A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for 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.

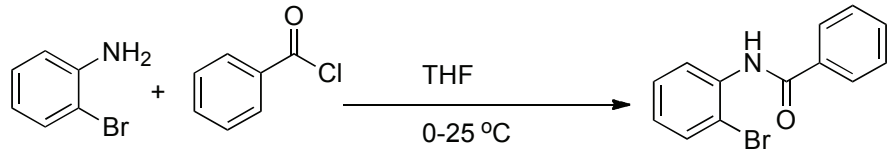
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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.

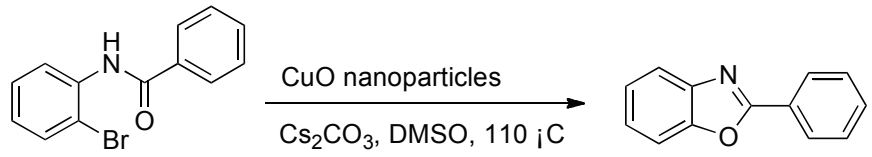
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

LIGAND-FREE COPPER(II) OXIDE NANOPARTICLES CATALYZED SYNTHESIS OF SUBSTITUTED BENZOXAZOLES

A.



B.



Submitted by Prasenjit Saha, Md Ashif Ali, and Tharmalingam Punniyamurthy.[1]
Checked by Kelvin Sham and Paul Harrington.

1. Procedure

A. *N-2-Bromophenylbenzamide.* An oven-dried, three-necked, 500-mL round-bottomed flask equipped with an egg-shaped magnetic stirring bar (¾″ x 1½″), a rubber septum, a calcium chloride guard tube, and a 25-mL pressure-equalizing addition funnel (capped with a rubber septum) is sequentially charged at room temperature with 2-bromoaniline (16.2 g, 94.0 mmol) (Note 1) and THF (100 mL) (Note 2). The solution is cooled to 0 °C in an ice-water bath. Benzoyl chloride (12.0 mL, 103 mmol, 1.10 equiv) (Note 3) is added dropwise into the flask via the addition funnel over 25 min. The resulting light purple suspension is allowed to warm to ambient temperature (21 °C) over 1 h, and stirring is continued for an additional 20 h. The solvent is removed by a rotary evaporator under reduced pressure (74 mmHg) at 40 °C, and the light pink solid is treated with EtOAc (300 mL). The light pink suspension is transferred into a 500-mL separatory funnel and washed successively with 5% (w/v) aqueous sodium bicarbonate (2 x 100 mL) (Note 4) and saturated aqueous sodium chloride (100 mL) (Note 5) solutions. The organic solution is dried over sodium sulfate (50 g) (Note 6), filtered through a fine-porosity fritted-glass funnel and the sodium sulfate is washed with ethyl acetate (20 mL). The solvent is removed by a

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rotary evaporator under reduced pressure (74 mmHg) at 40 °C to give a tan solid, which is dissolved in 80% aqueous ethanol (150 mL) at 72 °C (Note 7). The solution is allowed to cool to ambient temperature and aged for 17 h. The resulting solid is collected by suction filtration on a Büchner funnel, washed with 10% aqueous ethanol (50 mL), transferred to a filter paper, air dried and then dried under high vacuum (0.11 mmHg) at 80 °C for 16 h to give the title compound as white needles (20.4 g, 79%) (Note 8).

B. 2-Phenylbenzoxazole. An oven-dried, 100-mL, single-necked, round-bottomed flask equipped with an egg-shaped (1″ x ½″) magnetic stirring bar, a rubber septum, and an argon inlet adapter is charged with *N*-2-bromophenylbenzamide (10.5 g, 38.0 mmol), cesium carbonate (18.6 g, 57.0 mmol, 1.50 equiv) (Note 9), copper oxide nanoparticles (302 mg, 10 mol%) (Note 10) and DMSO (38 mL) (Note 11). The resulting black mixture is stirred in an oil bath at 110 °C until the *N*-2-bromophenylbenzamide is completely consumed as judged by LC-MS analysis (40 h) (Note 12). The mixture is removed from the oil bath, allowed to cool to ambient temperature, and transferred to a 500-mL separatory funnel with the aid of ethyl acetate (150 mL) and water (200 mL). The layers are separated, and the aqueous layer is extracted with ethyl acetate (4 x 100 mL). The combined organic extracts are dried over Na_2SO_4 (50 g) and filtered through a fine-porosity fritted-glass funnel. The Na_2SO_4 is suspended in dichloromethane (100 mL) and stirred at room temperature for 18 h and filtered through a fine-porosity fritted-glass funnel. The filtrates are combined and the solvent is removed by a rotary evaporator under reduced pressure (35 mmHg) at 40 °C to give a black solid. The black solid is dissolved in a minimum amount of dichloromethane and adsorbed onto 15 g of silica gel (Note 13). The solvent is removed under reduced pressure and the resulting solid is charged onto a silica gel chromatography column (80 g RediSep® R_f) (Note 13) and eluted using ethyl acetate in hexane to afford the title compound as a white solid (5.90 g, 80%) (Note 14).

2. Notes

1. 2-Bromoaniline was purchased from Aldrich Chemical Company, Inc. and used without further purification.

2. THF (anhydrous, ≥ 99.9%) was purchased from the Aldrich Chemical Company, Inc. and used as received.

3. Benzoyl chloride was purchased from the Aldrich Chemical Company, Inc. and used as received.

4. Sodium bicarbonate was purchased from the Aldrich Chemical Company, Inc. and used as received.

5. Saturated sodium chloride solution was purchased from Teknova.

6. Sodium sulfate was purchased from the Aldrich Chemical Company, Inc.

7. Ethanol was purchased from Aaper Alcohol and Chemical Co.

8. The product (white solid) exhibits the following properties: mp 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98–706 (m, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.47–7.63 (m, 4 H), 7.94 (d, J = 7.2 Hz, 2 H), 8.46 (br s, 1 H), 8.56 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 113.7, 121.7, 125.2, 127.1, 128.5, 128.9, 132.1, 132.2, 134.6, 135.8, 165.2; IR (ATR: Attenuated Total Reflectance): 3217, 1651, 1575, 1515, 1500, 1428, 1296, 1251, 1044, 1026 cm^{-1}; MS (ESI) *m/z*: 277.0 (M^{+}+1). Anal. calcd. for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.38; H, 3.67; N, 4.87.

9. Cesium carbonate (99%) was purchased from the Aldrich Chemical Company, Inc. and used without further purification.

10. Copper oxide nanoparticles (particle size = 28 nm, surface area 33 m^2/g) were purchased from the Aldrich Chemical Company, Inc. The reaction rate appeared to be highly dependent on the size of the copper oxide nanoparticles. For example, under the reaction conditions described above, an 84:13 ratio of *N*-2-bromophenylbenzamide:2-phenylbenzoxazole was observed by LCMS after 15 h using 40 nm copper oxide nanoparticles, while the same reaction using 28 nm copper oxide nanoparticles yielded a ratio of 45:49.

11. DMSO (anhydrous, ≥99.9%) was purchased from the Aldrich Chemical Company, Inc. and used as received.

12. A small amount of the reaction mixture was taken out and diluted with ethyl acetate and water. The organic extract was analyzed by an Agilent 1100 Series LCMS with UV detection at 254/220 nm and a low resonance electrospray mode (ESI). Using a 5-minute method (Agilent Zorbax SB-C18 column, 3.0 mm x 50 mm, 3.5 mm; A: 0.1% TFA in water and B: 0.1% TFA in acetonitrile; 1.5 mL/min; 0.0-0.2 min: 10% B; 0.2-3.0 min: 10-100% B; 3.0-4.5 min: 100% B; 4.5-5.0 min: 100-10% B; 1.5 min post time; 2.0 μL injection), the retention times of *N*-2-bromophenylbenzamide and 2-phenylbenzoxazole are determined to be 2.16 min and 2.37 min, respectively.

13. Silica gel (200-400 mesh) was purchased from the Aldrich Chemical Company, Inc.

14. The crude product is purified using a CombiFlash® R_f flash chromatography system equipped with an 80 g RediSep® R_f silica column. The product is eluted with 0% to 15% ethyl acetate/hexane and the product separation is monitored by an internal UV detector at 254 nm. The product (white solid) exhibits the following properties: mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–7.41 (m, 2 H), 7.47–7.63 (m, 4 H), 7.77–7.80 (m, 1 H), 8.19–8.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.6, 120.0, 124.6, 125.1, 127.1, 127.6, 128.9, 131.5, 142.1, 150.8, 163.1; IR (ATR): 1617, 1552, 1472, 1446, 1344, 1241, 1197, 1052, 1021 cm^{-1}; MS (ESI) *m/z*: 195.9 (M^++1). Anal. calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.95; H, 4.60; N, 7.11. The second run was run on half the scale and the yield obtained was 79%.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

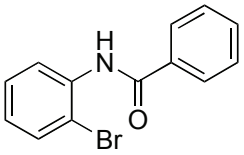
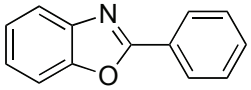
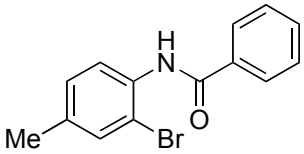
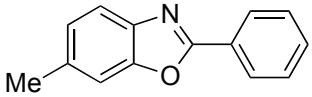
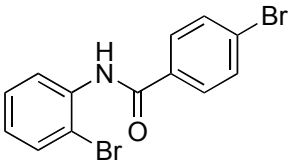
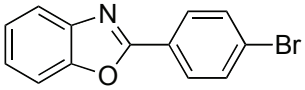
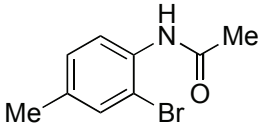
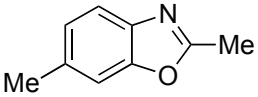
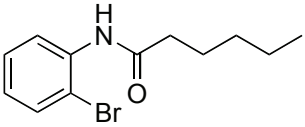
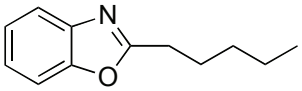
Benzoxazoles are important structural motifs present in numerous natural products and biologically active compounds.[2] The classical methods used for their preparation involve the condensation of 2-aminophenol with either carboxylic acids in the presence of acids or aldehydes under oxidative reaction conditions.[3] These methods, however, have limitations due to non-availability of the suitably substituted starting materials and, in some cases, the requirement for harsh reaction conditions, such as elevated temperature and strong acid. The recent development of cross-coupling reaction using copper-catalysis provides a straightforward route to substituted benzoxazoles by intramolecular *C-O* cross-coupling under relatively milder conditions.[4]

The present protocol describes the cyclization of *N*-2-bromophenylbenzamide to afford 2-phenylbenzoxazole via *C-O* cross-coupling in the presence of 10 mol % of CuO nanoparticles and 1.5 equiv of Cs_2CO_3 in DMSO at moderate temperature.[5] The catalyst is cheap,

commercially available, air stable, recyclable and catalyzes under ligand-free conditions.

Table 1 represents the scope of the procedure. Both the aromatic and aliphatic *N*-2-bromophenylamides undergo cyclization to give the corresponding 2-aryl and 2-alkyl benzoxazoles in good to high yield.

Table 1. CuO Nanoparticles Catalyzed Synthesis of 2-Substituted Benzoxazoles

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		15		86
2		16		83
3		34		55[b]
4		16		68
5		16		73

[a] With the exception of entry 1 (38 mmol scale), all reactions are performed on a 20 mmol scale and the products are purified by column chromatography using hexane and ethyl acetate as eluent. [b] Reaction performed at 120 °C with 2.0 equiv of Cs_2CO_3.

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2. (a) Easmon, J.; Pürstinger, G.; Thies, K.-S.; Heinisch, G.; Hofmann, J. *J. Med. Chem.* **2006**, *49*, 6343–6350. (b) Sun, L.-Q.; Chen, J.; Bruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Malhe, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14,* 3799–3802. (c) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997–4004. (d) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775–1783. (e) Huang, S.-T.; Hsei, I-J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14,* 6106–6109.

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5. Saha, P.; Tamminana, R.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719–8725.

Appendix
Chemical Abstracts Nomenclature;(Registry Number)

2-Phenylbenzoxazole; (833-50-1)
N-2-Bromophenylbenzamide; (70787-27-8)
2-Bromoaniline: Benzenamine, 2-bromo-; (615-36-1)
Benzoyl chloride; (98-88-4)
Cesium carbonate: Carbonic acid, cesium salt (1:2); (534-17-8)
Copper(II) oxide nanoparticles: Copper oxide (CuO); (1317-38-0)

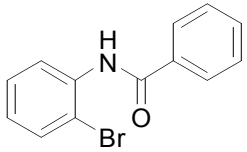
Tharmalingam Punniyamurthy was born in 1964 in Tiruchirapalli, India. He completed his graduate studies at Bharathidasan University and his Ph.D. at IIT Kanpur with Prof. Javed Iqbal. He spent one year with Prof. Mukund Sibi (Fargo), two years with Prof. Tsutomu Katsuki (Fukuoka), one year with Prof. Andre Vioux (Montpellier) and six months with Prof. Joel J. E. Moreau (Montpellier) as a postdoctoral researcher. Since 2001, he has been a member of the faculty at IIT Guwahati and also spent eight months with Dr John M. Brown (Oxford) as a visiting professor. His research interests include new synthetic methods, asymmetric catalysis and natural product synthesis.

Prasenjit Saha was born in Barpeta, India. He received his M.Sc. degree in chemistry from Gauhati University in 2006. Currently, he is pursuing his Ph.D. with Prof. T. Punniyamurthy at the Indian Institute of Technology Guwahati. His research interests are cross-coupling reactions, asymmetric catalysis and molecular recognition.

Md Ashif Ali was born in Burdwan, India. He received his M.Sc. degree in chemistry from the Indian Institute of Technology Guwahati in 2007. He is currently pursuing his Ph.D. at the Indian Institute of Technology Guwahati under supervision of Prof. T. Punniyamurthy. His research interests include cross-coupling reactions, medicinal chemistry and natural product synthesis.

Kelvin Sham was born in Sabah, Malaysia in 1967. He obtained his B.A. in Chemistry from Wartburg College in 1989 and M.S. in Organic Chemistry from Iowa State University in 1992, where he investigated the utility and scope of palladium-catalyzed heteroannulation reactions between *o*-iodophenol and internal alkynes under the guidance of Professor Richard C. Larock. After a seven-year stint as a medicinal chemist at SmithKline Beecham (now GSK) in King of Prussia, Pennsylvania, Kelvin joined Amgen in 1999 where he is currently a Scientist in the Chemistry Research and Discovery group at Amgen.

Paul Harrington was born in 1974 in Wolfville, Canada. He earned his B.Sc. in Chemistry in 1996 from Acadia University and worked in Professor Michael Kerr's laboratories while there. He attended the University of Hawaii and received his Ph.D. in 2002 under the supervision of Professor Marcus Tius. He did his postdoctoral research with Professor Barry Trost at Stanford University. He is currently a medicinal chemist in the Chemistry Research and Discovery group at Amgen.



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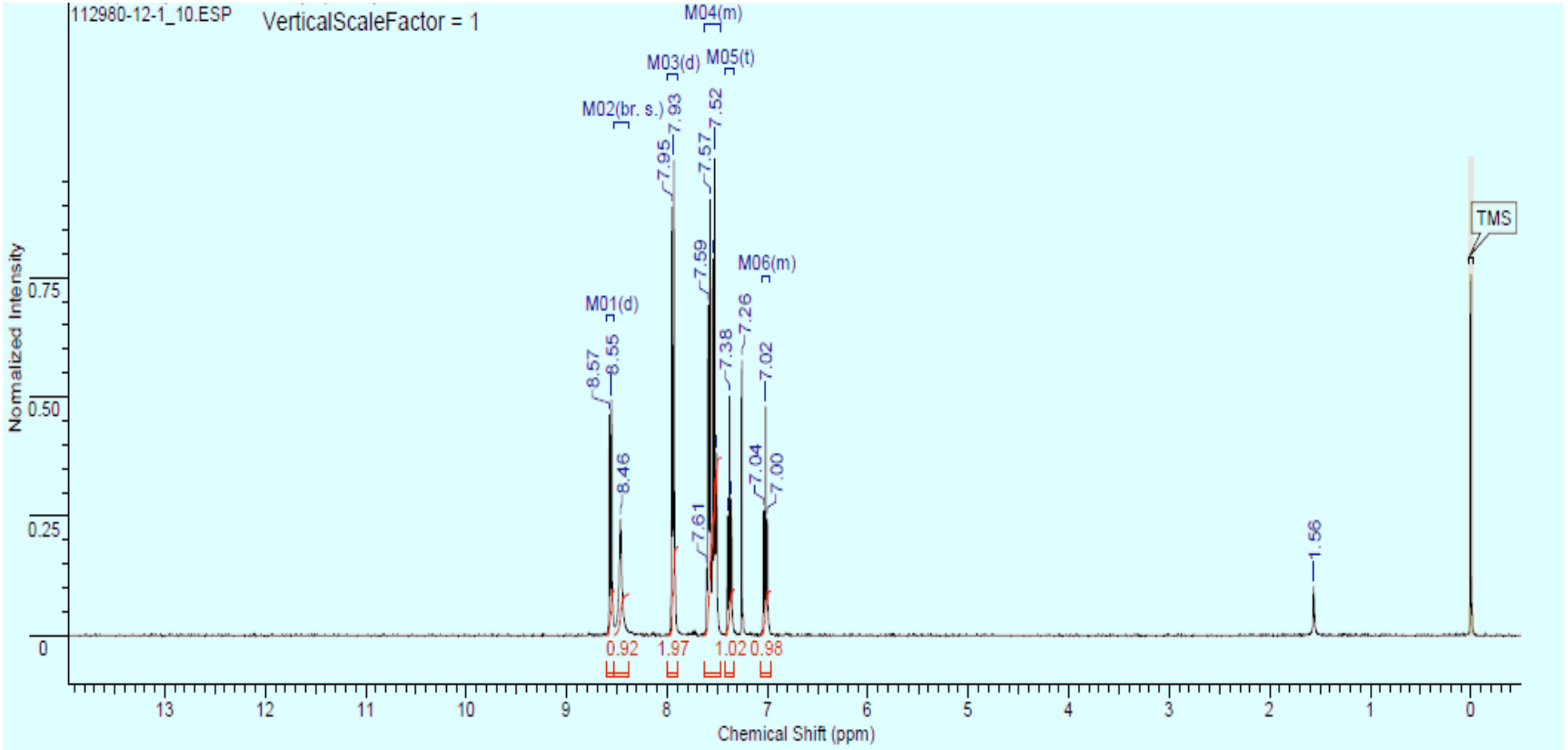

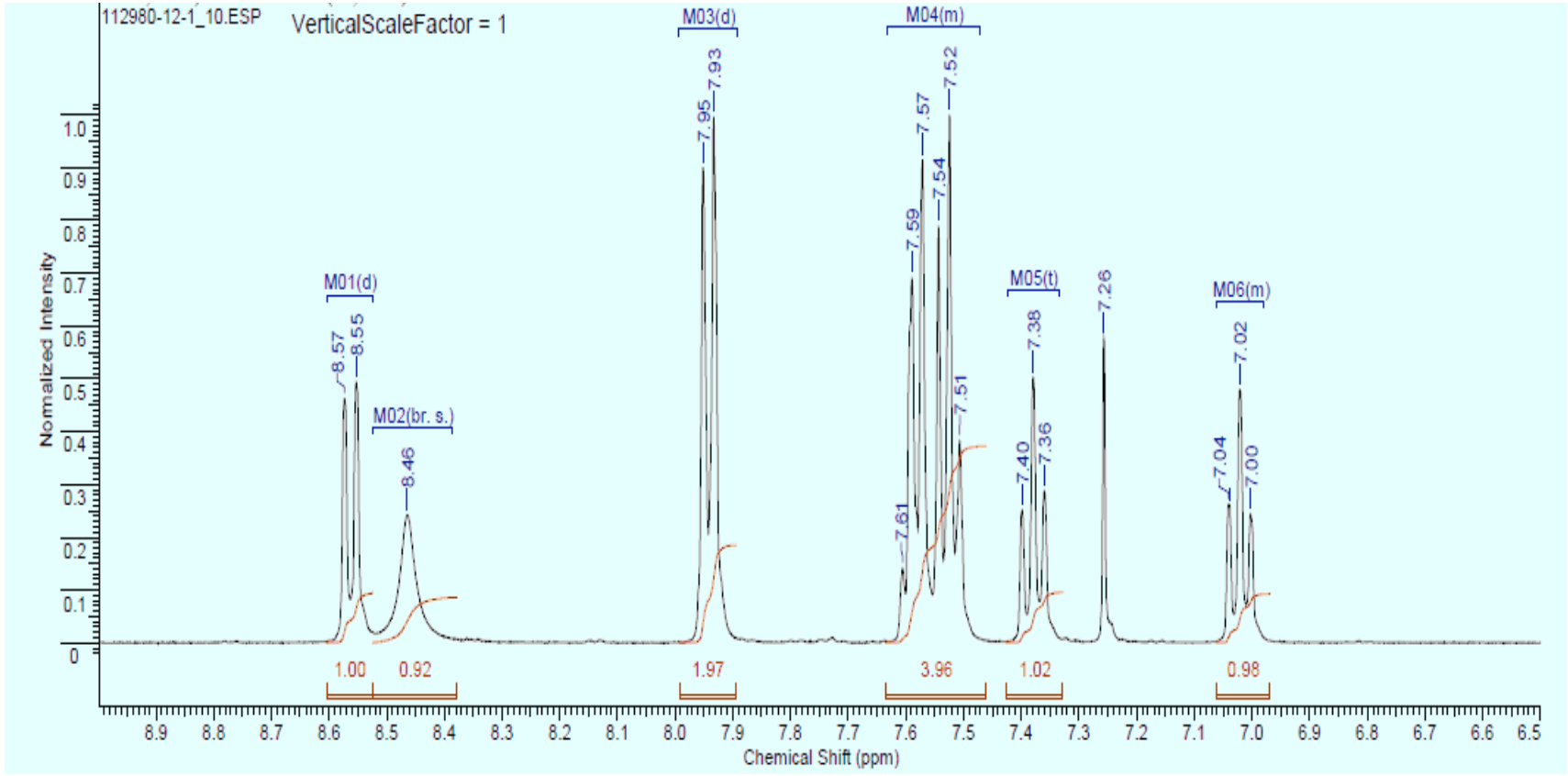
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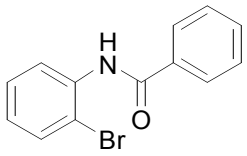

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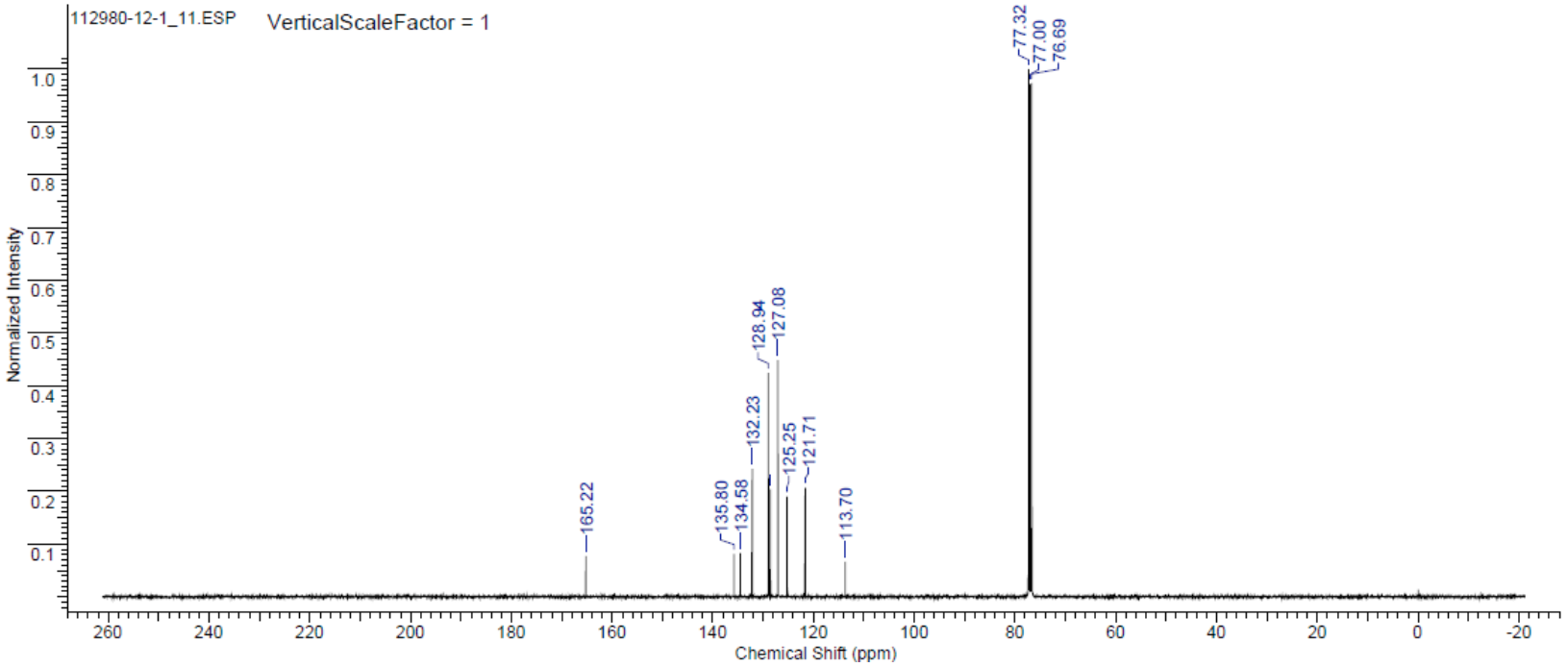

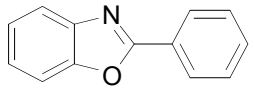

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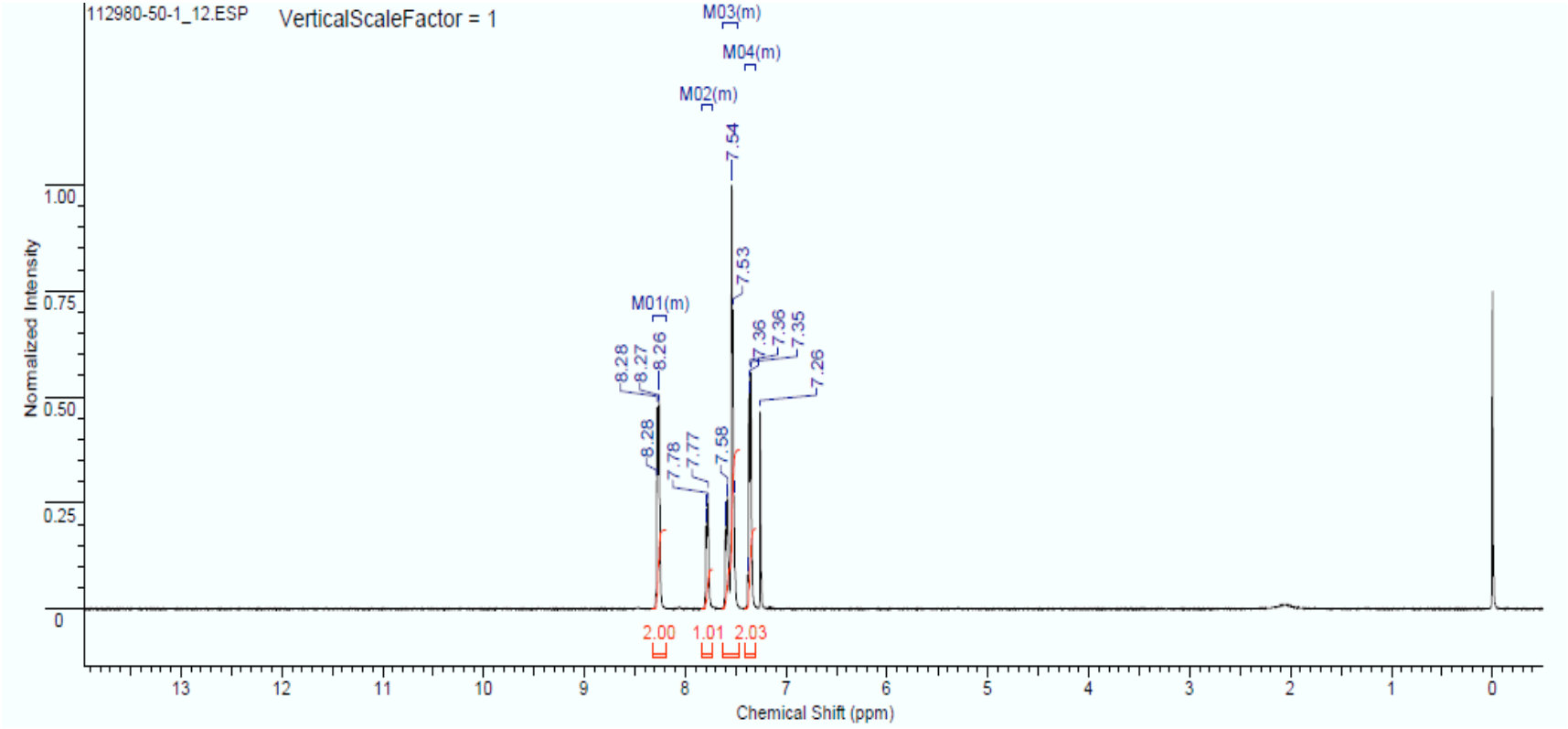

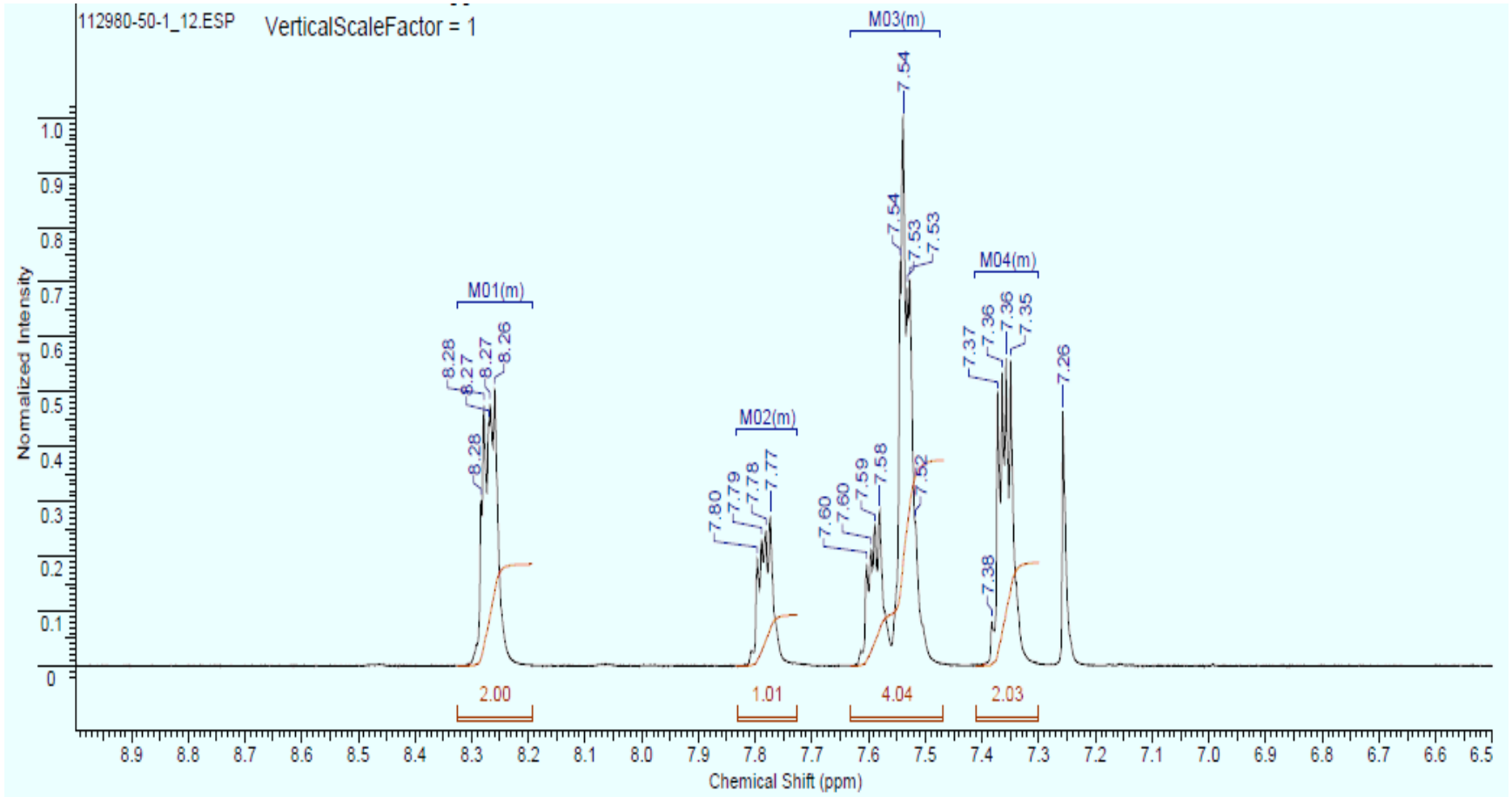
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