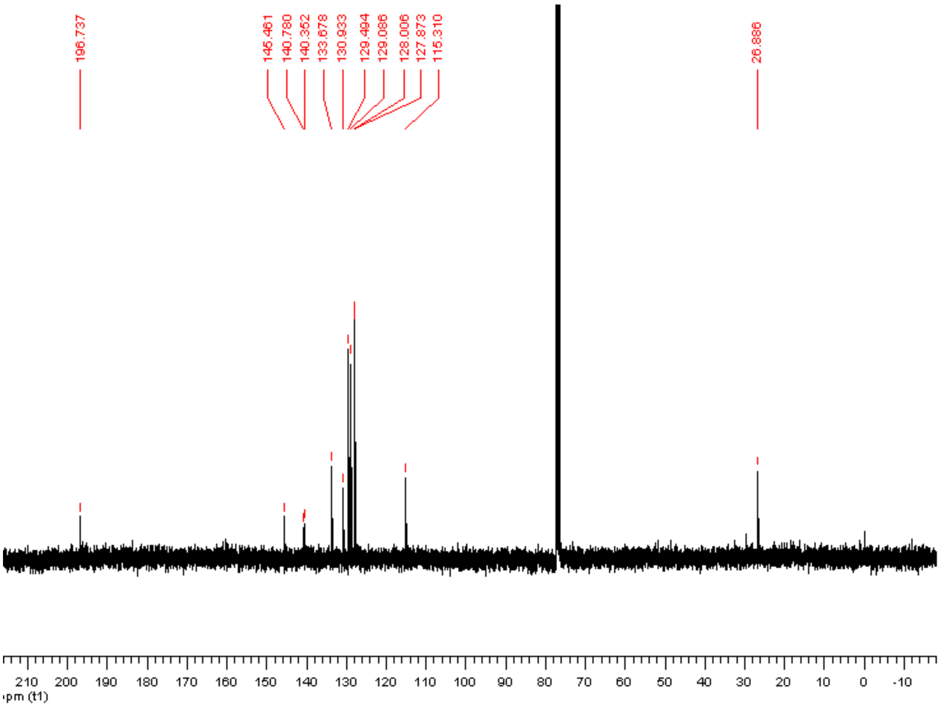
1-(4-(Phenylsulfonyl)phenyl)ethanone 3f:



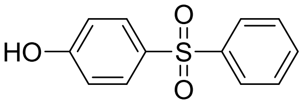
^{1}H NMR



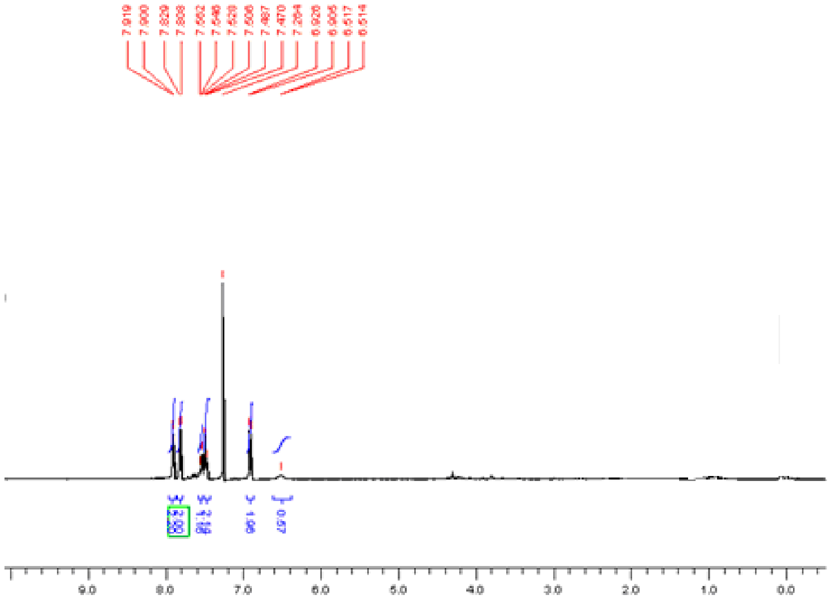
^{13}C NMR



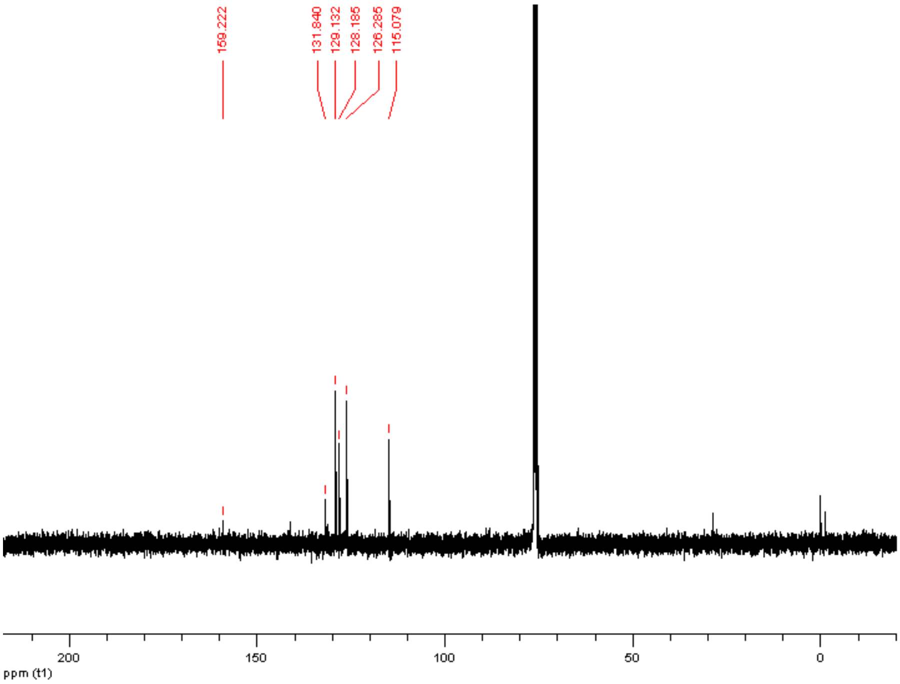
4-(Benzenesulfonyl)phenol 3g:



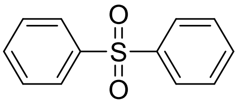
^{1}H NMR



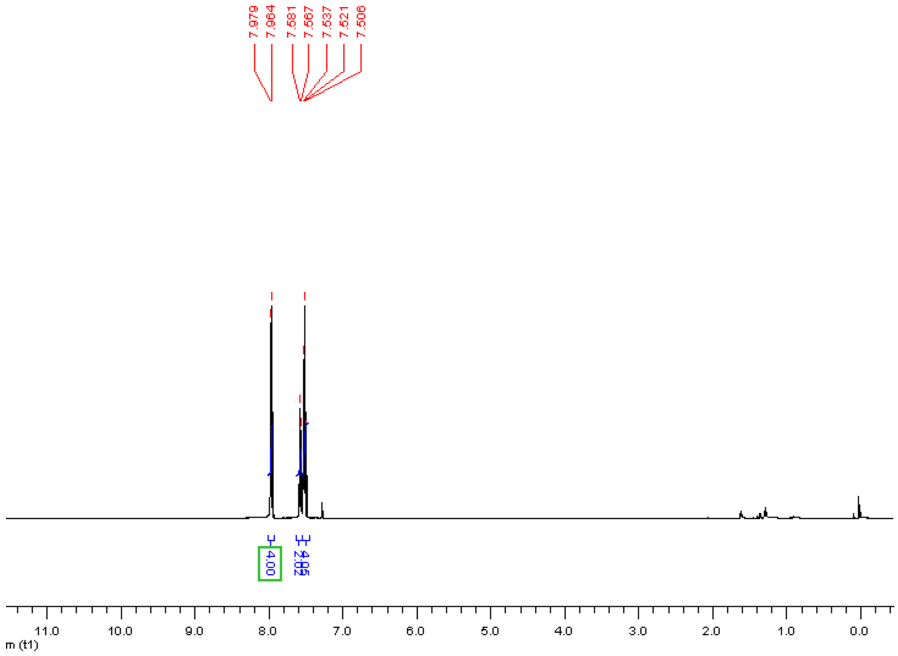
^{13}C NMR



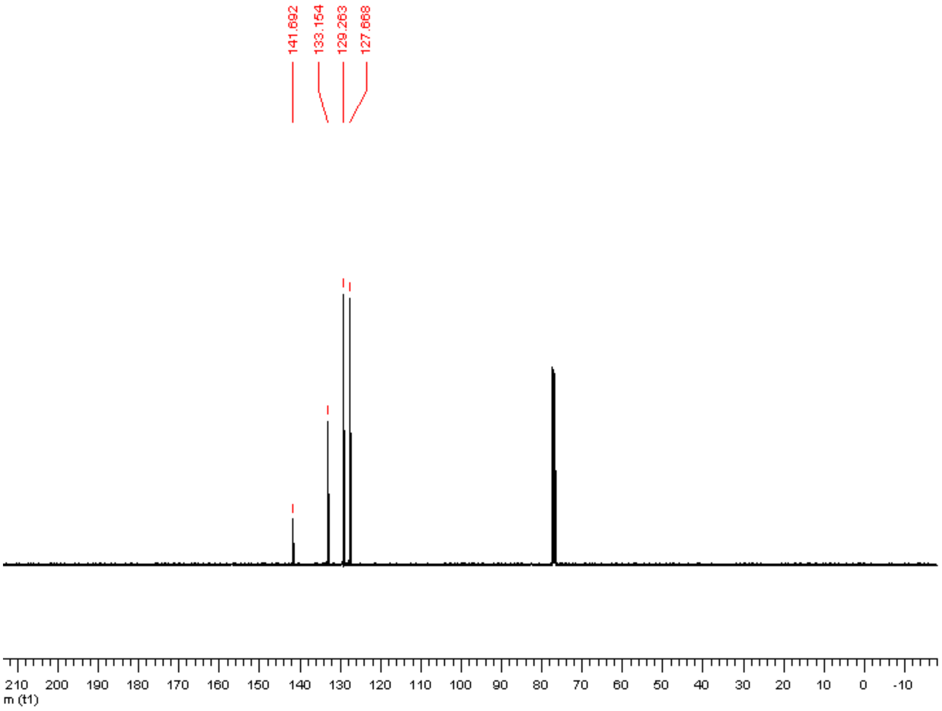
1-(Phenylsulfonyl)benzene 3h:



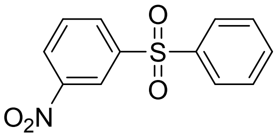
^{1}H NMR



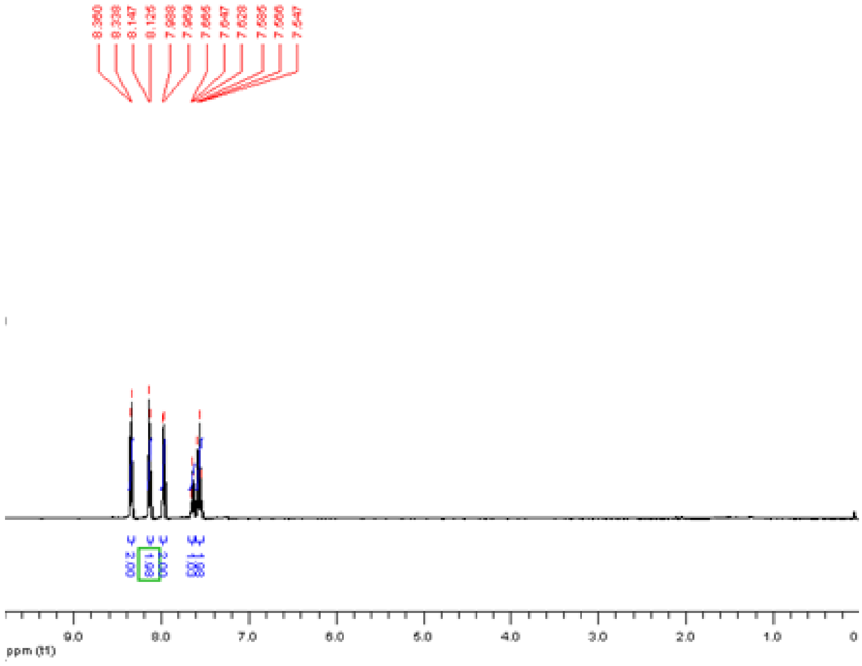
^{13}C NMR



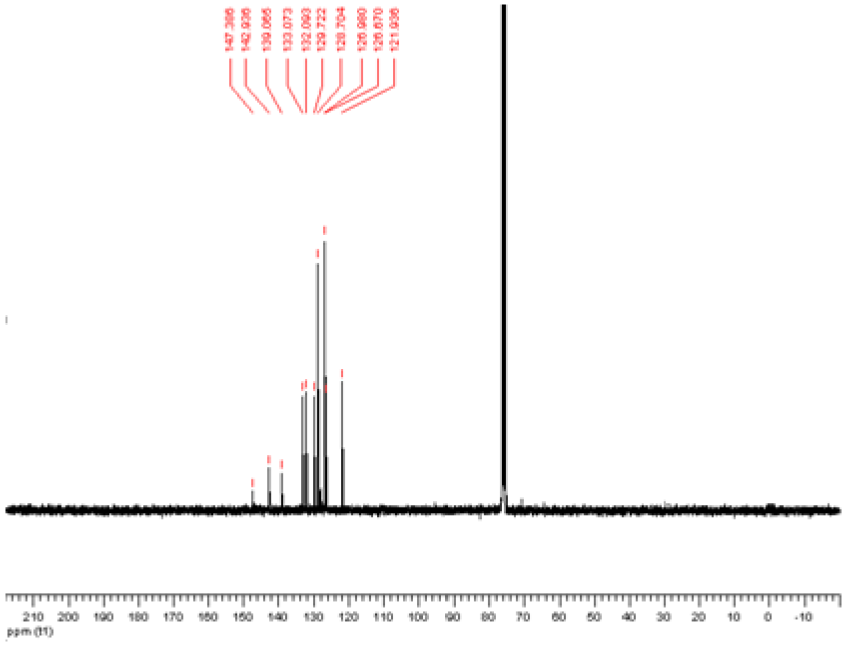
3-Nitrol-(phenylsulfonyl)benzene 3i:



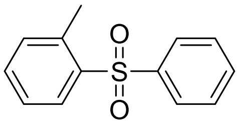
^{1}H NMR



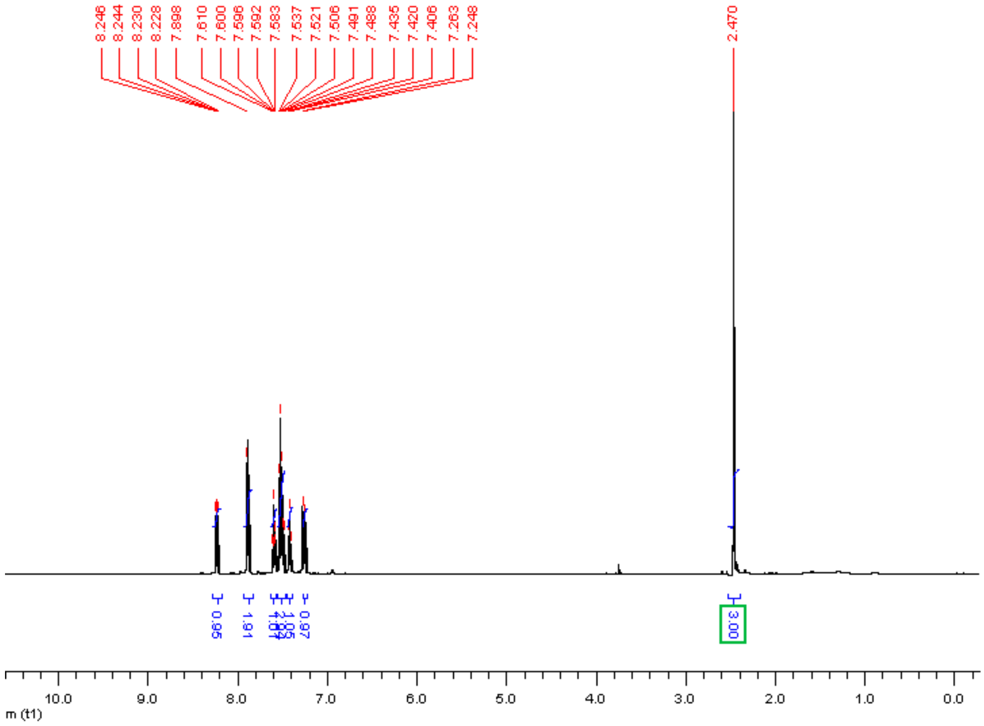
^{13}C NMR



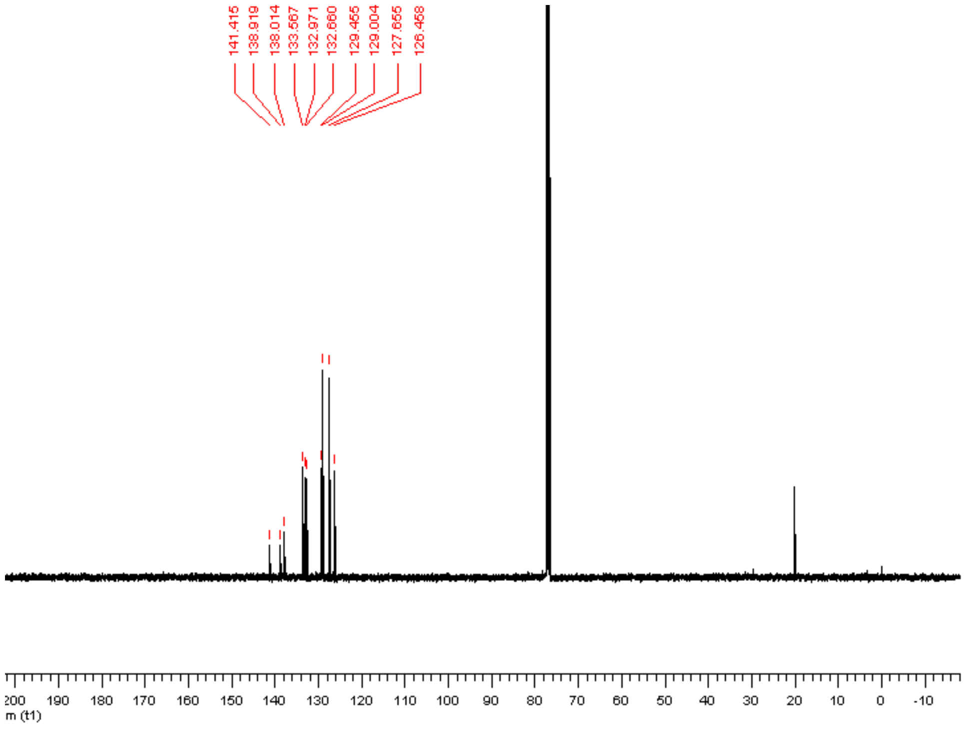
1-Methyl-2-(phenylsulfonyl)benzene 3j:



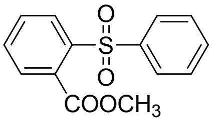
^{1}H NMR



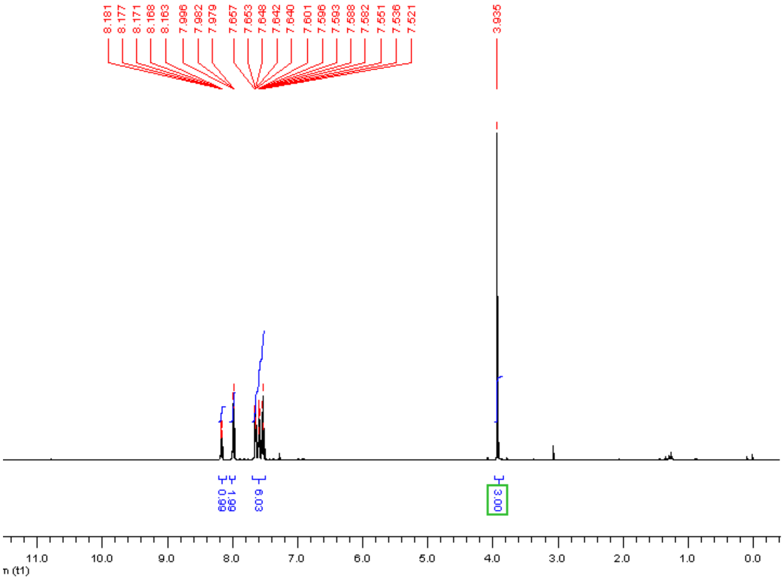
^{13}C NMR



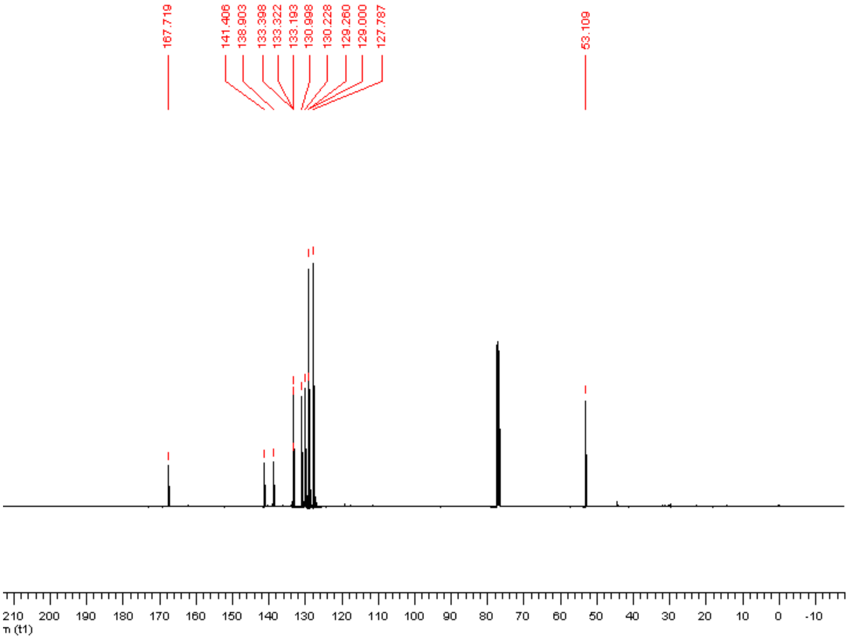
Methyl 2-(phenylsulfonyl)benzoate 3k:



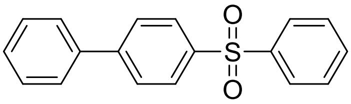
^{1}H NMR



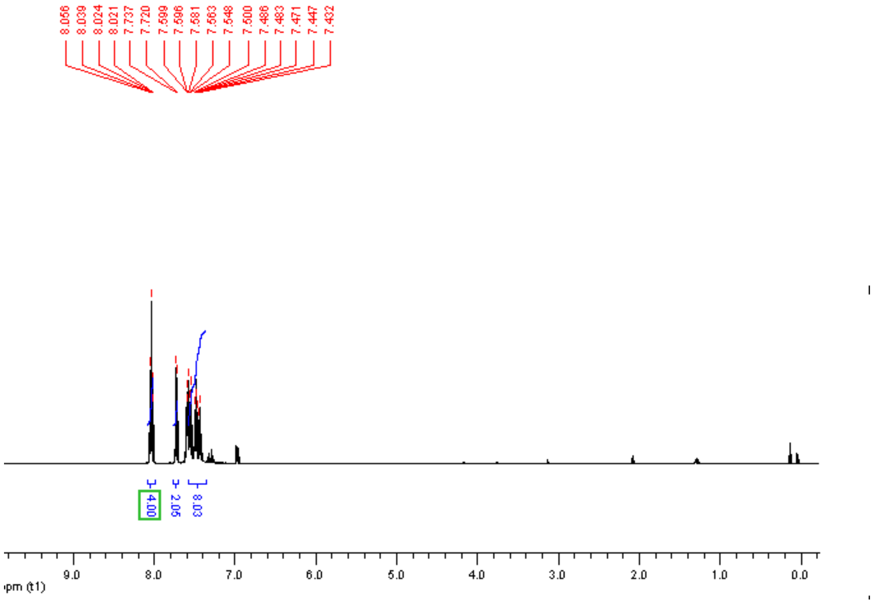
^{13}C NMR



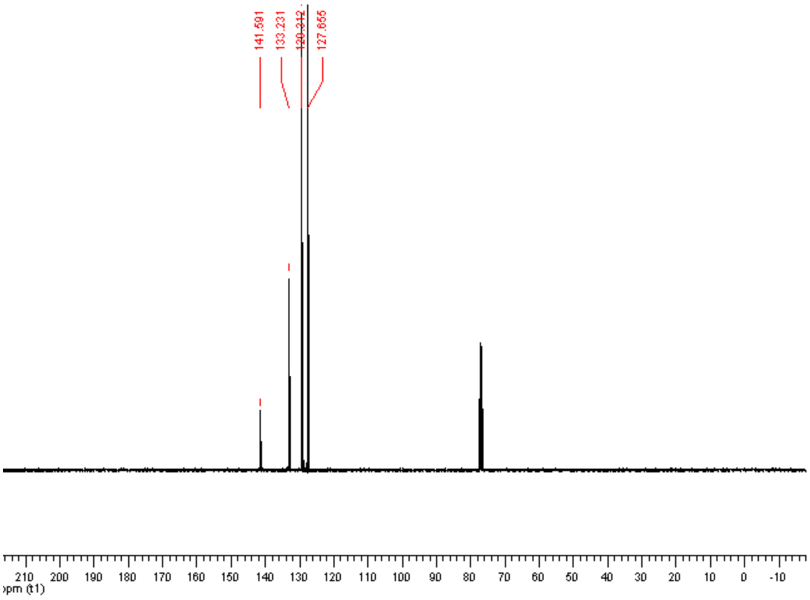
4-(Phenylsulfonyl)-1,1'-biphenyl 3l:



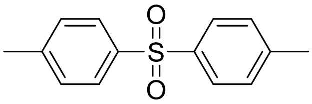
^{1}H NMR



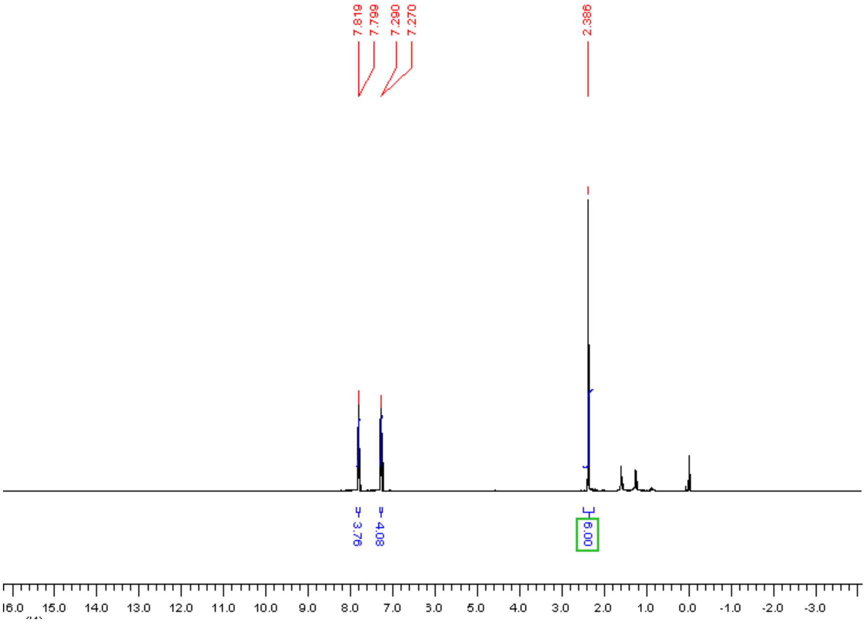
^{13}C NMR



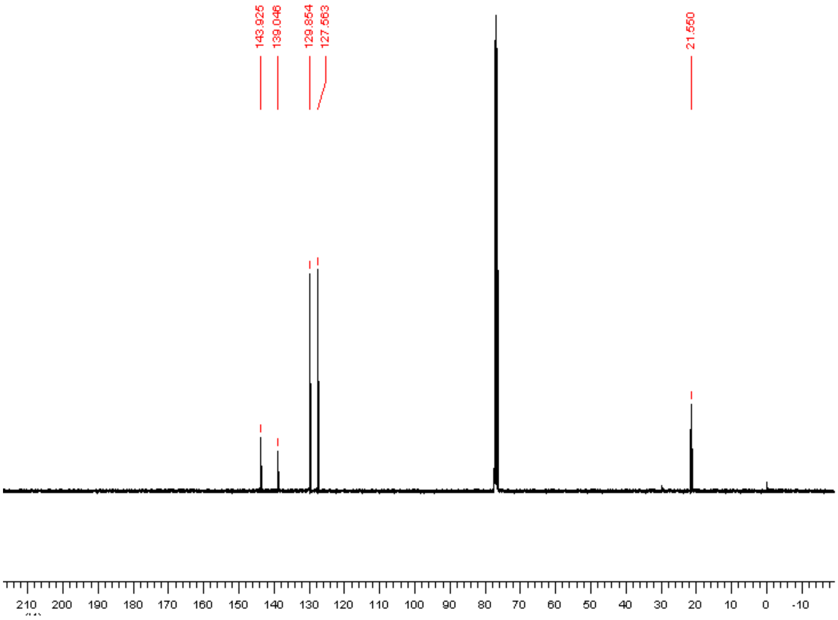
4,4'-Sulfonylbis(methylbenzene) 3m:



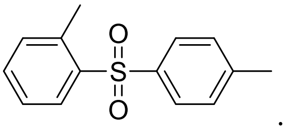
^{1}H NMR



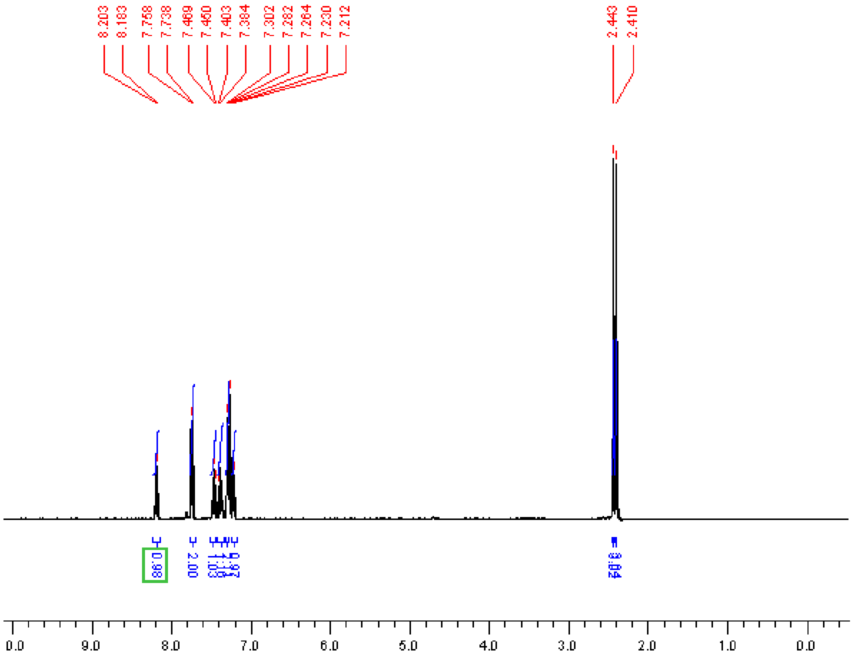
^{13}C NMR



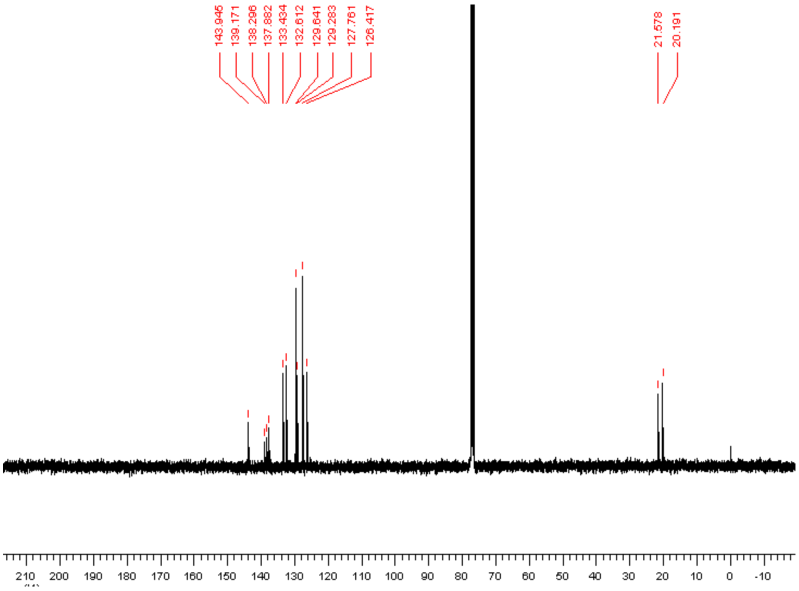
1-Methyl-2-tosylbenzene 3n:



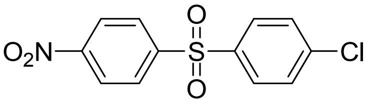
^{1}H NMR

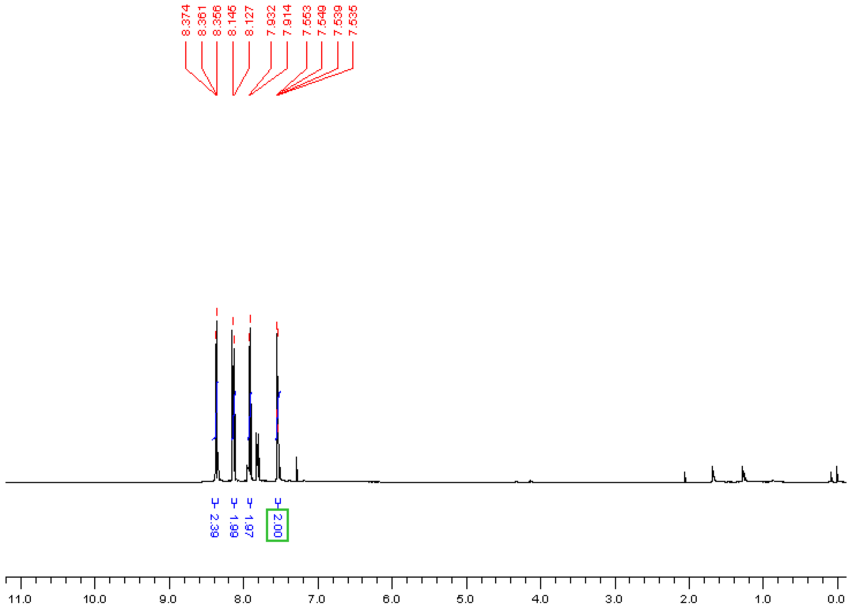


^{13}C NMR

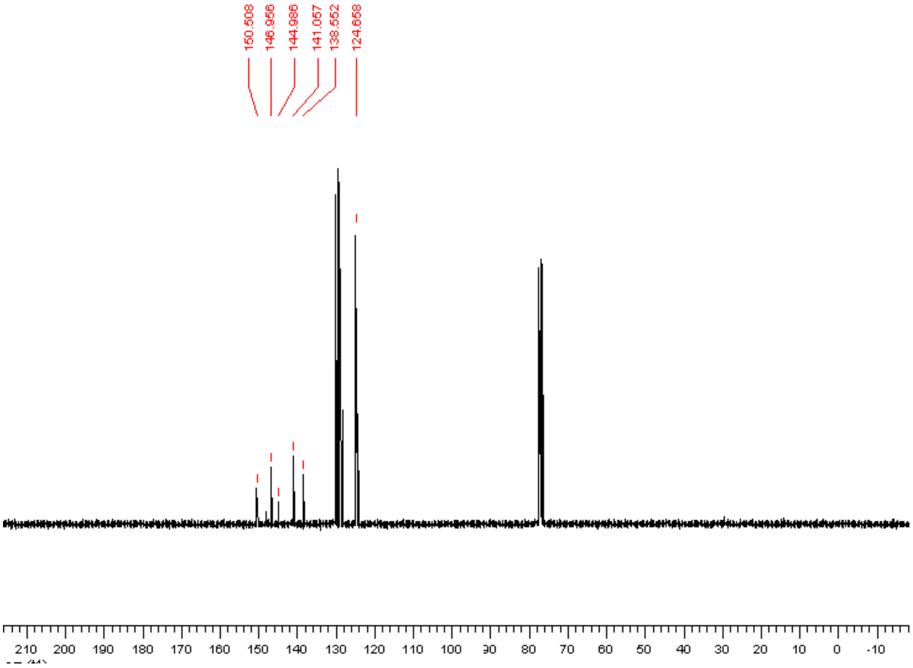


1-Chloro-4-((4-nitrophenyl)sulfonyl)benzene 3o:

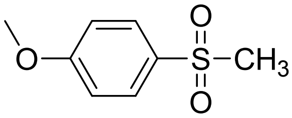




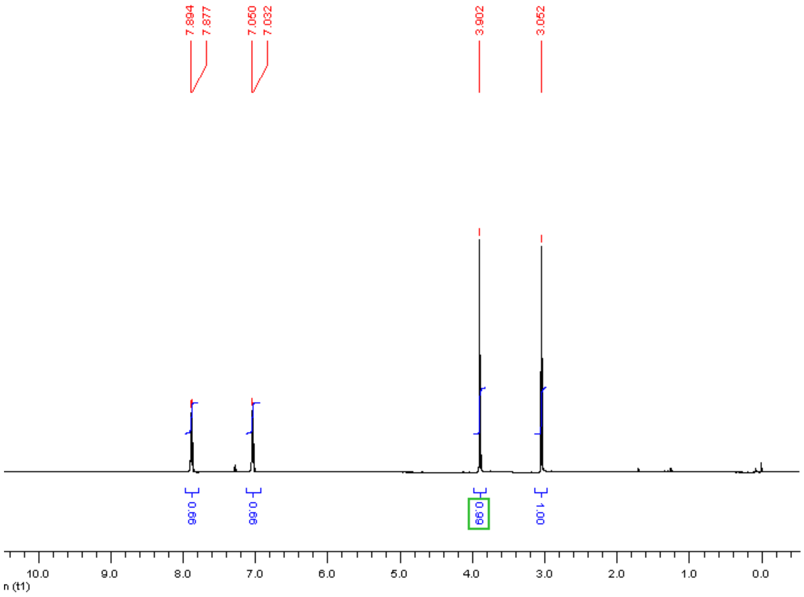
^{13}C NMR



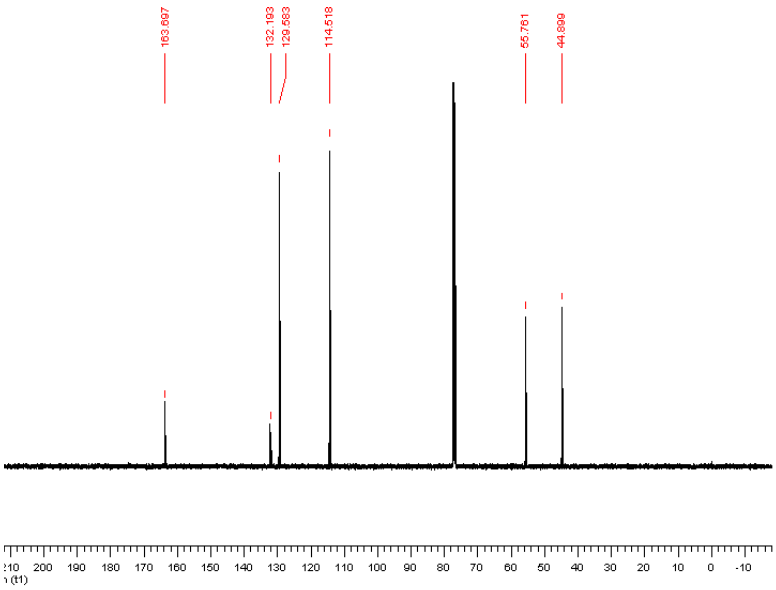
1-Methoxy-4-(methylsulfonyl)benzene 3p:



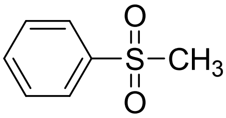
^{1}H NMR



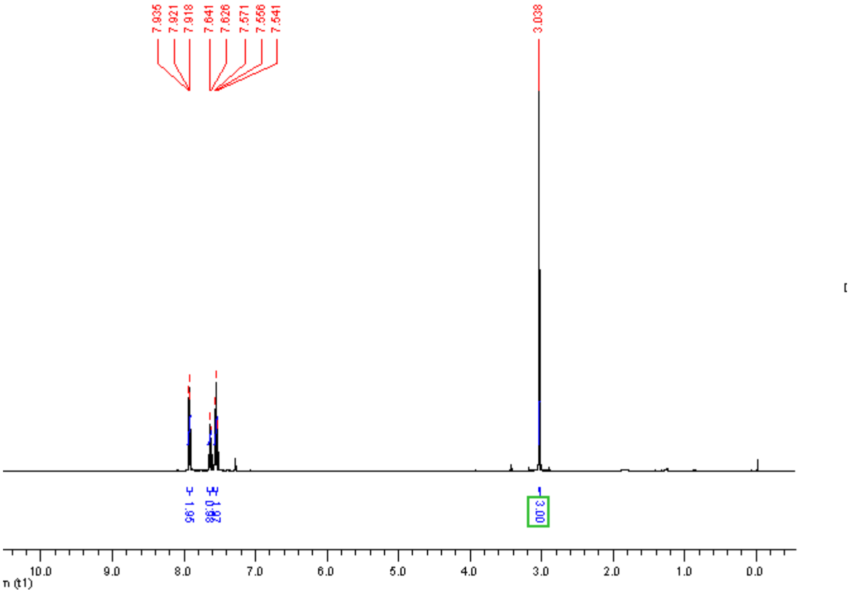
^{13}C NMR



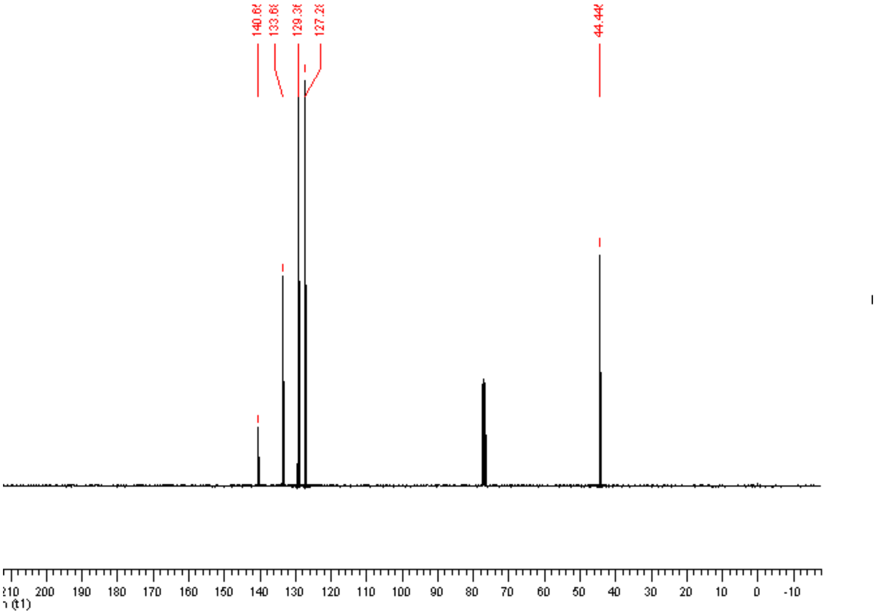
4-(Methanesulfonyl)benzene 3q:



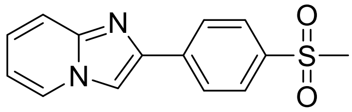
^{1}H NMR



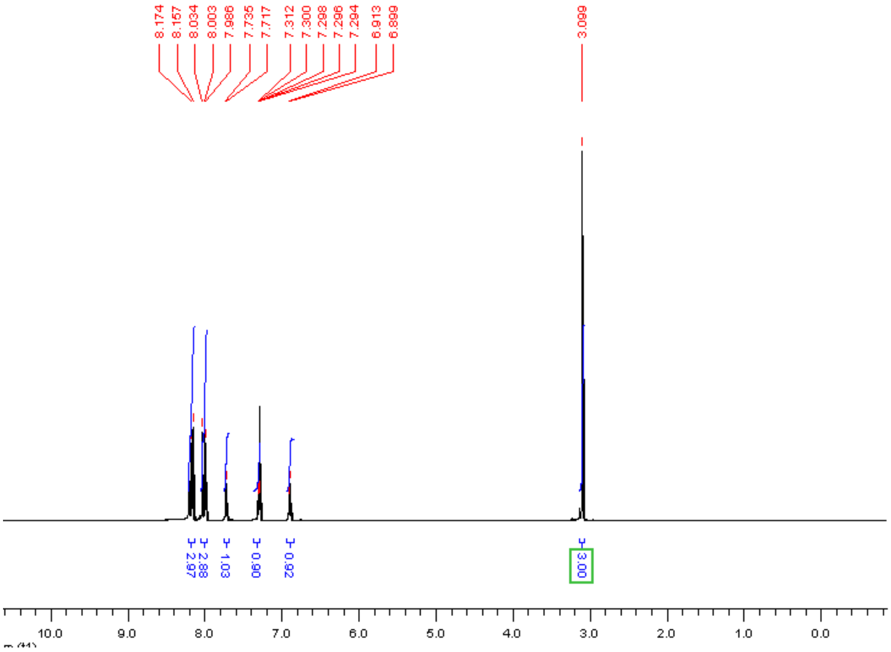
^{13}C NMR



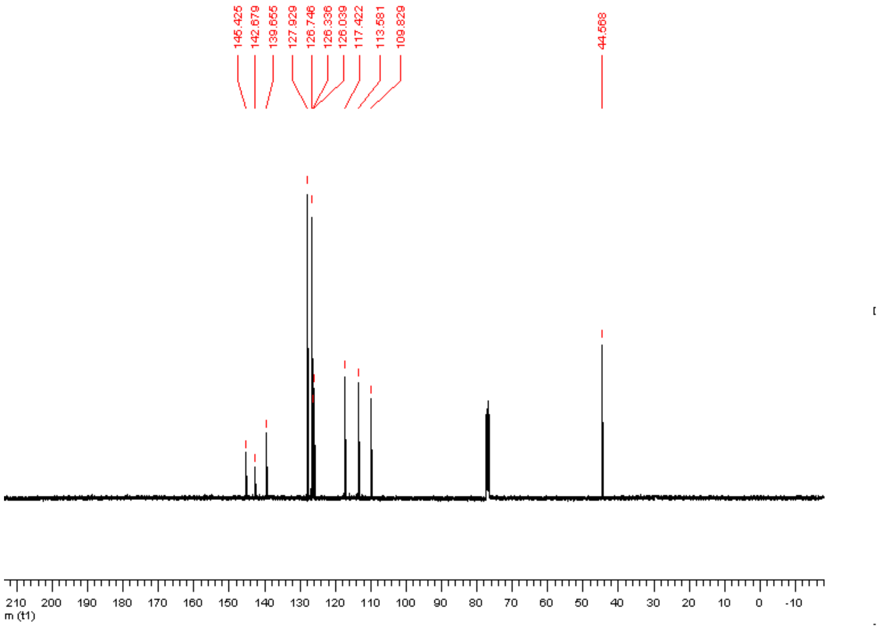
Zolimidine



^{1}H NMR

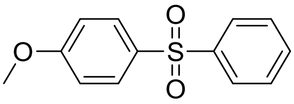


^{13}C NMR

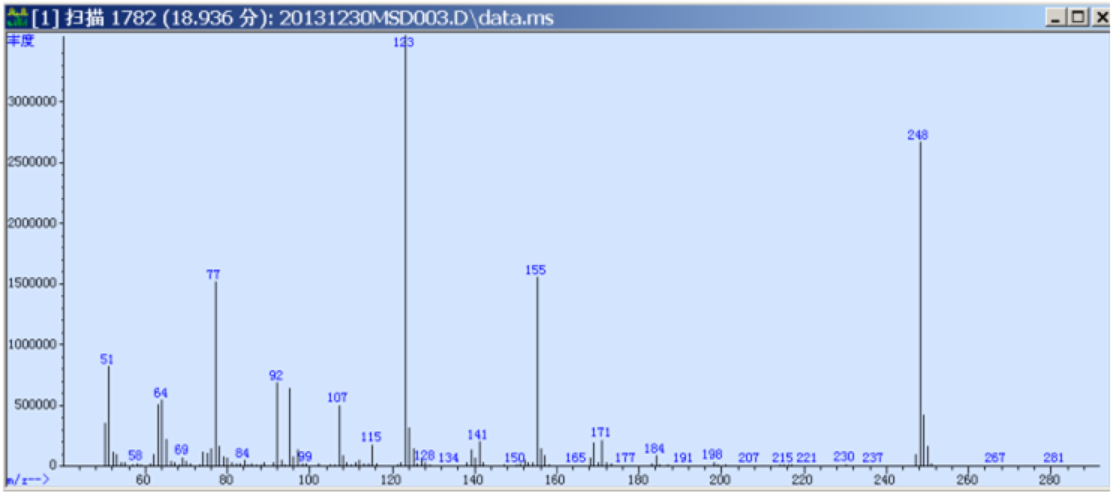


The selected GCMS chromatogram of products:

1-(4-Methoxyphenylsulfonyl)benzene 3a:

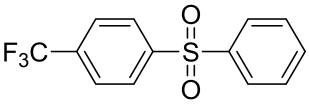


GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}O_3S$: 248.0, found: 248.

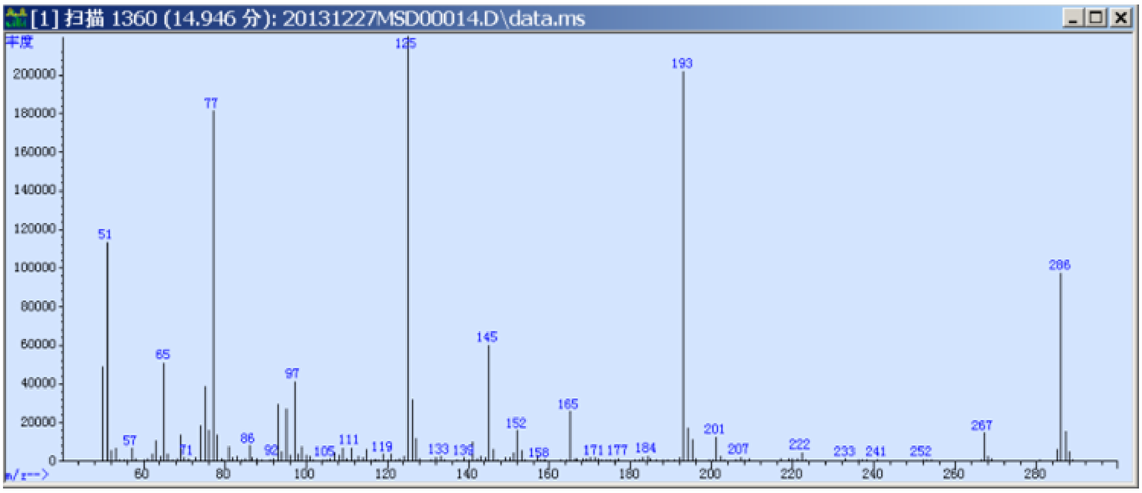


[1] 扫描 1782 (18.936 分): 20131230MSD003.D\data.ms

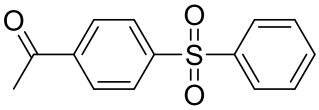
1-(Trifluoromethyl)-4-(phenylsulfonyl)benzene 3e:



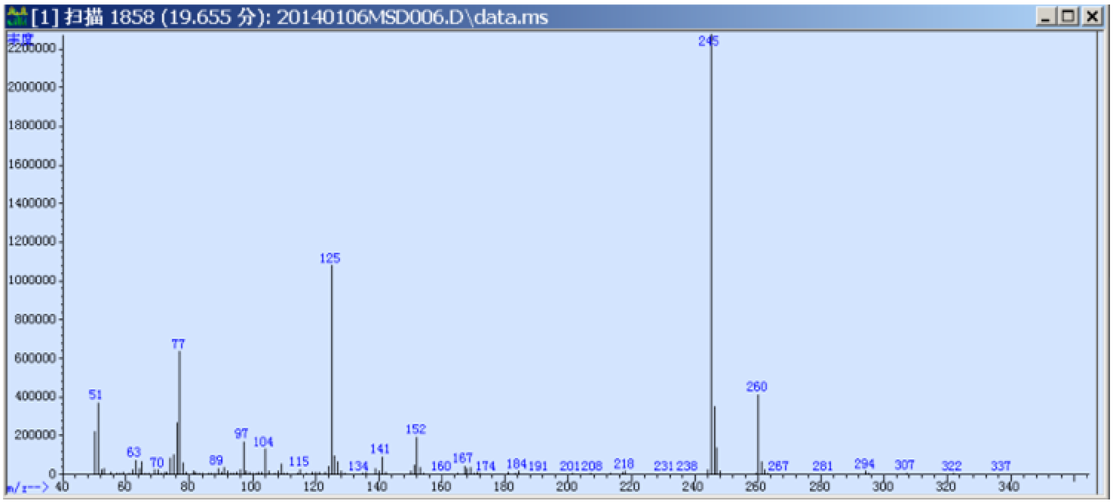
GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_9F_3O_2S$: 286.0, found: 286.



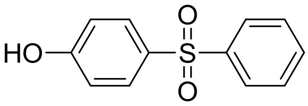
1-(4-(Phenylsulfonyl)phenyl)ethanone 3f:



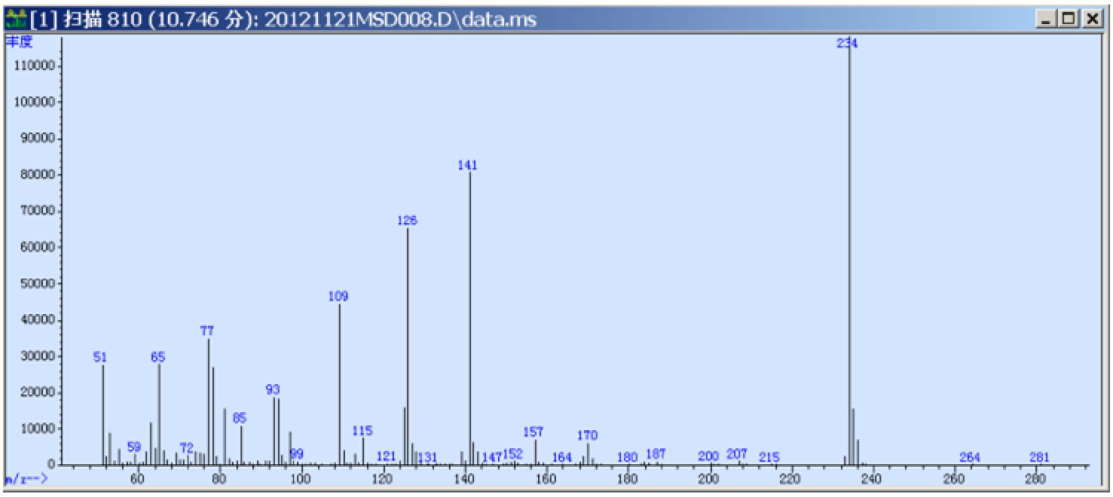
GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}O_3S$: 260.0, found: 260.



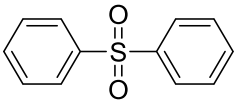
4-(Benzenesulfonyl)phenol 3g:



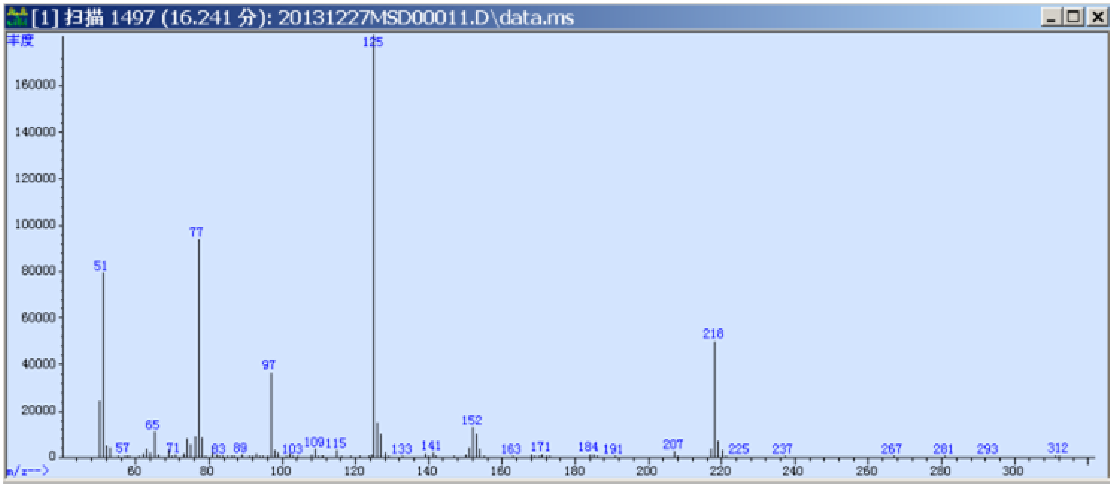
GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_3S$: 234.0, found: 234.



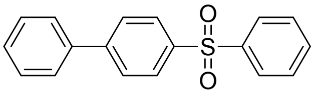
1-(Phenylsulfonyl)benzene 3h:



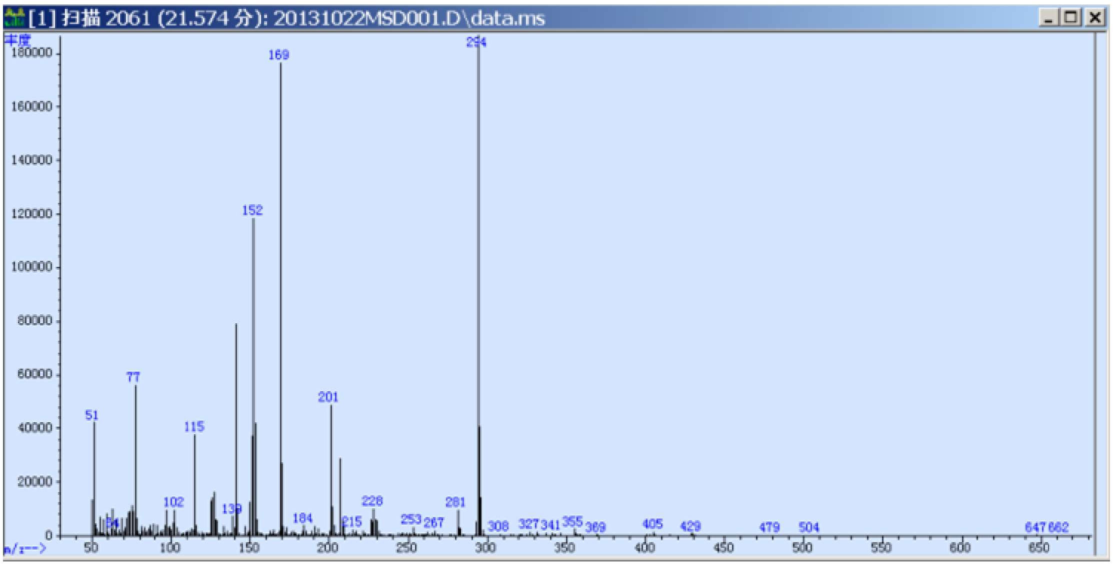
GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_2S$: 218.0, found: 218.



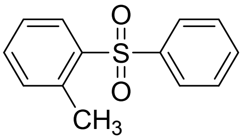
4-(phenylsulfonyl)-1,1'-biphenyl 3l:



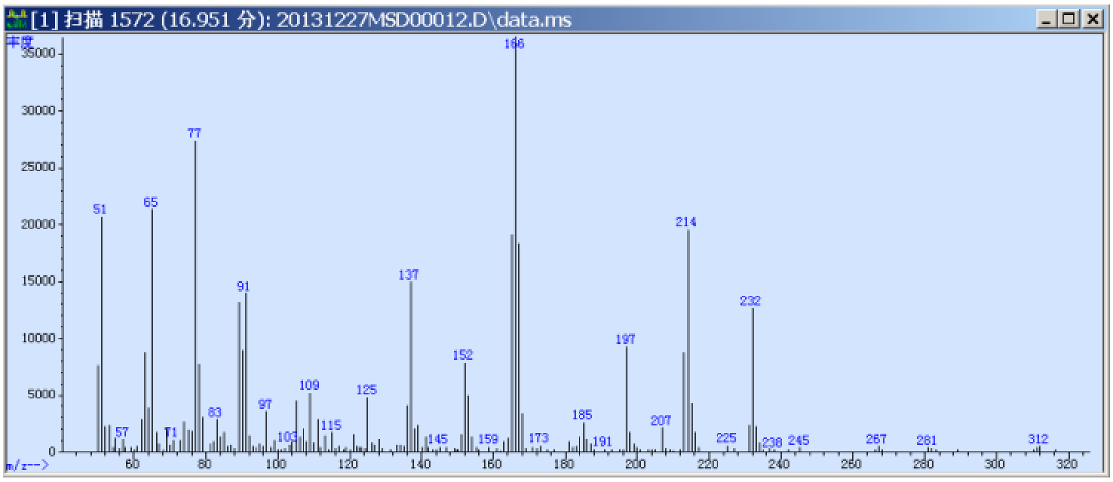
GC-MS (EI) [M]+: m/z calcd. for $C_{18}H_{14}O_2S$: 294.0, found: 294.



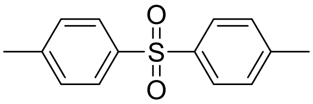
1-Methyl-2-(phenylsulfonyl)benzene 3j:



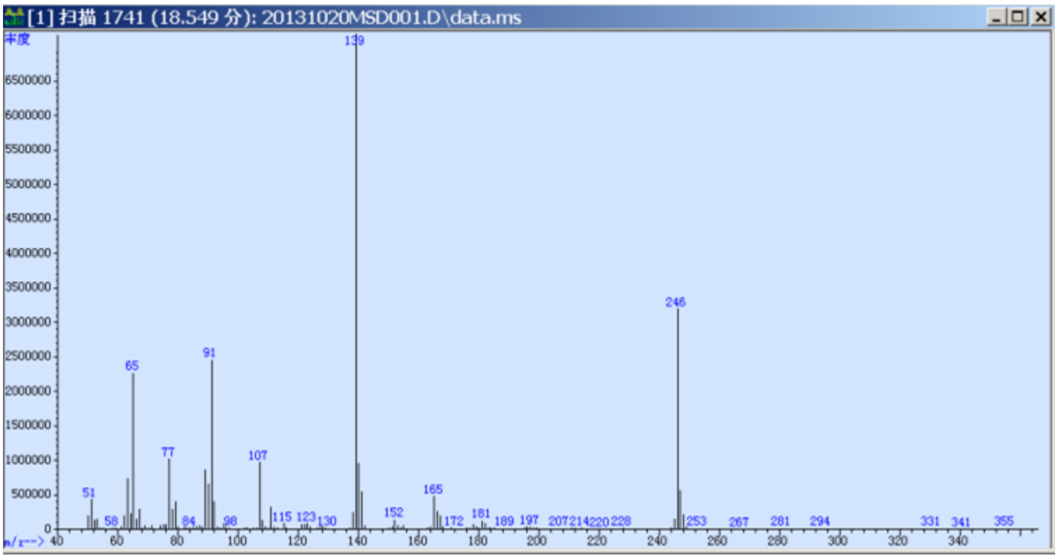
GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}O_2S$: 232.0, found: 232.



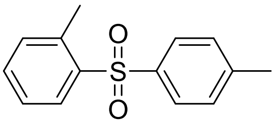
4,4'-Sulfonylbis(methylbenzene) 3m[1]:



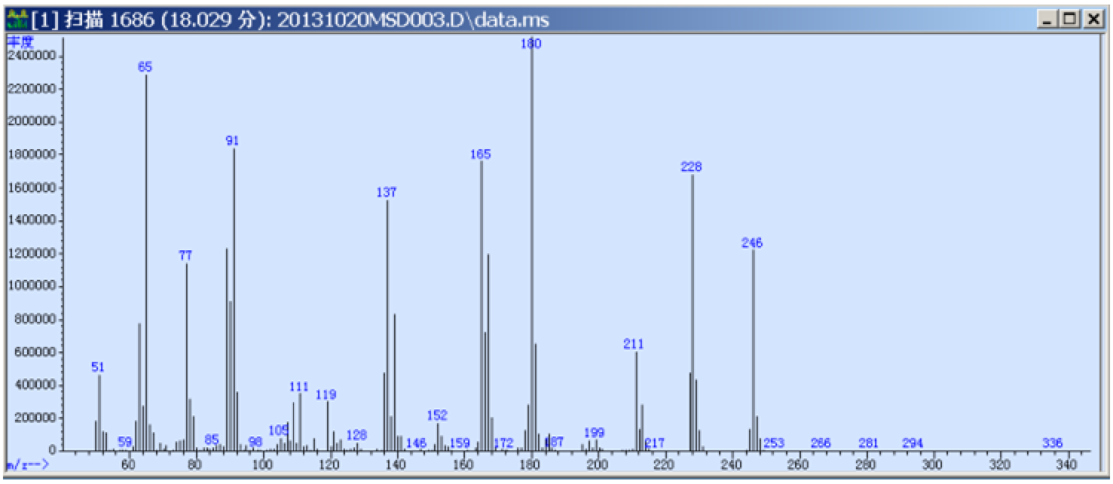
GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{14}O_2S$: 246.0, found: 246.



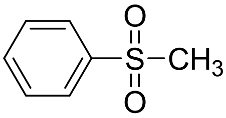
1-Methyl-2-tosylbenzene 3n:



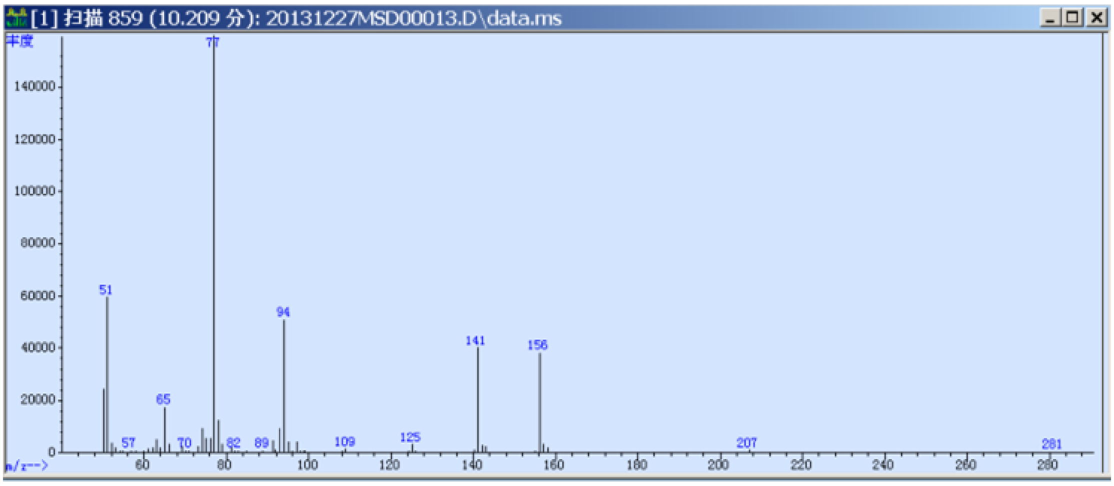
GC-MS (EI) [M]+: m/z calcd. For $C_{14}H_{14}O_2S$: 246.0, found: 246.



4-(Methanesulfonyl)benzene 3q:



GC-MS (EI) [M]+: m/z calcd. for $C_7H_8O_2S$: 156.0, found: 156.



4. References

1) S. Cacchi, G. Fabrizi, A. Goggoamani, L. M. Parisi and R. Bernini, *J. Org. Chem*. 2004, **69**, 5608.

2) S. Cacchi, G. Fabrizi, A. Goggiamani and L. M. Parisi, *Org. Lett.* 2002, **4**, 4719.

3) N. Umierski and G. Manolikakes, *Org. Lett.* 2013, **15**, 188.

4) W. Zhu and D. Ma, *J. Org. Chem.* 2013, **70**, 2696.

5) C. He, J. Hao, H. Xu, Y.-P. Mo, H.-Y. Liu, J.-J. Han, A. Lei, *Chem. Commun.* 2012, **48**, 11073;

6) Y.-F. Zhang, Z.-K. Chen, W.-L. Wu, Y.-H. Zhang and W.-P. Su, *J. Org. Chem.* 2013, **78**, 12494.