Organic Syntheses

Synthesis of 2,3-Disubstituted Benzofurans by the Palladium-Catalyzed Coupling of 2-Iodoanisoles and Terminal Alkynes, Followed by Electrophilic Cyclization: 3-Iodo-2-phenylbenzofuran

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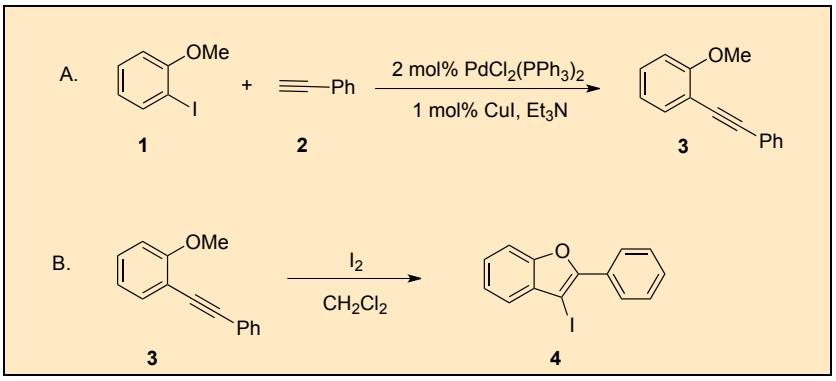
Checked by Michael Rombola and Viresh H. Rawal



Procedure

A. *2-(Phenylethynyl)anisole (**3**).* A 250-mL, one-necked round-bottomed flask, equipped with a 15 mm × 32 mm ellipsoid-shaped magnetic stirring bar, is charged with 2-iodoanisole (**1**, 7.02 g, 30.0 mmol, 1.0 equiv) (Note 1), phenylacetylene (**2**, 36.0 mmol, 3.68 g, 1.2 equiv) (Note 2), triethylamine (60 mL) (Note 3) and bis(triphenylphosphine)palladium(II) dichloride (0.6 mmol, 0.421 g, 0.02 equiv) (Note 4). After stirring for 5 min, copper(I) iodide (0.3 mmol, 0.057 g, 0.01 equiv) (Note 5) is added and stirring is continued for another 2 min (Note 6). The flask is then capped with a rubber septum, into which is inserted a nitrogen inlet, and subjected to

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three cycles of evacuation and refilling with nitrogen. While being maintained under a slight positive pressure of nitrogen, the mixture is allowed to stir at room temperature for 3 h (Notes 7 and 8). The resulting dark gray solution is filtered through a medium porosity fritted glass funnel and EtOAc (4 x 25 mL) is used to rinse the flask and wash the filter cake. The combined organic phases are concentrated by rotary evaporation (28 °C, 150 to 8 mmHg) to give a dark brown oil (Note 9). The crude product is purified by flash column chromatography on silica gel (Note 10) to afford alkyne **3** as an amber oil (Note 11) (6.19–6.24 g, 99%).

B. *3-Iodo-2-phenylbenzofuran (**4**).* A 500-mL, three-necked round-bottomed flask, equipped with a 15 mm × 32 mm ellipsoid-shaped magnetic stirring bar, is charged with 2-(phenylethynyl)anisole (**3**, 5.15 g, 24.7 mmol, 1.0 equiv) and dichloromethane (250 mL) (Note 12). Two necks are capped with rubber septa, and to the third neck is attached a 50 mL screw feed solid addition funnel. The side port of the addition funnel is capped with a rubber septum. A nitrogen inlet is inserted into the middle septum and the flask is subjected to three cycles of evacuation and refilling with nitrogen. Solid iodine (I_2) (12.6 g, 49.6 mmol, 2.0 equiv) (Note 13) is added *via* a solid addition funnel over 20 min. The addition funnel is replaced with a rubber septum and the reaction is allowed to stir at room temperature under nitrogen for 5 h (Notes 14 and 15). The dark purple solution is transferred to a 500-mL separatory funnel. The original round-bottomed flask is rinsed with dichloromethane (2 x 25 mL) and the rinse is also transferred to the 500-mL separatory funnel. A saturated aqueous $Na_2S_2O_3$ solution (150 mL) (Note 16) is added. After shaking for 1 min, the layers are separated. The organic phase is dried over anhydrous sodium sulfate (Na_2SO_4) (Note 17), filtered through a medium porosity fritted glass funnel, which was rinsed with dichloromethane (2 x 25 mL), and concentrated by rotary evaporation (28 °C, 150 to 8 mmHg) to give a brown oil. The residue is purified by flash column chromatography on silica gel (Note 18) to afford benzofuran **4** as a beige solid (Note 19) (6.85–6.88 g, 87%yield).

Notes

1. 2-Iodoanisole (**1**, 98%) was purchased from Sigma-Aldrich and used as received.

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2. Phenylacetylene (**2**, 98%) was purchased from Sigma-Aldrich and used as received.
3. Triethylamine (Et_3N, ≥ 99%) was purchased from Sigma-Aldrich and used as received.
4. Bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 98%) was purchased from Sigma-Aldrich and used as received.
5. Copper(I) iodide (CuI, 98%) was purchased from Sigma-Aldrich and used as received.
6. The color of the reaction changes to dark green and a considerable amount of triethylamine hydroiodide salt precipitates.
7. The speed of stirring might need to be adjusted, since precipitation of the triethylamine hydroiodide salt could impede efficient stirring of the solution.
8. Completeness of the reaction is judged by the disappearance of 2-iodoanisole by thin-layer chromatography (TLC), performed on glass-backed pre-coated silica gel plates (250 μm, Merck Millipore) with a UV254 indicator, using 33:1 hexane/ethyl acetate as the eluent (R_f of 2-iodoanisole = 0.54; R*f* of the product **3** = 0.23). The product is visualized with a 254 nm UV lamp.
9. The crude product is dried on a rotary evaporator (28 °C, 7.5 mmHg) for 45 min.
10. Column chromatography was performed on a 4 cm diameter column, dry-packed with 110 g of silica gel (SiliaFlash® P60 230 × 400 mesh, 60Å), and eluted with 33:1 hexanes/ethyl acetate (1 L). Fifty 20 mL fractions were collected. Fractions 19-42 contained the desired product and were concentrated by rotary evaporation (28 °C, 7.5 mmHg) and dried under vacuum (3 mmHg) for 24 h while occasionally rotating the flask.
11. The physical properties of **3** are: R_f = 0.23 (TLC, Note 8); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.92 (s, 3 H), 6.90 (d, *J* = 8.5, 1 H), 6.95 (t, *J* = 7.5, 1 H), 7.30–7.37 (m, 4 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.56–7.58 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 56.0, 86.0, 93.6, 111.0, 112.7, 120.7, 123.8, 128.3, 128.4, 129.9, 131.9, 133.8, 160.2; IR (neat) 3059, 2835, 2216, 1593, 1574 cm^{-1}; Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.54; H, 5.76.
12. Dichloromethane (DCM, 99.9%) was purchased from Fisher Scientific and used as received.
13. The checkers purchased iodine (I_2, 1 – 3 mm beads, 99.7%) from Sigma-Aldrich and used it as received.

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14. The completeness of the reaction is judged by the disappearance of 2-(phenylethynyl)anisole by thin-layer chromatography performed on glass-backed pre-coated silica gel plates (250 μm, Merck Millipore) with a UV254 indicator, using 33:1 hexane/ethyl acetate as the eluent (R_f of 2-(phenylethynyl)anisole = 0.23; R_f of the product **4** = 0.53). The product is visualized with a 254 nm UV lamp.
15. A minor side product is present and possesses a very similar R_f to 2-(phenylethynyl)anisole upon TLC analysis.
16. The checkers purchased sodium thiosulfate pentahydrate ($Na_2S_2O_3 \bullet 5H_2O$, Certified ACS) from Fisher Scientific and used it as received.
17. Anhydrous sodium sulfate (Na_2SO_4, ≥ 99%) was purchased from Fisher Scientific and used as received. To ensure proper dryness, 35 g of Na_2SO_4 was added to the organic phase and the resulting mixture was kept at room temperature for 10 min with occasional swirling.
18. Column chromatography is performed on a 4 cm diameter column, dry-packed with 95 g of silica gel (SiliaFlash® P60230 × 400 mesh, 60Å) and eluted with 33:1 hexanes/ethyl acetate. Fifteen 20 mL fractions are collected. Fractions 8–14 contained the desired product. They were combined, concentrated by rotary evaporation (28 °C, 150 to 8 mmHg), dried under vacuum (3 mmHg) at 23 °C for 6 h and kept in the refrigerator (1 °C) for 3 days. The solid obtained was ground up and dried under vacuum (4 mbar) at 23 °C for 2 h until a constant weight (6.85–6.88 g) was obtained.
19. The physical properties of **4** are: mp 40–42 °C; R_f = 0.53 (TLC, Note 14); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31–7.38 (m, 2 H), 7.42–7.52 (m, 5 H), 8.18–8.19 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 61.4, 111.4, 122.1, 123.7, 125.9, 127.7, 128.7, 129.4, 130.2, 132.7, 153.3, 154.1; IR ($CHCl_3$) 3062, 1590, 1453 cm^{-1}; HRMS *m*/*z* calcd. for $C_{14}H_9IO$ $[M]^+$ 319.9698, found 319.9688. Anal. Calcd. for $C_{14}H_9OI$: C, 52.53; H, 2.83. Found: C, 52.60; H, 2.88.

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work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

The benzo[*b*]furan nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.[3] There has been growing interest in developing a general and versatile synthesis of benzo[*b*]furans. A number of synthetic approaches to this class of compounds have been introduced in recent years.[4] One common approach to heterocycles has been the electrophilic cyclization of alkynes using ICl and I_2. Cacchi and co-workers have previously reported the synthesis of 3-iodobenzo[*b*]furans by the iodocyclization of alkynylphenols.[5] Unfortunately, the protecting and deprotecting steps required to synthesize the alkynylphenol are not particularly attractive synthetically. We have successfully made this overall approach more synthetically attractive by employing the corresponding

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methyl ethers and using I_2 and ICl as electrophiles.[6] The preparation of 3-iodo-2-phenylbenzofuran described here illustrates a general protocol for the palladium/copper-catalyzed cross-coupling of various *o*-iodoanisoles and terminal alkynes, followed by electrophilic cyclization with I_2. Since this process was first communicated in 2005, it has been subsequently employed in the synthesis of coumestans,[7] permethylated anigopreissin A[8] and XH-14[9] derivatives, inhibitors of mycobacterium protein tyrosine phosphatase B,[10] and retinoic acid receptor agonists.[11]

This approach to 2,3-disubstituted benzofurans is very versatile. The substituents attached to the triple bond can be vinylic groups or aromatic rings bearing certain types of functionality. Unfortunately, alkynes bearing an alkyl group fail to undergo electrophilic cyclization. This approach has also been successfully applied to the synthesis of furopyridines (Table 1).

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Table 1. Synthesis of Benzo[*b*]furans by Electrophilic Cyclization[a]

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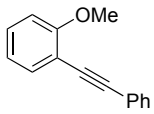
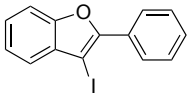
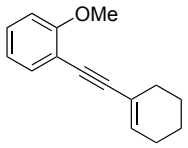
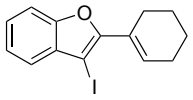
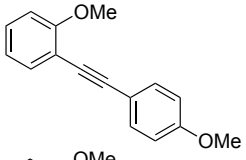
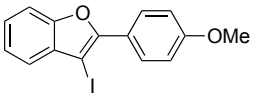
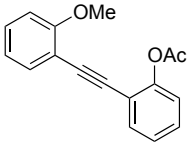
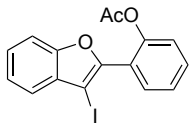
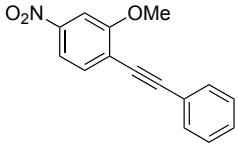
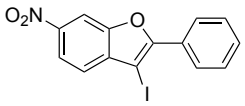
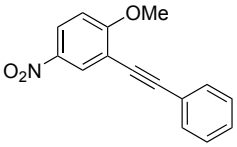
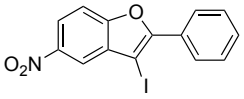
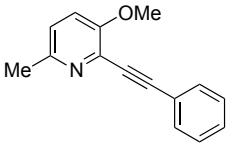
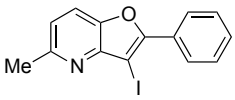
1			3	87
2			3	80
3			3	100
4			3	95
5			12	67
6			12	80
7			12	67

[a] All reactions were run with 0.25 mmol alkyne and 2 equiv of I_2 in 5 mL of CH_2Cl_2 at 25 °C.

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References

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2. Department of Chemistry, Iowa State University, Ames, IA 50011; larock@iastate.edu.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

2-Iodoanisole; (529-28-2)
Phenylacetylene; (536-74-3)
Triethylamine; (121-44-8)
Bis(triphenylphosphine)palladium(II) dichloride; (13965-03-2)
Copper(I) iodide; (7681-65-4)
Iodine; (7553-56-2)

Tuanli Yao earned his B.S. and M.S. degrees in chemistry from Peking University in China. He obtained his Ph.D. in 2005 from Iowa State University working with Professor Richard C. Larock. His graduate research at Iowa State focused on new approaches to heterocycles and carbocycles. After postdoctoral research with Professor Richmond Sarpong at U.C. Berkeley, he joined Deciphera Pharmaceuticals in Lawrence, Kansas. Currently, he is a Research Associate at University of Kansas Specialized Chemistry Center. His research interests include palladium catalysis and medicinal chemistry.

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Richard C. Larock, University Professor and Distinguished Professor Emeritus at Iowa State University, received his B.S. at the University of California, Davis in 1967. He then joined the group of Prof. Herbert C. Brown at Purdue University, where he received his Ph.D. in 1972. He worked as an NSF Postdoctoral Fellow at Harvard University in Prof. E. J. Corey's group and joined the Iowa State University faculty in 1972. His research interests have included aryne chemistry, electrophilic cyclization, palladium catalysis, and polymer chemistry based on biorenewable resources.

Dawei Yue received his B.S. degree in Chemistry from Xiamen University in 1997, where he conducted research with Professor Huilin Wan. He then moved to the United States, where he received his Ph.D. degree from Iowa State University in 2004 under the mentorship of Professor Richard C. Larock. He was a postdoctoral fellow with Professor Michael E. Jung at the University of California, Los Angeles in 2004 and with Professor Sheng Ding at the Scripps Research Institute (2004-2006) before beginning his career in pharmaceutical industry. He is currently director of chemistry at BroadPharm, a customer-focused research and development company based in San Diego, CA.

Michael Rombola was born in 1989 in Rochester, NY. He studied as an undergraduate at Cornell University, where he completed a B.S. degree in biology in 2011. He is now pursuing his doctoral degree at the University of Chicago, working under the guidance of Professor Viresh H. Rawal. He is currently developing novel chiral diene ligands for use in asymmetric catalysis.

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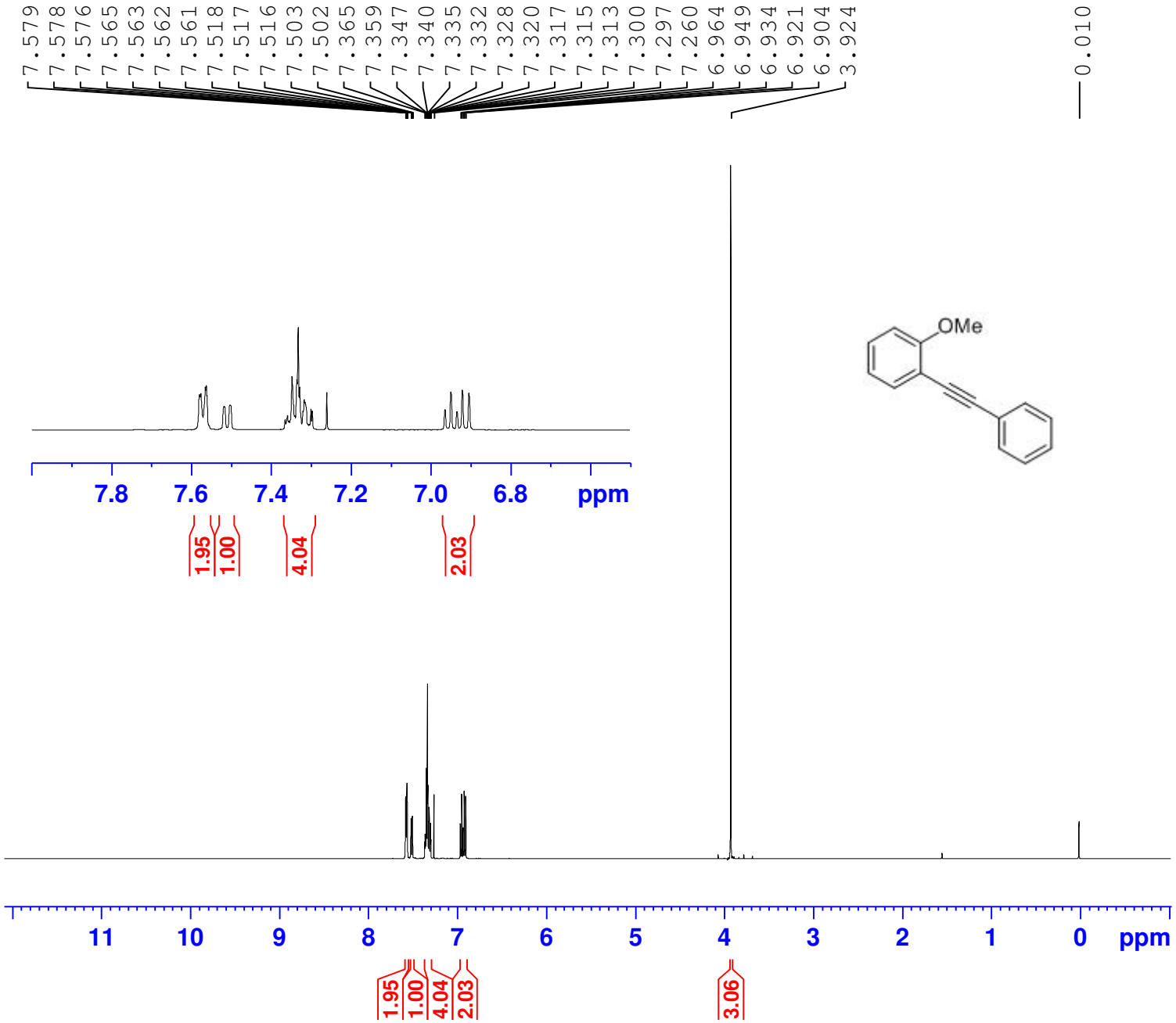


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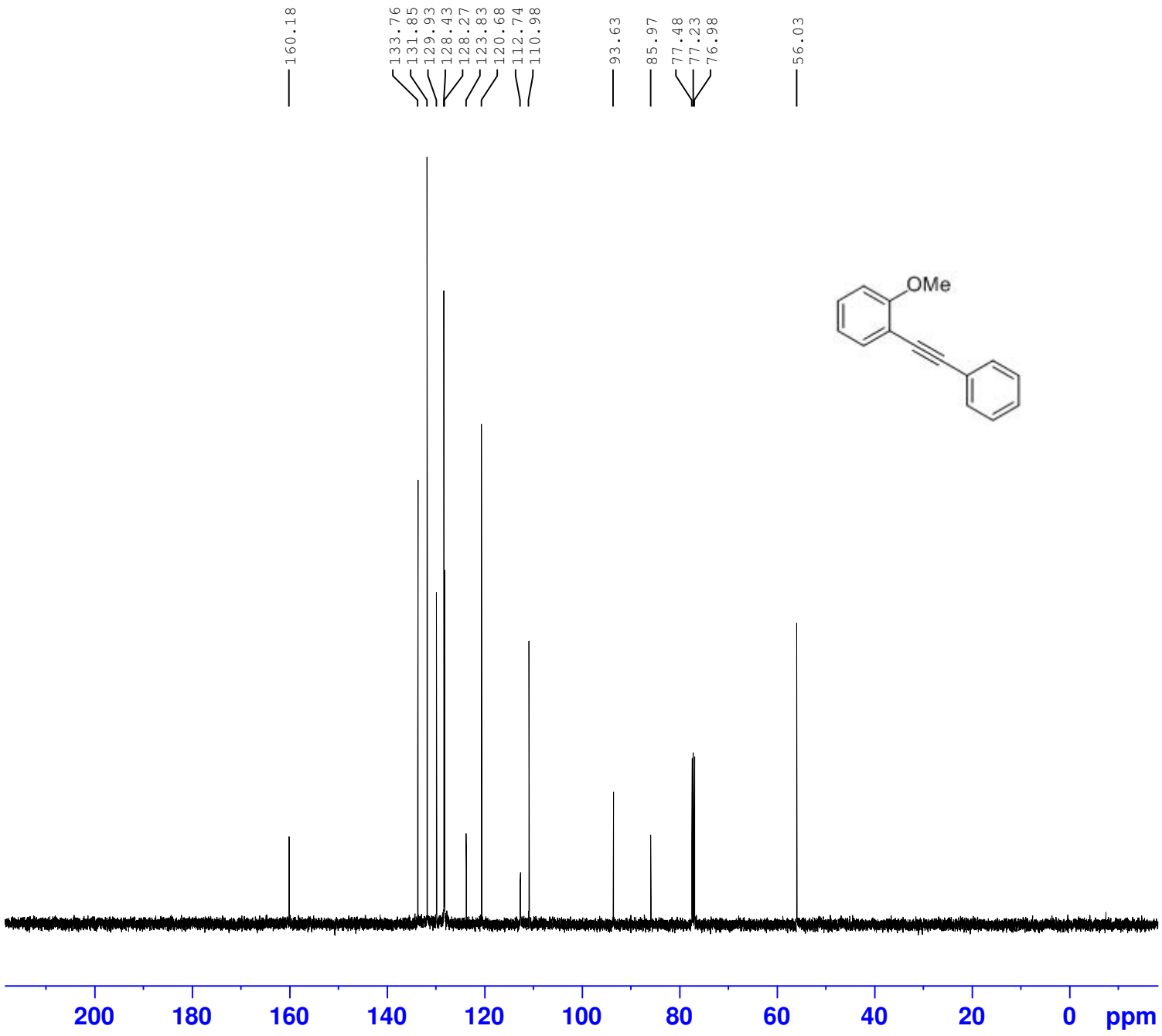


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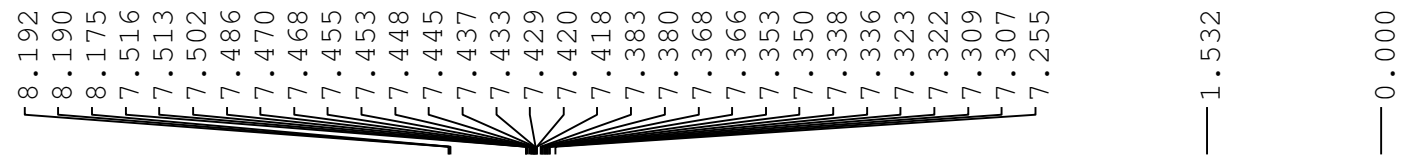
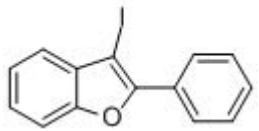
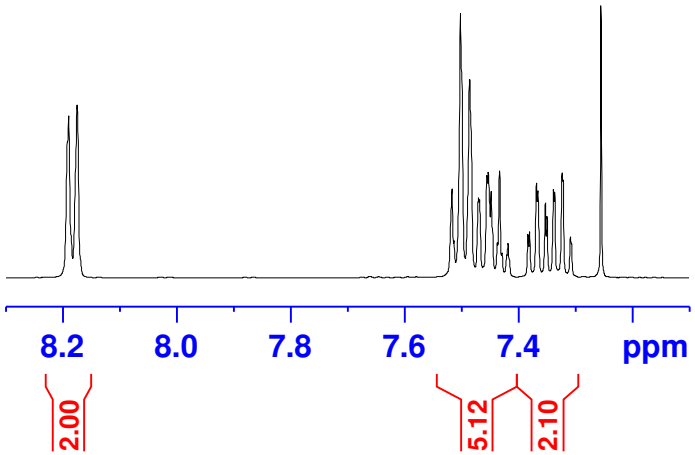
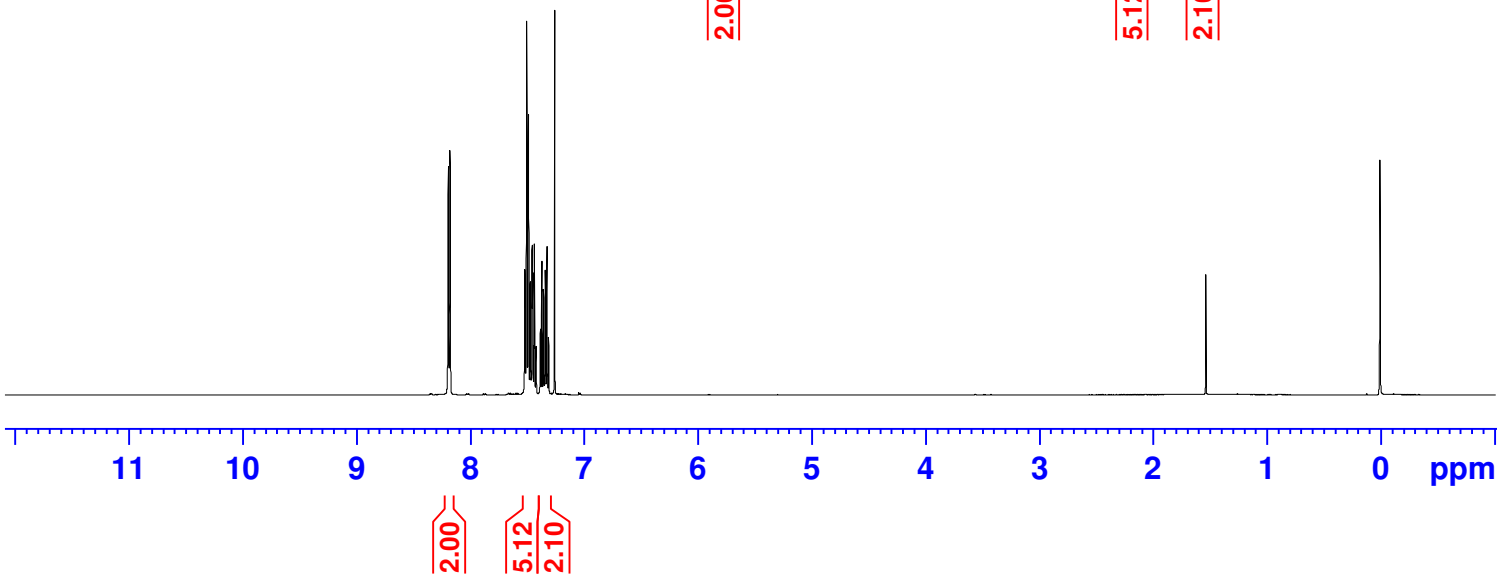






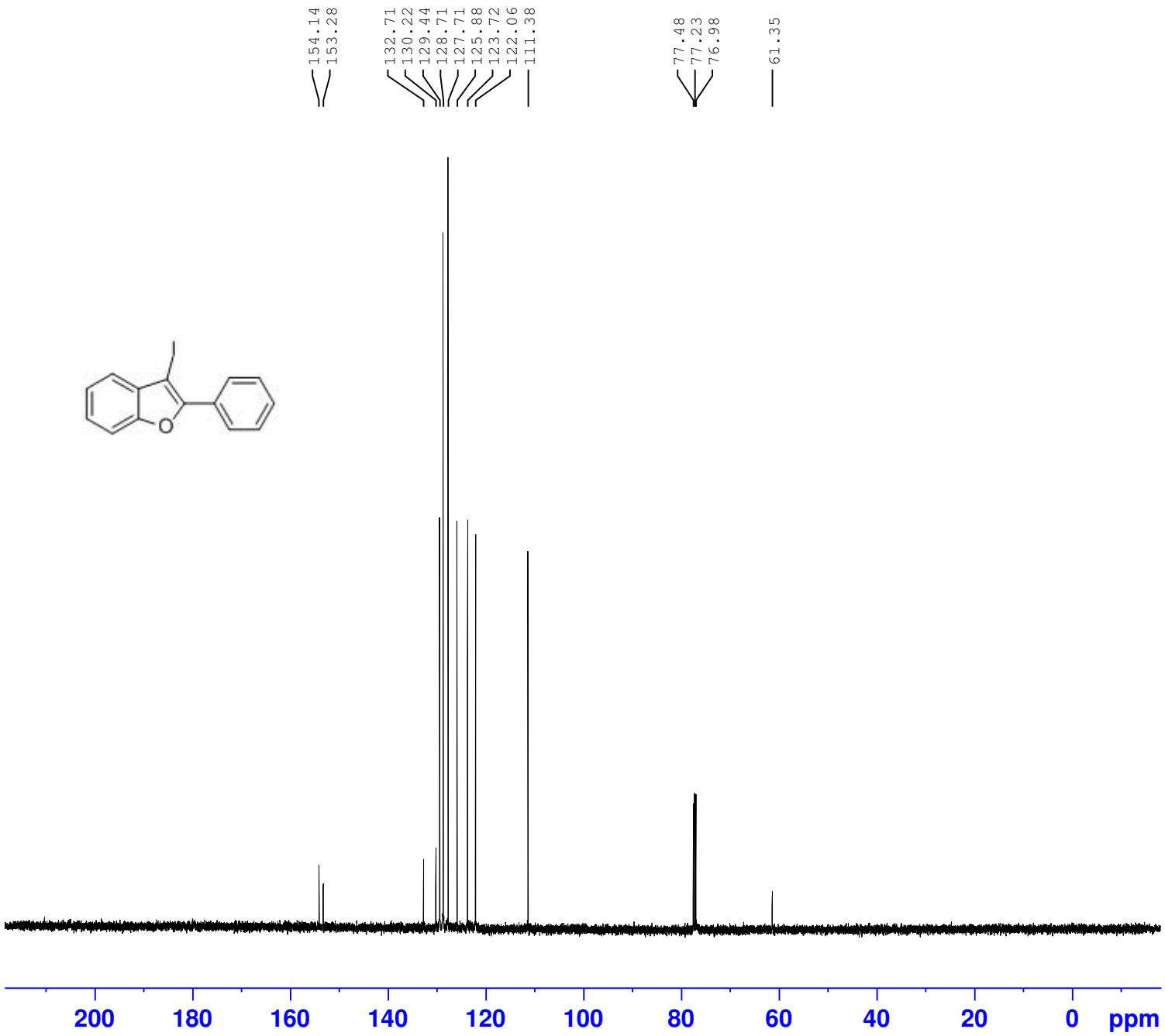



```
Current Data Parameters
NAME                  2_44_H
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20140421
Time                  15.46
INSTRUM               spect
PROBHD    5 mm PATXI 1H/
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                       32
DS                        0
SWH              10000.000 Hz
FIDRES           0.166672 Hz
AQ               2.9999001 sec
RG                   196.79
DW                   50.000 usec
DE                   10.00 usec
TE                   296.2 K
D1             9.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           500.1330885 MHz
NUC1                    1H
P1                   8.00 usec
PLW1           12.19999981 W

F2 - Processing parameters
SI                    65536
SF             500.1300168 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```




```
Current Data Parameters
NAME            2_44_13C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140422
Time               12.00
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG             zgdc
TD                178568
SOLVENT             CDCl3
NS                    230
DS                      0
SWH            29761.904 Hz
FIDRES          0.166670 Hz
AQ             2.9999423 sec
RG                196.79
DW                16.800 usec
DE                10.00 usec
TE                297.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7703643 MHz
NUC1                13C
P1                14.00 usec
PLW1       170.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         12.19999981 W
PLW12         0.20893000 W

F2 - Processing parameters
SI                131072
SF           125.7577684 MHz
WDW                 EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```