# Regioselective Nitration of Halogenated Benzo[c]cinnolines and Benzenoids

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Abstract:

Electrophilic nitration of halo-substituted benzo[c]cinnolines and benzenoids has been achieved regioselectively. The nitro group entry was always ortho to the halo group or/and the aromatic ring. This regioselective electrophilic ortho-nitration was accomplished in mixed acid/mild temperature conditions. Regioselectivity ortho to the halo/ring group(s) was observed with or without proximal steric hindrance. Chlorides and bromides worked equally well in directing these high-yielding ortho-selective reactions.

Graphical Abstract:
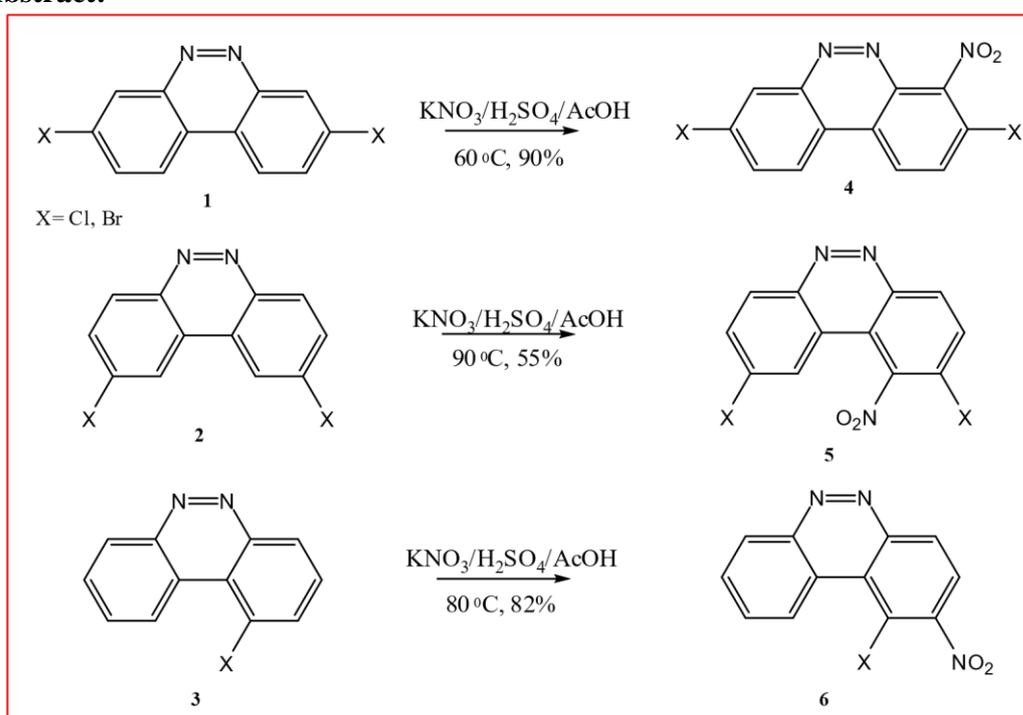

Introduction:

The importance of electrophilic aromatic nitration as an industrial process cannot be overstated.[1] Nitroaromatics continue to play an indispensable role as intermediates in synthetic applications ranging from pharmaceuticals to explosives. As a classical reaction, the electrophilic aromatic (E_{Ar}) nitration has been extensively studied and reviewed over the past two decades.[2] the mechanism of this reaction, first proposed by Ingold and Hughes has, since, been modified by several authors casting doubts on both the proposed mechanism and its reported regioselectivity. In fact, the latter is still a subject of animated discussion as it has proved intriguing and difficult to predict. Attempts to rationalize the results have only led to more disagreement.[3-8] notwithstanding the well documented, yet challenging work by Olah and coworkers on nitration of highly deactivated aromatics in superacids.[9-10] a simpler route to nitroaryl halides using classical conditions, and with view to regioselectivity was a starter.[11-12]

Especially as we became intrigued when a routine mixed acids nitration of 2,3- dichloronitrobenzene afforded 2,3-dichloro-1,4-dinitrobenzene selectively. Our facile synthesis of halogenated benzo[*c*]cinnolines (BCs) has

provided the stage to test this theory.[13-14] Benzo[*c*]cinnoline (BC) and its derivatives are interesting because of their biological activities, their potential as ligands for metals, and also for their highly stable molecular conformations with different symmetries. BCs are being increasingly investigated as highly organized materials.[15-18] We have envisioned building up annulated BCs starting from a regioselective *ortho*-nitration of dihalobenzo[*c*]cinnolines. Upon further investigation, we can report on numerous examples of *ortho*-, also known as *ipso*-nitration at work in a general manner with both aryl chlorides and bromides without being affected by steric hindrance nearby.

Results and Discussion

We have been investigating the electrophilic aromatic nitration of nitroaryl halides, and benzo[*c*]cinnolines in order to prepare substrates for our HSBM Ullmann coupling reactions.[19] Benzo[*c*]cinnoline **0** and dichlorinated benzo[*c*]cinnolines **1-4** were previously prepared in our laboratory from simple chlorinated nitrobenzenes as outlined in the scheme below.
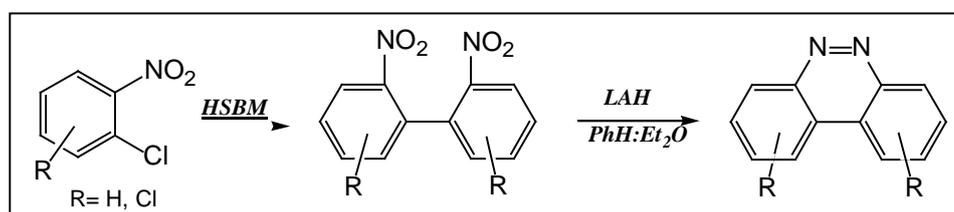
Scheme 1: *Synthesis of Benzo[c]cinnoline and Chlorinated Benzo[c]cinnolines in two steps.*

Aryl halides have been shown to undergo nitration with ortho/para selectivity owing to the halogen's lone pair.[20] Nitration of diazo-deactivated aryl halides promised to inform on the regioselectivity of the reaction with respect to activation at *ortho* relative to the halo group, deactivation *meta* relative to the electron-withdrawing diazo group, and on the synergy of the different electronic as well as steric effects. Starting from previously synthesized dihalobenzo[*c*]cinnolines **1-4** below, electrophilic aromatic nitration afforded the dihalonitrobenzo[*c*]cinnolines **6-8** using classical conditions (see scheme 2). A solution of Potassium nitrate dissolved in sulfuric acid was, first, diluted in acetic acid. Then the solid dihalobenzo[*c*]cinnoline was added to the solution which was gradually warmed with a noticeable change of color, and brown fume formation. The same procedure was utilized for nitration of parent benzo[c]cinnoline **0** and the benzenoids **10** and **12** as further evidence of a general method.
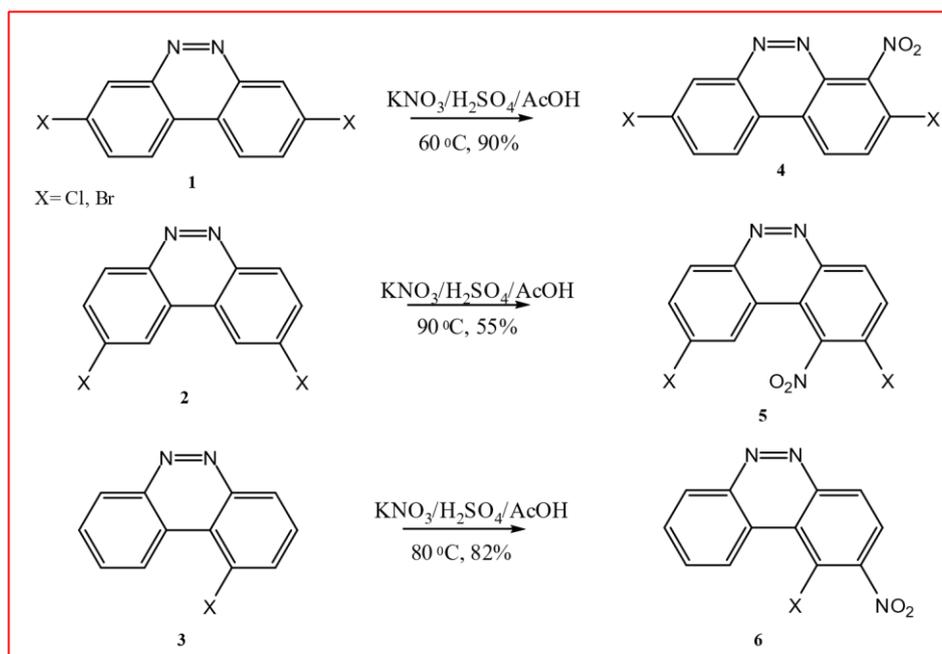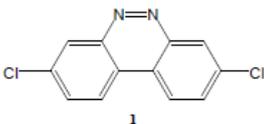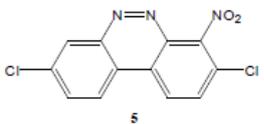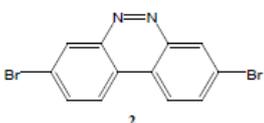
Scheme 2:

Table 1 below summarizes our results for the syntheses of nitrated benzo[*c*]cinnolines **5-8** and nitroaryl halides **11**, and **13** from the benzo[c]cinnolines **0-4** and the aryl halides **10**, **12** respectively. Nitration of benzo[c]cinnoline **0** and its halo derivatives **1-4** with a slight excess (2.2 molar equivalents) of potassium nitrate in a moderately warm mixed acid solution was regioselective in every case. Using these conditions, nitration of 3,8-dichlorobenzo[c]cinnoline **1** afforded 3,8-dichloro-4-nitro-benzo[c]cinnoline **5** in quantitative yield. Similar result was obtained when we switched to the brominated compound **2**, which afforded 3,8-dibromo-4nitro-benzo[c]cinnoline **6** in equally quantitative yield. Using a large excess of nitrating reagent (4.0 molar equivalent) confirmed previous results. Seemingly, nitration occurred at *ortho* position to both the halo group and the cinnoline ring, regardless of the congestion at that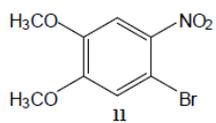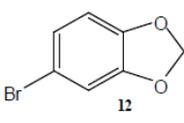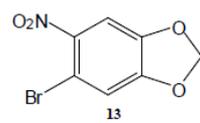 position.   Meta substituted 2,9-dichlorobenzo[c]cinnoline **3** was, similarly, nitrated ortho to both the halo group and the ring albeit the most sterically hindered position, to afford 2,9-dichloro-1nitrobenzo[c]cinnoline **7** in modest yield, due probably to the mentioned steric congestion. In order to rule out the "deactivating" influence of the diazo group, previously described 1chlorobenzo[c]cinnoline **4** was also nitrated in good yield regioselectively at *ortho*, or adjacent to the chloro group to afford 1-chloro-2-nitrobenzo[c]cinnoline **8**.

Table 1:

| Entry	Aryl Halide	Nitroaryl Halide	% Yield*
1	**1**	**5**	90
2	**2**	**6**	90
3	**3**	**7**	55
4	**4**	**8**	82
5	**0**	**9**	80
6	**10**	**11**	95
7	**12**	**13**	85
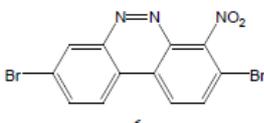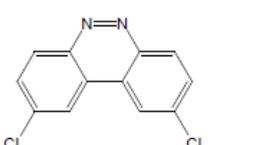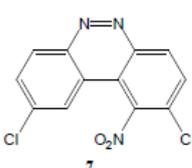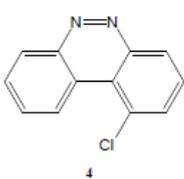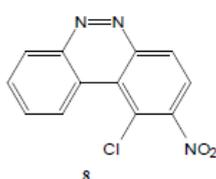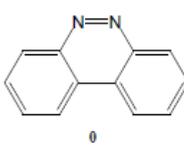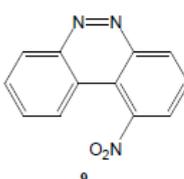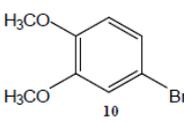
*Isolated yields

Heating the reaction mixture moderately achieved *ortho* selectivity as a general principle in these systems. This *ortho*-selectivity has been explained as a 1,2- rearrangement of the NO$_2$ group, which occurs subsequent to the formation of the Wheland's *ipso* σ-complex[21] during electrophilic aromatic nitration (Scheme 3).

Ipso σ-Complex
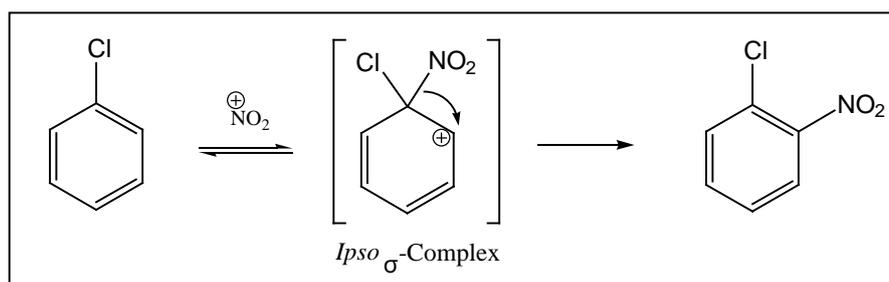
Scheme 3:

Examples of the occurrence of *ortho*-selectivity during nitration are numerous, usually in conjunction with greater para-selectivity yield of products.[22] Lower temperatures, and shorter reaction time are usually associated with *ortho* selectivity, as suggested by Tanaka as well.[23] By applying these kinetically favorable conditions, we noticed a trend of nitration adjacent to chloro groups, and adjacent to both the chloro and the cinnoline ring,
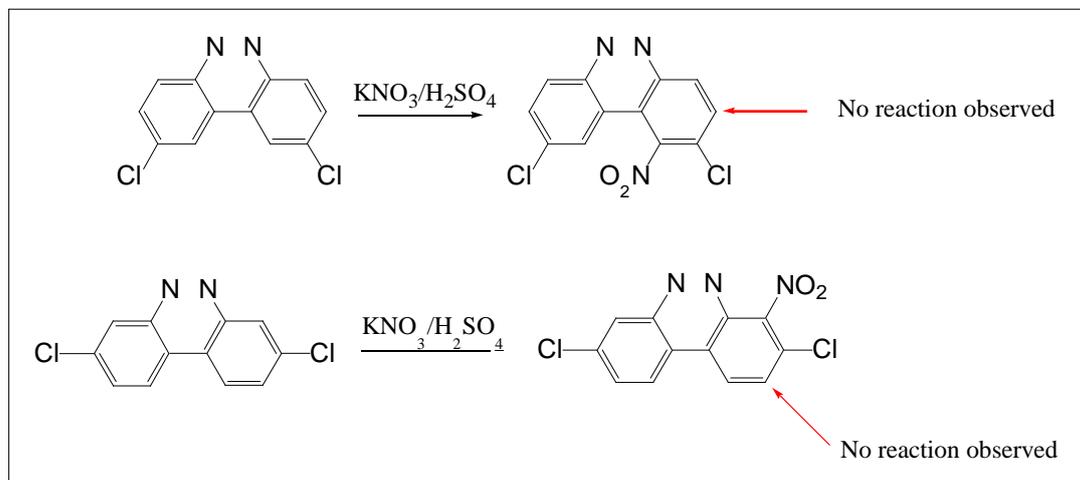
despite existing steric hindrance. This is in agreement with observation by others on the synergy of these effects.[24] It is noteworthy to point out that in the chlorinated benzo[*c*]cinnoline series (entries 1-4), the combined electronic effects of the halo substituent and the adjacent cinnoline ring directed *ortho*selectivity exclusively to the most electronically favored yet sterically hindered *ortho* positions instead of the sterically unhindered *ortho* position to the halo group in a demonstration of the synergetic electronic effects from both substituents (Scheme 4). Further evidence of this regioselectivity was provided when parent benzo[*c*]cinnoline **0** was nitrated with an excess of potassium nitrate, as shown in entry 5, resulting in a unique nitration product, the somewhat congested 1-nitrobenzo[*c*]cinnoline **9**. Interestingly, the formation of **9** rather than 4nitrobenzo[*c*]cinnoline establishes the proximity of the aromatic ring, rather than the diazo moiety in the adjacent cinnoline, as the main factor in stabilizing the positive charge.

Scheme 4:

The trend seems to be general with other halides such as bromides. To demonstrate the general nature of the reaction, we conducted a similar nitration of the previously synthesized 3,8dibromobenzo[*c*]cinnoline **2** to afford 4-nitro-3,8-dibromobenzo[*c*]cinnoline **6** (entry 2). In the benzenoid series (entries 6, and 7), we used 3,4-dimethoxybromobenzene **10** and 3,4methylenedioxybromobenzene **12** to selectively direct nitration at *ortho* position to the bromo group in either compound to afford nitrated aryl halides **11** and **13** respectively.

We have observed a trend consisting in regioselective nitration of deactivated aryl halides and halobenzo[c]cinnolines at ortho position relative to the adjacent halo group, the aromatic ring or both despite noted steric hindrance. This regioselective nitration can be rationalized by the formation of an ipso σ-complex which is stabilized by either an adjacent halo group's lone pair or a ring's π system.[25]

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Experimental Section

Commercially available reagents were ACS grade and used without further purification. NMR spectra were recorded on a Varian 400 MHz (CDCl$_3$ as solvent). GC-MS (Direct Probe) and ESI-MS were recorded at the University of South Carolina.

General Procedure

A 50mL Erlenmeyer flask, equipped with a magnetic bar was clamped and placed on a hot plate/stirrer, and then charged with concentrated sulfuric acid (10-20mL), and potassium nitrate (1.1 or 2.2 molar equivalents of the chlorinated aromatic compound, see table) while stirring. The mixture was diluted with acetic acid (40mL) before being warmed, and the heat was adjusted to 90 °C to dissolve the solid. The compound (1 mol) was then quickly added in portions while the temperature was kept near 90 °C. Gradually the mixture became colored, darkening over several minutes before becoming clear after a noticeable brown gas above the liquid has receded. In some instances, the mixture became dark-red/brown immediately after adding the compound. After 1h, the reaction mixture was cooled to room temperature, and poured into a beaker containing crushed ice. The precipitate was collected with suction (Buchner) and dried to provide a crude compound which was recrystallized (commonly with ethanol or/and a mixture of ethanol/acetone) or/and chromatographed in silica gel using a 4:1 hexane/ethyl acetate eluent.

Synthesis of 3,8-dichloro-4-nitrobenzo[*c*]cinnoline 5: 3,8-Dichloro-benzo[*c*]cinnoline **1** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a hot (90 °C) mixture of $KNO_3/H_2SO_4/AcOH$ for 1h. The crude precipitate was vacuum filtered, dried and recrystallized in hot ethanol to afford 3,8-dichloro-4-nitrobenzo[*c*]cinnoline **5** as brown crystals. M.p. 187-190 °C.
^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 7.94(d, 1H), 7.97(d, 1H), 8.46(d, 1H), 8.56(d, 1H), 8.79(s, 1H)
GCMS: Calculated 293.55, Found: 293

Synthesis of 3,8-dibromo-4-nitrobenzo[*c*]cinnoline 6: 3,8-Dibromo-benzo[*c*]cinnoline[*] **2** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a hot (90 °C) mixture of KNO_3/H_2SO_4 for 1h. The crude precipitate was vacuum filtered, dried and recrystallized in hot ethanol to afford 3,8-dibromo-4-nitrobenzo[*c*]cinnoline **6** as brown crystals. M.p. 207-209 °C.
Recrystallized in hot ethanol to afford 2,9-dichloro-1-nitrobenzo[*c*]cinnoline **7** as brown crystals. M.p. 156-159 °C.
^{2}H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 8.00(d, 1H), 8.06(d, 1H), 8.12(s, 1H), 8.80(d, 1H), 8.88(d, 1H)
GCMS: Calculated 293.55, Found: 293

Synthesis of 1-chloro-2-nitrobenzo[*c*]cinnoline 8: 1-Chloro-benzo[*c*]cinnoline[*] **4** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a warm (90 °C) mixture of KNO_3/H_2SO_4 for 1h. The crude precipitate was vacuum filtered, dried and recrystallized in hot ethanol to afford 1-chloro-2-nitrobenzo[*c*]cinnoline **8** as yellow crystals. M.p. 150-155 °C.
^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 7.30(s, 2H), 7.59(d, 2H), 8.22(d, 2H)

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[1] H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 7.90(d, 1H), 7.99(d, 1H), 8.40(d, 1H), 8.6(d, 1H), 8.9(s, 1H)

Synthesis of 2,9-dichloro-nitrobenzo[*c*]cinnoline 7: 2,9-Dichloro-benzo[*c*]cinnoline[*] **3** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a warm (90 °C) mixture of KNO_3/H_2SO_4 for 1h. The crude precipitate was vacuum filtered, dried and

[2] H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 3.9(s, 3H), 4.0(s, 3H), 7.11(s, 1H), 7.59(s, 1H)

GCMS: Calculated 260.96, Found: 261

Synthesis of 1,2-methylenedioxy-4-bromo-5-nitro-benzene 13: 1,2-methylenedioxy-4bromobenzene **12** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a warm (90 °C) mixture of KNO_3/H_2SO_4 for 1h. The crude precipitate was

^{13}C NMR (400 MHz, CDCl$_3$, TMS) δ(ppm) 118.5, 119.2, 125.1, 128.0, 129.2, 130.3, 131.0, 131.5, 131.7, 134.2, 146.1, 146.5

GCMS: Calculated 260.35, Found: 214 (NO$_2$ flight: 46) = 260

Synthesis of 1-nitrobenzo[*c*]cinnoline 9: Parent benzo[*c*]cinnoline **0** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a warm (90 °C) mixture of KNO$_3$/H$_2$SO$_4$ for 1h. The crude precipitate was vacuum filtered, dried and recrystallized in hot ethanol to afford 1-nitrobenzo[*c*]cinnoline **9** as yellow crystals. M.p. 137-140 °C.

^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 7.30(s, 2H), 7.59(d, 2H), 8.22(d, 2H)

^{13}C NMR (400 MHz, CDCl$_3$, TMS) δ(ppm) 114.0, 116.2, 123.1, 126.0, 128.2, 131.3, 133.0, 133.5, 134.2, 136.1, 145.0, 146.2

GCMS: Calculated 225.55, Found: 225

Synthesis of 1-bromo-2-nitro-4,5-dimethoxybenzene 11: 1-bromo-3,4-dimethoxybenzene **10** (1.0 molar equivalent) was added into an oven-dried 100mL round-bottomed flask, and stirred in a warm (90 °C) mixture of KNO$_3$/H$_2$SO$_4$ for 1h. The crude precipitate was vacuum filtered, dried and recrystallized in hot ethanol to afford 1-bromo-2-nitro-4,5-dimethoxybenzene 11 as yellow crystals. M.p. 117-120 °C.
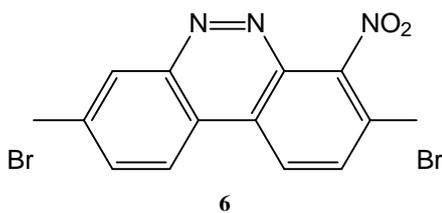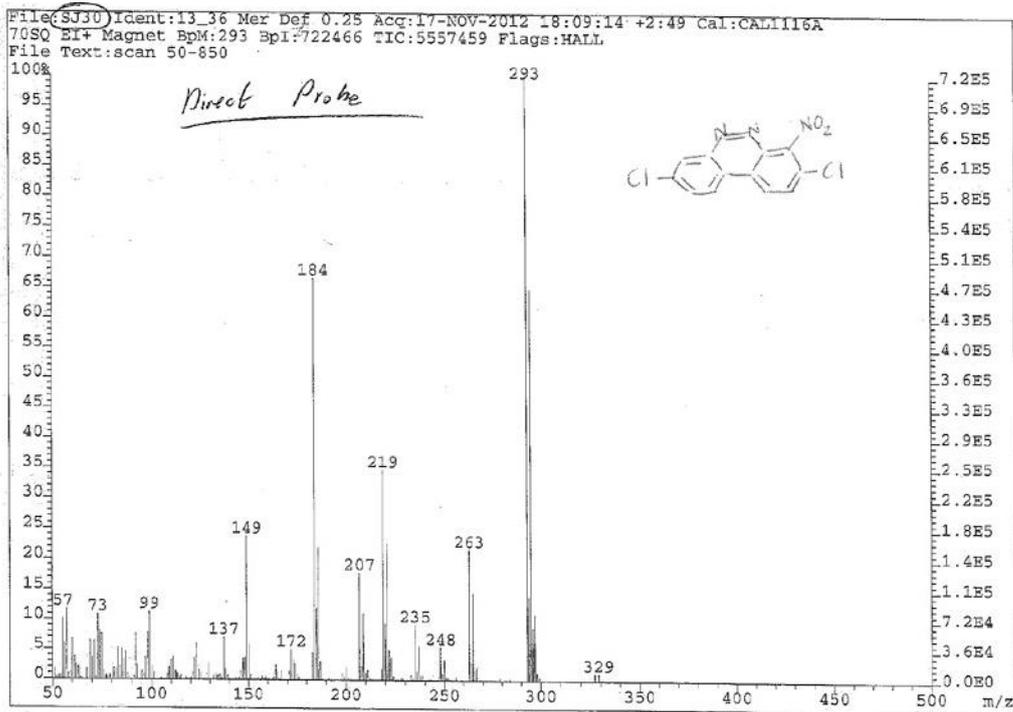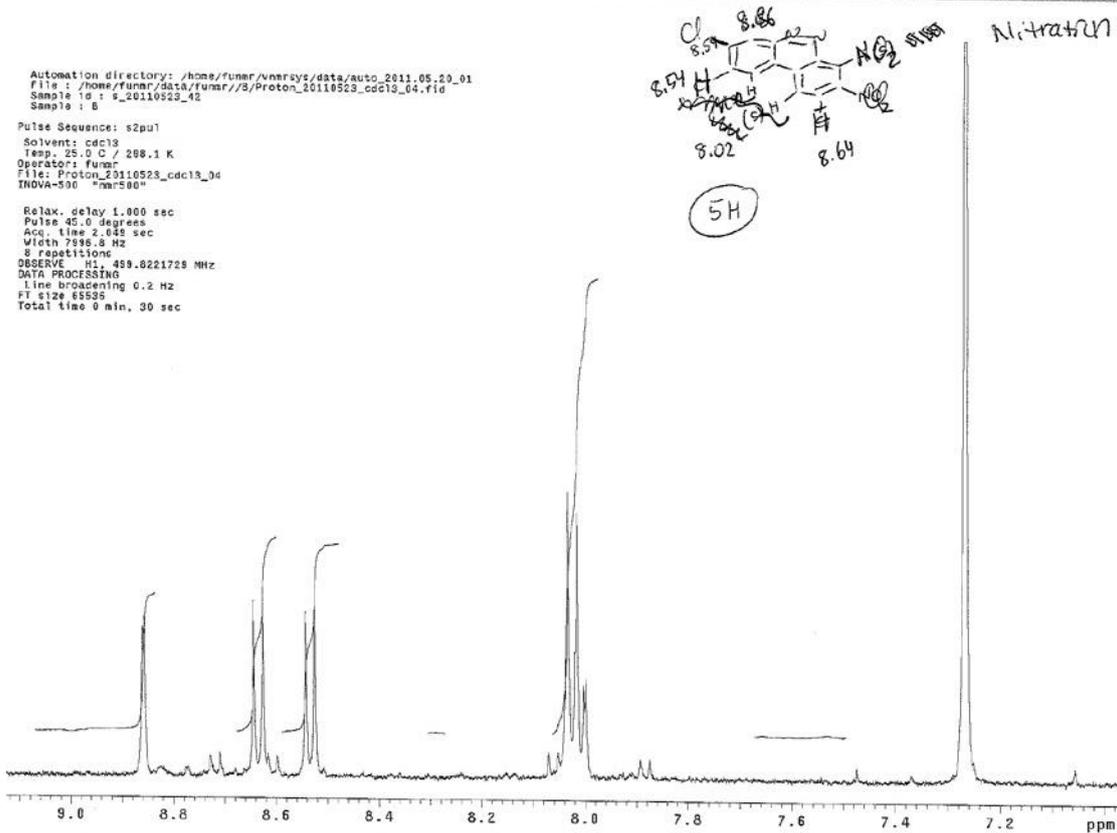
Vacuum filtered, dried and recrystallized in hot ethanol to afford 1,2-methylenedioxy-4-bromo5-nitro-benzene 13 as yellow crystals. M.p. 142-144 °C.

^{1}H NMR (400 MHz, CDCl$_3$, TMS): δ(ppm) 6.17(s, 2H), 7.12(s, 1H), 7.45(s, 1H)

^{13}C NMR (400 MHz, CDCl$_3$, TMS) δ(ppm) 104.0, 107.2, 109.1, 115.0, 144.2, 147.3, 152.0 GCMS: Calculated 246.55, Found: 167 (Br = 79) 146
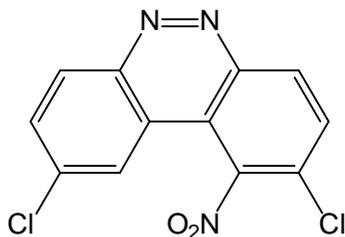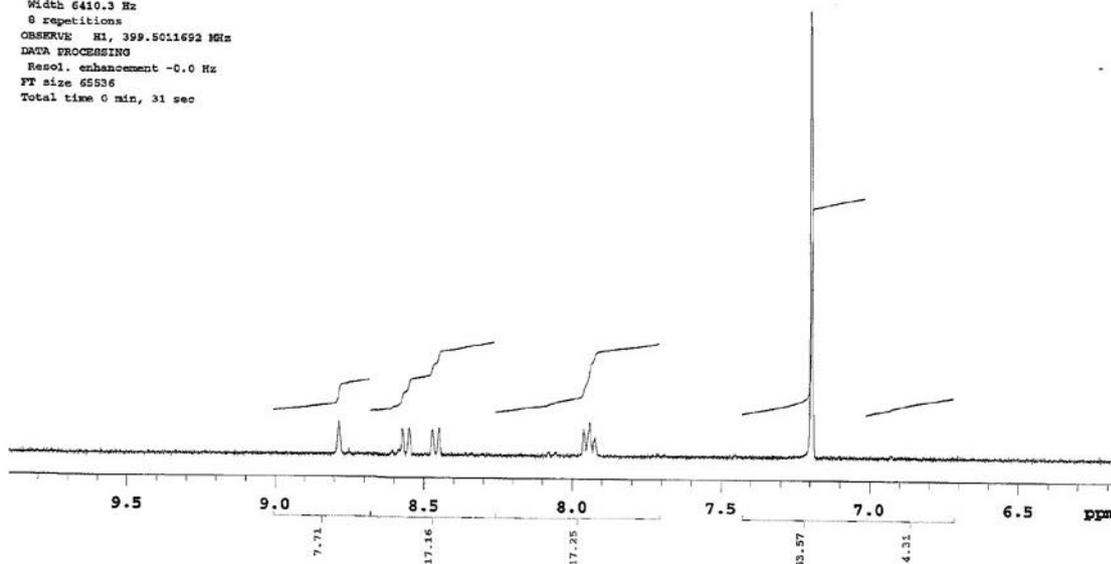
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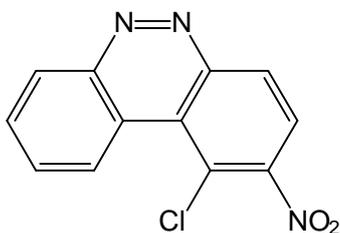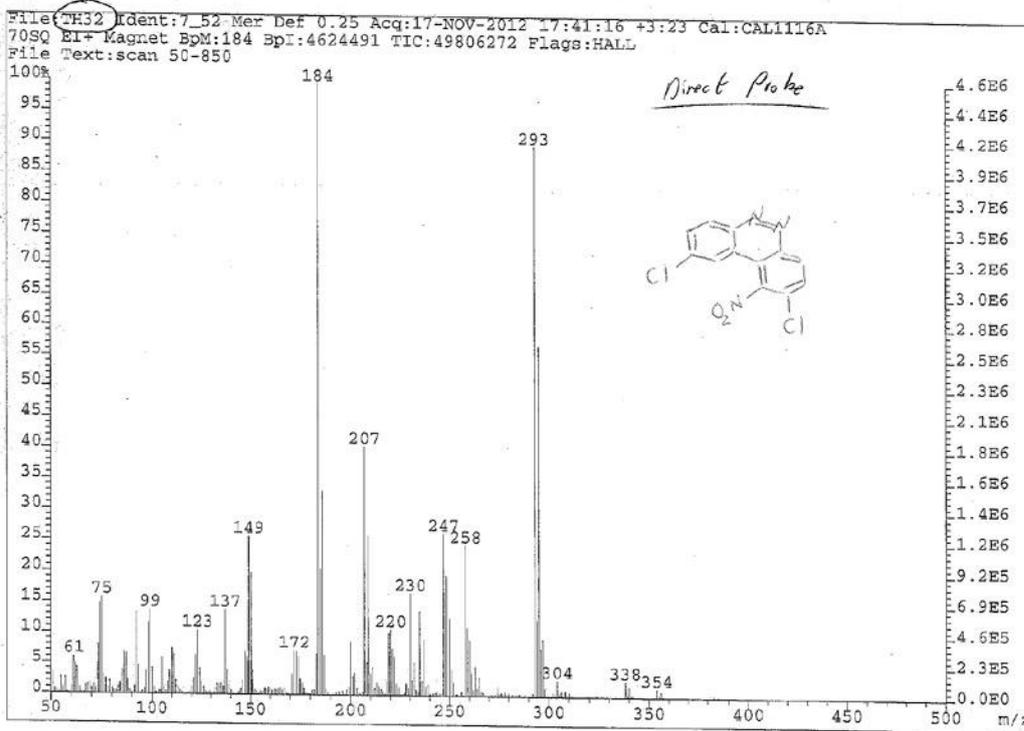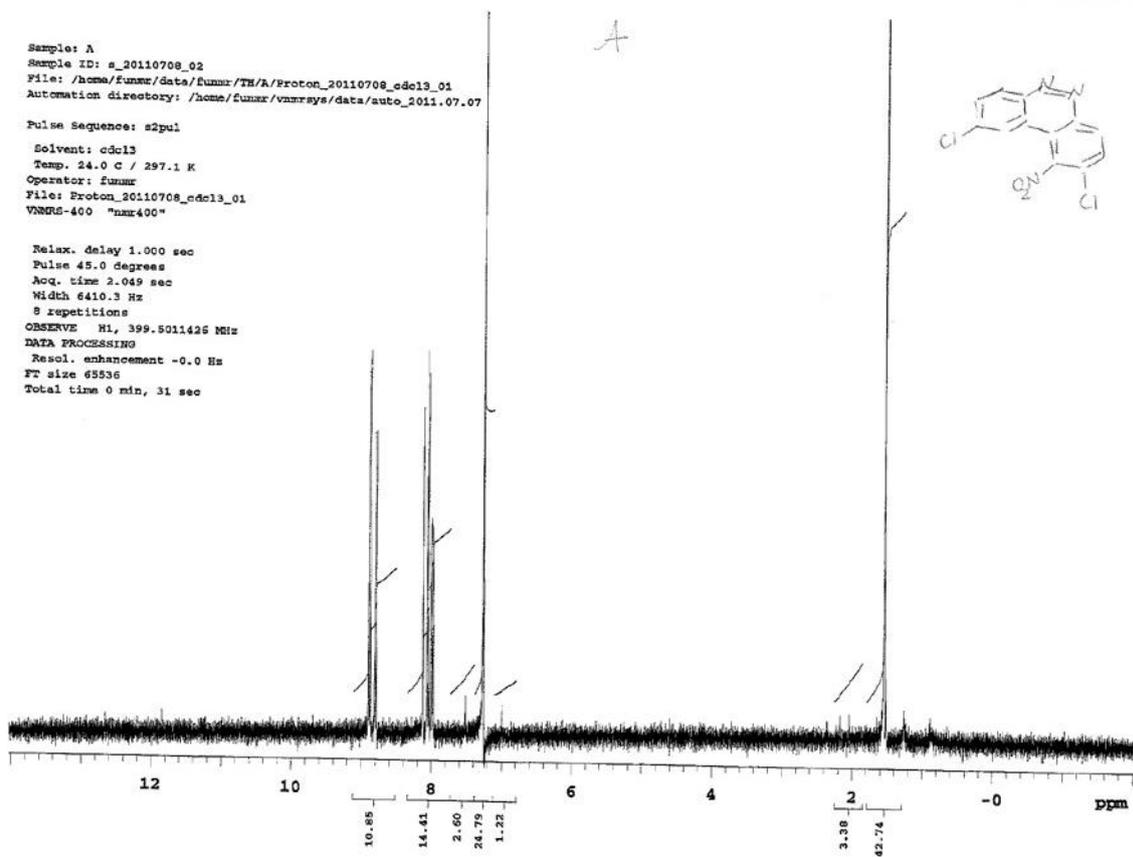

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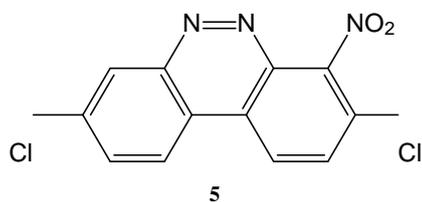
Nitration   234 C

Sample: ShaNese
Sample ID: s_20110603_06
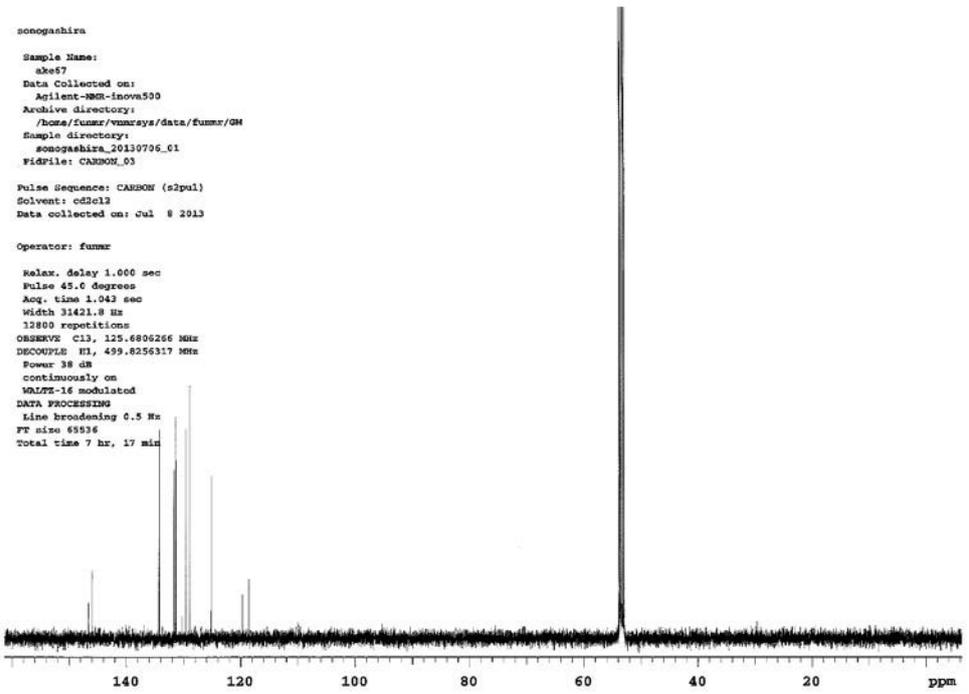File: /home/funmr/data/hanks/TN/ShaNese/Proton_20110603_cdcl3_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: hanks
File: Proton_20110603_cdcl3_01
VNMRS-400 "nmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE   H1, 399.5011692 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec

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Sample: A
Sample ID: s_20110708_02
File: /home/funmr/data/funmr/TH/A/Proton_20110708_cdcl3_01
Automation directory: /home/funmr/vnmrsys/data/auto_2011.07.07

Pulse Sequence: s2pul

  Solvent: cdcl3
  Temp. 24.0 C / 297.1 K
  Operator: funmr
  File: Proton_20110708_cdcl3_01
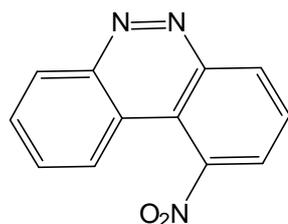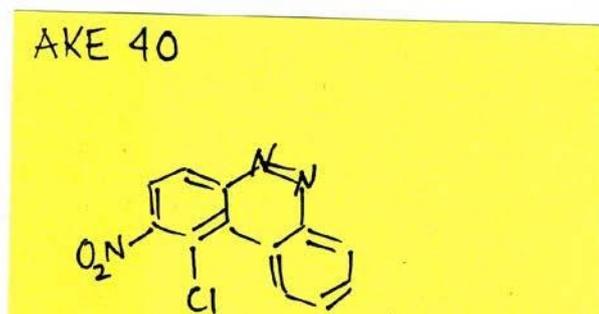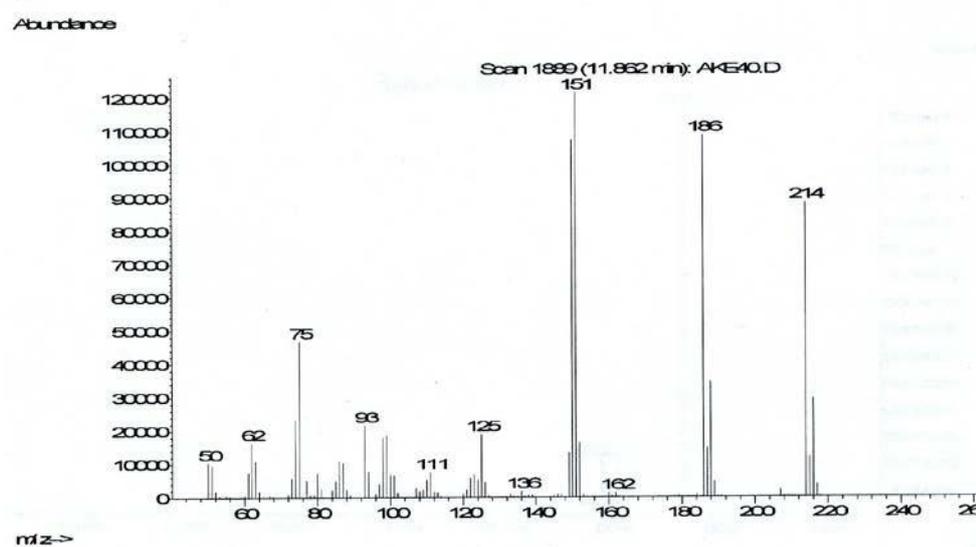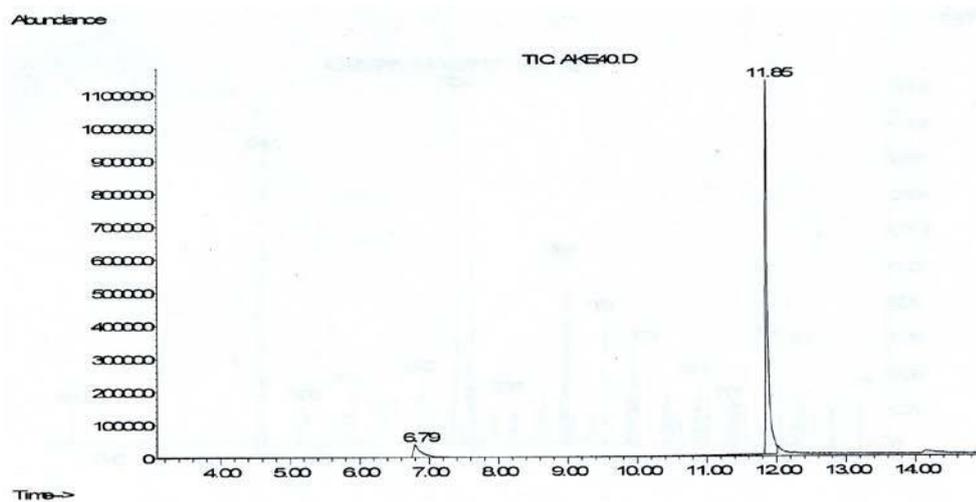 VNMRS-400 "nmr400"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 6410.3 Hz
  8 repetitions
  OBSERVE   H1, 399.5011425 MHz
  DATA PROCESSING
  Resol. enhancement -0.0 Hz
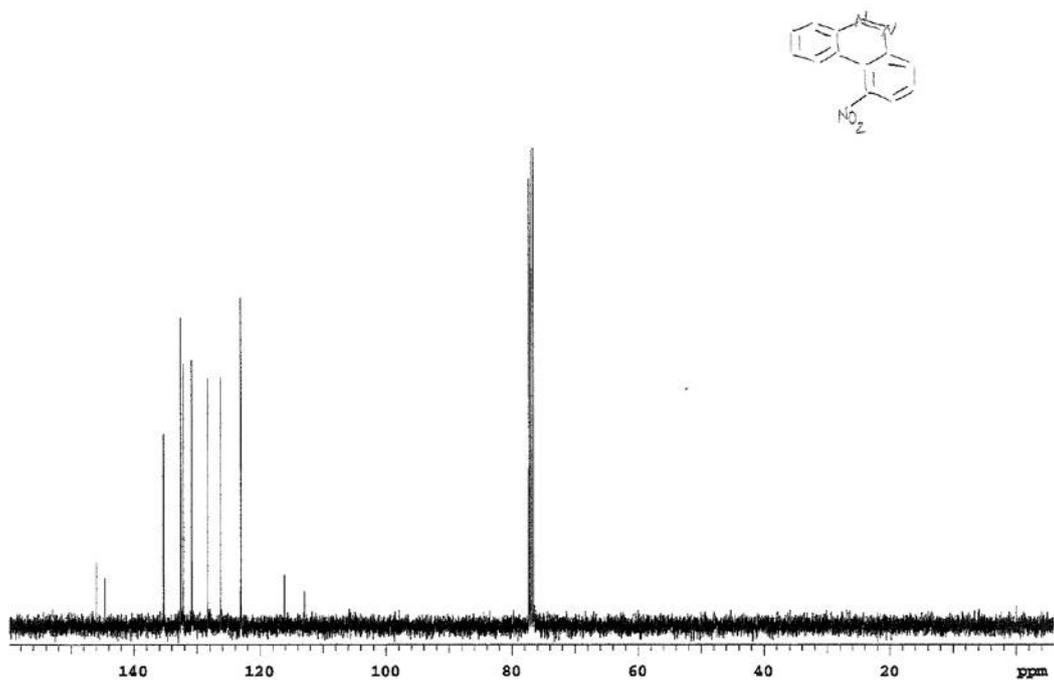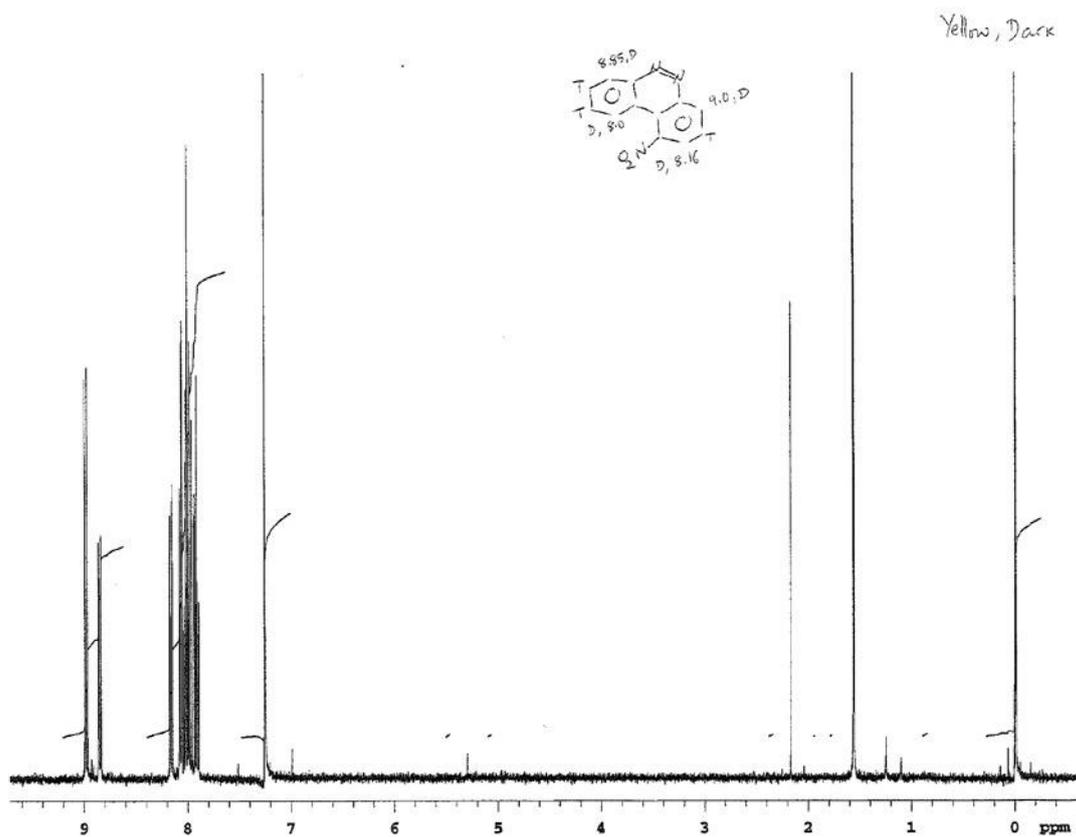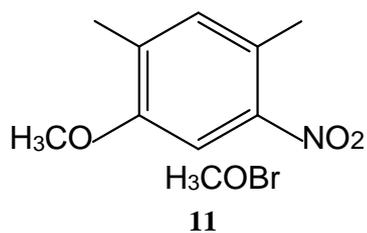 FT size 65536
  Total time 0 min, 31 sec

File: TH32 Ident:7_52 Mer Def 0.25 Acq:17-NOV-2012 17:41:16 +3:23 Cal:CAL1116A
70SQ EI+ Magnet BpM:184 BpI:4624491 TIC:49806272 Flags:HALL
File Text:scan 50-850

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sonogashira

Sample Name:
  ake67
Data Collected on:
  Agilent-NMR-inova500
Archive directory:
  /home/funmr/vnmrsys/data/funmr/GM
Sample directory:
  sonogashira_20130706_01
FidFile: CARBON_03

Pulse Sequence: CARBON (s2pul)
Solvent: cd2cl2
Data collected on: Jul 8 2013

Operator: funmr

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 1.043 sec
  Width 31421.8 Hz
  12800 repetitions
OBSERVE C13, 125.6806266 MHz
DECOUPLE H1, 499.8256317 MHz
  Power 38 dB
  continuously on
  WALTZ-16 modulated
DATA PROCESSING
  Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 17 min

TIC AKE40.D

Scan 1889 (11.862 min): AKE40.D

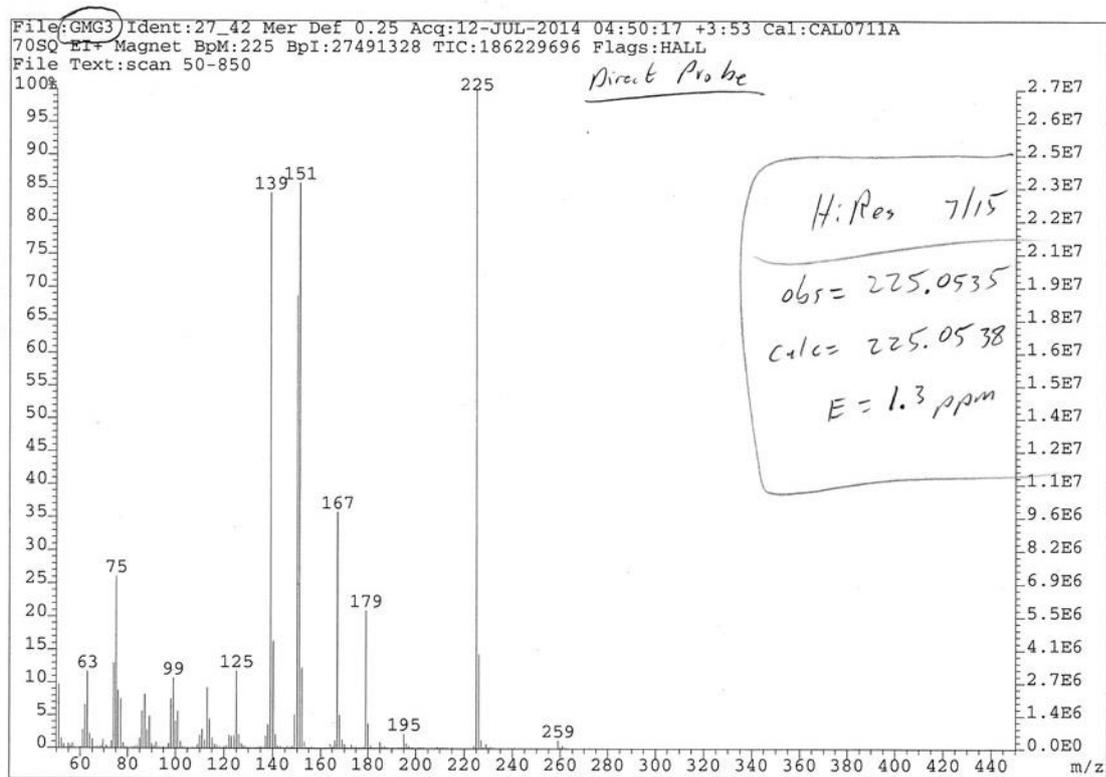AKE 40

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August 2015

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Gradient Shimming

Sample Name:
  gs
Data Collected on:
  Agilent-NMR-mercury400
Archive directory:
  /home/asul/vnmrsys/data
Sample directory:
  Brandon_NMR3_20140418_01
FidFile: PROTON_64

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 12 2014

Temp. 26.0 C / 299.1 K
Operator: asul

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions
OBSERVE   H1, 399.9395586 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 57 sec

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