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of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

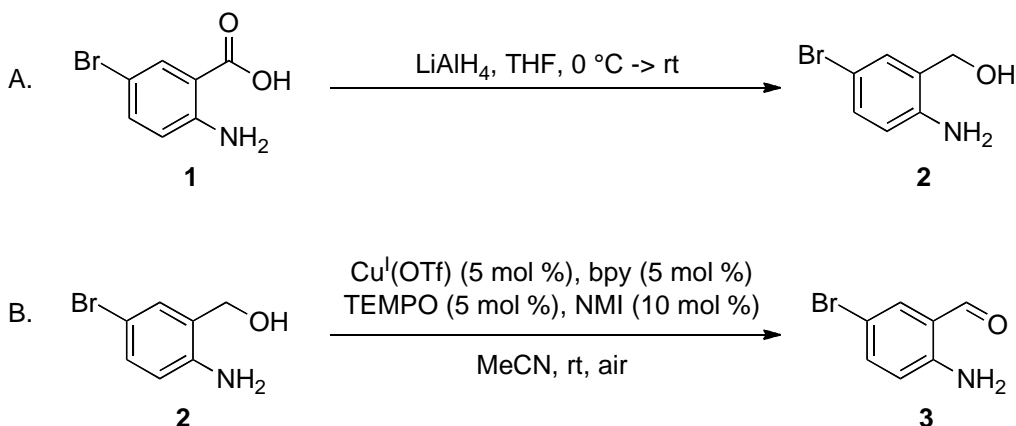
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

## Air Oxidation of Primary Alcohols Catalyzed by Copper(I)/TEMPO. Preparation of 2-Amino-5-bromobenzaldehyde



Submitted by Jessica M. Hoover and Shannon S. Stahl.<sup>1</sup>

Checked by Guido P. Möller and Erick M. Carreira.

### 1. Procedure

A. *2-Amino-5-bromobenzyl alcohol (2)*. To a one-necked 1-L round-bottomed flask equipped with a Teflon-coated magnetic stir bar (5 cm x 7 mm) is added 2-amino-5-bromobenzoic acid (**1**) (9.87 g, 45.7 mmol, 1.0 equiv) and dry THF (400 mL) (Note 1). The flask is fitted with a septum and nitrogen inlet needle. The solution is cooled in an ice bath under an atmosphere of nitrogen gas. Lithium aluminum hydride (5.00 g, 132 mmol, 2.9 equiv) (Note 2) is added portion-wise (0.5 g portions) over the course of 1 h by temporarily removing the septum. The reaction mixture is allowed to warm slowly to room temperature overnight with stirring (20 h). When the reaction is complete as determined by TLC (Note 3) the crude reaction mixture is poured slowly into ethyl acetate (400 mL) in a 2 L Erlenmeyer flask equipped with a magnetic stir bar cooled in an ice bath (Note 4). The excess  $\text{LiAlH}_4$  is quenched by the slow addition of water (50 mL) to the stirred mixture over 30 min. Additional water is added (450 mL) and the mixture is stirred until two distinct layers form (~30 min). The mixture is transferred to a 2 L separatory funnel and the layers separated. The aqueous layer is extracted twice with ethyl acetate (2 x 500 mL) (Note 5). The combined organic layers are transferred to a 4 L separatory funnel, washed

with brine (600 mL) and dried for 30 min over Na<sub>2</sub>SO<sub>4</sub> (100 g). After filtration, the solvent is removed by rotary evaporation (25 °C, 30 mmHg) to give a light yellow solid. Analytically pure material is obtained after recrystallization. Into a one-necked, 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3 cm x 5 mm) the crude material is dissolved in a minimum amount of refluxing ethyl acetate (15 mL). Hexanes (~100 mL) is added over 10 min to the stirred and refluxing mixture until the product precipitates (Note 6). The mixture is allowed to cool to room temperature and then stored in the freezer at –15 °C for 3 h. The product is isolated by suction filtration on a Büchner funnel, washed with hexanes (50 mL), and dried by vacuum (0.01 mmHg, 23 °C) to provide a first crop (6.53–7.01 g). A second crop is obtained from the combined filtrates after removal of the solvent by rotary evaporation (25 °C, 30 mmHg). The resulting solids are dissolved in a one-necked, 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3 cm x 5 mm) in a minimum amount of refluxing ethyl acetate (5 mL). To the refluxing, stirred solution is added hexanes (50 mL) over 10 min until precipitation begins. After cooling to room temperature the suspension is stored in a freezer at –15 °C overnight for collection of a second crop (0.91–1.09 g) by suction filtration on a Büchner funnel. The alcohol **2** is obtained in 80–88% yield (7.44–8.10 g.) as a light tan powder (Note 7).

B. *2-Amino-5-bromobenzaldehyde* (**3**). To a one-necked 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar (5 cm x 7 mm) is added 2-amino-5-bromobenzyl alcohol (**2**) (6.10 g, 30.0 mmol, 1 equiv) and MeCN (60 mL) (Note 8). [Cu<sup>I</sup>(MeCN)<sub>4</sub>](OTf) (569 mg, 1.51 mmol, 0.05 equiv), 2,2'-bipyridine (bpy) (236 mg, 1.51 mmol, 0.05 equiv), and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (236 mg, 1.51 mmol, 0.05 equiv) (Note 9) are each added as a solid, and the weighing vessel (often a small test tube) is rinsed with MeCN (30 mL each) to ensure complete delivery of the reagents and a total reaction volume of 150 mL. After the addition of *N*-methyl imidazole (NMI) (240 µL, 248 mg, 3.02 mmol, 0.1 equiv) (Note 10), the dark red/brown reaction mixture is stirred open to air at 500 rpm (Note 11) at room temperature until the starting material is consumed as determined by TLC (2–3 h) (Note 3) (Note 12). Upon completion, the reaction mixture is diluted with ethyl acetate (300 mL), filtered through a plug of silica (Note 13), and washed with ethyl acetate (400 mL). The solvent is concentrated by rotary evaporation (20 °C, 0.04 mmHg) to afford the crude aldehyde as a yellow brown solid (Note 14).

Analytically pure material is obtained after purification by silica column chromatography. The solid is dissolved in a minimum amount of  $\text{CHCl}_3$  (20 mL) and loaded onto a column prepared from silica gel (150 g, Silicycle SiliaFlash<sup>®</sup> P60, 230-400 mesh) slurried in 10% EtOAc-hexanes (column dimensions: 5.5 cm diameter x 30 cm height, 18 cm packed height). Elution with 10% EtOAc-hexanes (200 mL initial collection followed by 30 mL fractions, 1.4 L total solvent volume eluted) affords the product in fractions 19-35. The product containing fractions are combined and the solvent is removed by rotary evaporation (0.1 mmHg, 20 °C). Subsequent drying at 0.01 mmHg (22 °C) provides aldehyde **3** in 89–91% yield (5.37–5.50 g) as a bright yellow powder (Notes 15 and 16).

## 2. Notes

1. Checkers used 2-amino-5-bromobenzoic acid (98%) from ABCR-Chemicals and used it as received. Submitters purchased 2-amino-5-bromobenzoic acid from Aldrich and used it as received. Inhibitor free THF was purchased from Sigma-Aldrich and passed through a column of alumina before use.

2. Checkers used lithium aluminum hydride powder purchased from Acros Organics and used it as received. Submitters purchased lithium aluminum hydride from Sigma-Aldrich as 0.5 g pellets and used it as received. Lithium aluminum hydride is pyrophoric and reacts violently with water.

3. TLC conditions: hexanes:ethyl acetate = 2:1, plates were visualized by UV and  $\text{KMnO}_4$  stain, silica gel stationary phase,  $R_f(\text{acid}) = 0.1\text{--}0.2$  (streak),  $R_f(\text{alcohol}) = 0.2$ ,  $R_f(\text{aldehyde}) = 0.7$ .

4. Ethyl acetate was purchased from Sigma-Aldrich and used as received.

5. The addition of a small amount of brine, ~50-100 mL, improves the separation of the layers.

6. Hexanes was purchased from Sigma-Aldrich Chemical Company and used as received.

7. 2-Amino-5-bromobenzyl alcohol (**2**) has the following physical and spectroscopic properties: mp 112 – 113 °C;  $^1\text{H}$  NMR (acetone- $d_6$ , 400 MHz)  $\delta$ : 4.19 (t,  $J = 5.5$ , 1 H), 4.55 (d,  $J = 5.5$ , 2 H), 4.82 (br s, 2 H), 6.65 (d,  $J = 8.5$ , 1 H), 7.12 (dd,  $J = 8.5$ , 2.4, 1 H), 7.22 (d,  $J = 2.4$ , 1 H).  $^{13}\text{C}$  NMR (acetone- $d_6$ , 100 MHz)  $\delta$ : 62.6, 108.3, 117.6, 128.7, 131.1, 242

131.3, 146.8. HRMS (ESI-TOF)  $m/z$ : Calcd. for  $C_7H_8BrNNaO$   $[M+Na]$ : 223.9681, found: 223.9687. IR (ATR,  $cm^{-1}$ ): 3381, 3201 (br), 1473, 1408, 1340, 1268, 1192, 1079. Anal. calcd for  $C_7H_8BrNO$ : C, 41.61; H, 3.99; N, 6.93. Found: C, 41.78; H, 3.94; N, 6.91.

8. Acetonitrile was purchased from Sigma-Aldrich and passed through a column of activated alumina using a solvent purification system. Although the procedure reported here involves the use of dry acetonitrile (MeCN) solvent, untreated MeCN shows similar yields and reaction times.

9. Tetrakisacetonitrile copper(I) trifluoromethanesulfonate and 2,2'-biyridine were purchased from Sigma-Aldrich and used as received. Checkers purchased 2,2,6,6-tetramethylpiperidine-*N*-oxyl from ABCR-Chemicals and used it as received. Submitters purchased 2,2,6,6-tetramethylpiperidine-*N*-oxyl from Sigma-Aldrich and used it as received.

10. *N*-Methylimidazole was purchased from Sigma-Aldrich and used as received.

11. For the synthesis of volatile aldehydes, the neck should be fitted with a water condenser and a septum with a balloon of house air fitted with a needle. For all alcohols, the reactions proceed more rapidly if an  $O_2$  balloon is employed instead of ambient air. *Users should be aware that the use of pure  $O_2$  with organic solvents is potentially explosive.*

12. Most reactions will change from the initial dark red/brown color to a dark green color upon completion. In the case of aldehyde **3**, the yellow/brown color of the crude product masks the typical color change of the reaction.

13. The silica plug is composed of 100 g of silica (Silicycle SilicaFlash<sup>®</sup> P60, 230-400 mesh) in a 250 mL M porosity fritted funnel.

14. The crude product is >95% pure by  $^1H$  NMR spectroscopy, but contains small amounts of TEMPO.

15. 2-Amino-5-bromobenzaldehyde (**3**) has the following physical and spectroscopic properties: mp 74–76 °C;  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$ : 6.14 (br s, 2 H), 6.56 (d,  $J = 8.8$ , 1 H), 7.37 (dd,  $J = 8.8, 2.3$ , 1 H), 7.58 (d,  $J = 2.4$ , 1 H), 9.79 (s, 1 H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$ : 107.4, 118.1, 120.1, 137.5, 138.0, 148.8, 192.9. HRMS (EI)  $m/z$ : Calcd. for  $C_7H_6BrNO$   $[M]^+$ : 198.9633, found: 198.9628. IR (ATR,  $cm^{-1}$ ): 3424, 3322, 1649, 1614, 1545, 1468, 1390, 1311, 1185. Anal. calcd for  $C_7H_6BrNO$ : C, 42.03; H, 3.02; N, 7.00. Found: C, 42.30; H, 3.02; N, 7.03. This aldehyde appears to be bench-stable and no decomposition was observed after storing the aldehyde on the bench under ambient conditions for weeks.

16. Submitters reported two runs. Starting from **2** (6.10 g, 30.2 mmol) **3** was obtained in 97% (5.81 g). Starting from **2** (5.8 g, 29 mmol) **3** was obtained in 97% (5.57 g).

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### 3. Discussion

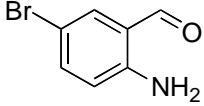
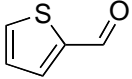
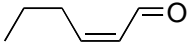
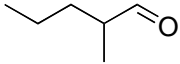
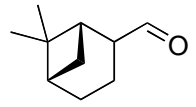
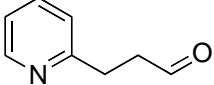
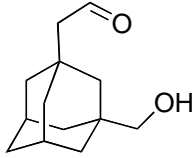
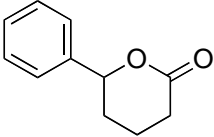
Aldehydes are useful synthetic intermediates commonly employed to access a variety of complex molecules. Unfortunately traditional methods for the selective oxidation of primary alcohols to aldehydes often involve the use, separation, and disposal of expensive or toxic stoichiometric reagents, particularly hypervalent iodine reagents<sup>2</sup> and metal oxides.<sup>3</sup> Other common methods require the careful maintenance of low temperature conditions (as in a Swern oxidation<sup>4</sup>), or the cautious handling of sensitive materials (such as 2-iodoxybenzoic acid [IBX]).

The use of molecular oxygen is an attractive alternative and significant progress has been made in the development of catalytic methods for the aerobic oxidation of alcohols.<sup>5</sup> For aerobic methods to compete with traditional routes, however, they must afford a broad scope of aldehydes (or ketones) in high yields, be operationally simple, and use inexpensive, readily available reagents and solvents. Unfortunately, few existing aerobic methods satisfy these criteria. For example, catalyst systems derived from Pd<sup>6</sup> and Ru<sup>7</sup> are often inhibited by heterocycles and other nitrogen-, oxygen-, and

sulfur-containing functional groups, or they promote oxidation of other functional groups (such as the Pd-catalyzed oxidation of alkenes<sup>8</sup>). Cu-based<sup>9,10</sup> catalysts often demonstrate broader functional group tolerance; however, several features of these systems limit their widespread adoption. For example, some catalysts exhibit low activity with aliphatic alcohols, thereby restricting their utility to the oxidation of 1° benzylic or allylic alcohols,<sup>9</sup> or they require pure O<sub>2</sub> as the oxidant, in some cases using non-traditional halogenated solvents (e.g., fluorobenzene).<sup>10</sup> The Cu<sup>I</sup>/TEMPO catalyst system described here<sup>11</sup> enables efficient aerobic oxidation of aliphatic alcohols while maintaining a broad substrate scope and functional-group compatibility, employs O<sub>2</sub> from ambient air as the oxidant, and utilizes common, readily available reagents and solvent. The practical features of this method, including its operational simplicity, predictability, reliability and chemoselectivity, make it a compelling alternative to traditional methods for the oxidation of primary alcohols.

Using this aerobic Cu<sup>I</sup>/TEMPO system, benzylic and allylic alcohols typically undergo complete oxidation within several hours. The oxidation of aliphatic alcohols often requires longer reaction times (20 – 24 h). Representative examples of the substrate scope are shown in Table 1. The method tolerates diverse functional groups including heterocycles such as pyridines, furans, and thiophenes (entries 2 and 6), in addition to alkenes (entry 3) and alkynes. Alcohols containing free anilines and aryl halides (entry 1) also undergo facile oxidation to the corresponding aldehyde, as do ethers, esters, thioethers, and acetals, although not included here.<sup>11</sup> The reaction conditions are sufficiently mild that *Z*-allylic alcohols (entry 3) and alcohols with adjacent stereocenters (entry 5), proceed efficiently without isomerization of alkene or stereocenter. A small number of functional groups remain challenging for this copper-based catalyst system. Alcohols bearing phenols or terminal alkynes do not yield the corresponding aldehydes, and alcohols containing a vicinal coordinating group, such as an ether or free amine, can be problematic.

**Table 1.** Aldehydes obtained by Cu<sup>I</sup>/TEMPO catalyzed aerobic oxidation of primary alcohols

entry	aldehyde	time (h)	% Yield <sup>a</sup>
1		2	89-91% <sup>b</sup>
2		3	83%
3		2	>98% <sup>c</sup> 20:1 Z:E
4		24 11	83% 98% <sup>d</sup>
5		24	>98%
6		3-4?	95%
7		2.5	>98%
8		24	88% <sup>e</sup>

<sup>a</sup> for 1 mmol scale, ref 11. Standard conditions: [Cu(MeCN)<sub>4</sub>](OTf) (0.01 M), bpy (0.01 M), TEMPO (0.01 M), NMI (0.02 M), 0.2 M alcohol in MeCN, rt, ambient air  
<sup>b</sup> this work <sup>c</sup> with air balloon <sup>d</sup> with O<sub>2</sub> balloon <sup>e</sup> reaction at 50 °C

In addition to the broad substrate scope, this new Cu<sup>I</sup>/TEMPO catalyst system has many appealing practical characteristics. The reaction setup is straightforward, employs standard glassware and commercially available reagents, and most reactions can be carried out in open reaction vessels employing ambient air as the source of oxidant. During the course of our



studies, we found that larger scale (>1 g) oxidations of aliphatic alcohols are sensitive to the reaction vessel and an oversized flask enables reproducible reaction times (1 L flask for 50 mmol reaction). Aliphatic alcohols with substituents in the alpha position (Table 1, entries 4 and 5) react more slowly and may need increased reaction temperatures (50 °C) or the use of an O<sub>2</sub> balloon in order to reach completion within 24 h. Because these reactions operate under ambient air conditions, low-boiling aldehydes can be lost to evaporation over the course of the reaction, in which case a sealed reaction vessel equipped with a balloon of house air (or O<sub>2</sub>) enables the aldehydes to be obtained in high yields (Table 1, entries 3 and 4). Detailed reaction conditions accounting for these substrate variations have been presented elsewhere.<sup>12</sup>

The separation and isolation of the aldehyde product is also straightforward, in most cases requiring only filtration of the reaction mixture through a silica plug or an aqueous extraction to remove the Cu salts to provide aldehyde product that is pure, based on <sup>1</sup>H NMR spectroscopic analysis. Given the volatility of many aldehydes and their propensity to undergo side reactions, the ability to achieve high purity with minimal handling is advantageous. This aspect of the Cu<sup>I</sup>/TEMPO system has recently been used to access amines from alcohols via a multi-step procedure.<sup>13</sup>

Finally, this Cu<sup>I</sup>/TEMPO catalyst system shows high selectivity for the oxidation of 1° alcohols in the presence of 2° alcohols, allowing for the selective oxidation of unprotected diols, to yield hydroxyaldehydes (Table 1, entry 7) or lactones (Table 1, entry 8). In most cases, the optimized Cu<sup>I</sup>/TEMPO catalyst system described here is suitable for achieving highly selective oxidations, enabling oxidation of 1° over 2° alcohols and showing high preference for sterically accessible alcohols. In some cases, the use of a milder catalyst system employing either a Cu<sup>I</sup>Br or Cu<sup>II</sup>Br<sub>2</sub> salt in place of [Cu<sup>I</sup>(MeCN)<sub>4</sub>](OTf) is required for achieving selectivity and these methods have been outlined elsewhere.<sup>11,12</sup>

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facilities were partially supported by the NSF (CHE-9208463) and NIH (S10 RR08389).

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## Appendix

### Chemical Abstracts Nomenclature; (Registry Number)

2-Amino-5-bromobenzyl alcohol; (20712-12-3)  
2-Amino-5-bromobenzaldehyde; (21924-57-0)  
2-Amino-5-bromobenzoic acid; (5974-88-7)  
Lithium aluminum hydride (LiAlH<sub>4</sub>); (16853-85-3)  
2,2'-Bipyridine (bpy); (366-18-7)  
2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO); (2564-83-2)  
*N*-Methylimidazole (NMI); (616-47-7)



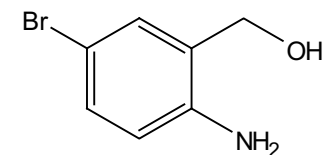
Shannon S. Stahl is a Professor of Chemistry at the University of Wisconsin-Madison, where he began his independent career in 1999. His research group specializes in homogeneous catalysis, with an emphasis on aerobic oxidation reactions and their applications in organic chemistry. He was an undergraduate at the University of Illinois at Urbana-Champaign, and subsequently attended Caltech (Ph.D., 1997), where he was an NSF predoctoral fellow with Prof. John Bercaw. From 1997–1999, he was an NSF postdoctoral fellow with Prof. Stephen Lippard at MIT.



Jessica Hoover received her B.S. degree in Chemistry from Harvey Mudd College in 2004 where she conducted research with Professor Adam Johnson. She then moved to Seattle where she received her Ph.D. degree from the University of Washington in 2009 under the mentorship of Professors James Mayer and Forrest Michael. She was a postdoctoral fellow with Professor Shannon Stahl at the University of Wisconsin Madison (2009-2012) before beginning her independent career as Assistant Professor of Chemistry at West Virginia University in Fall 2012.



Guido Möller studied chemistry at the Westfälische Wilhelms-Universität Münster (Dipl.-Chem. 2011). In the same year, he joined the research group of Prof. Erick M. Carreira at the ETH Zurich to pursue his Ph.D.



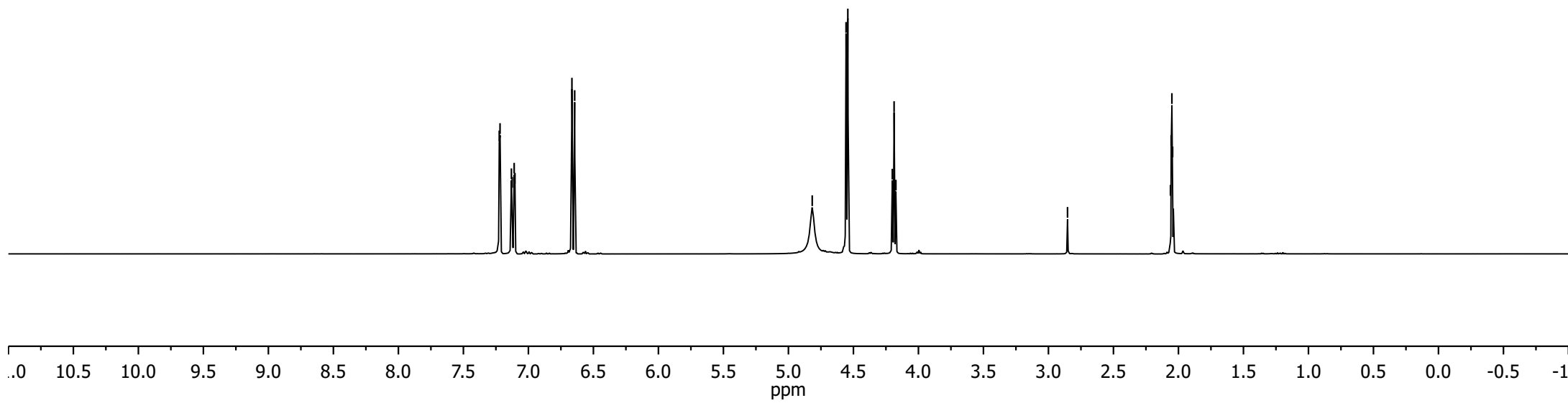
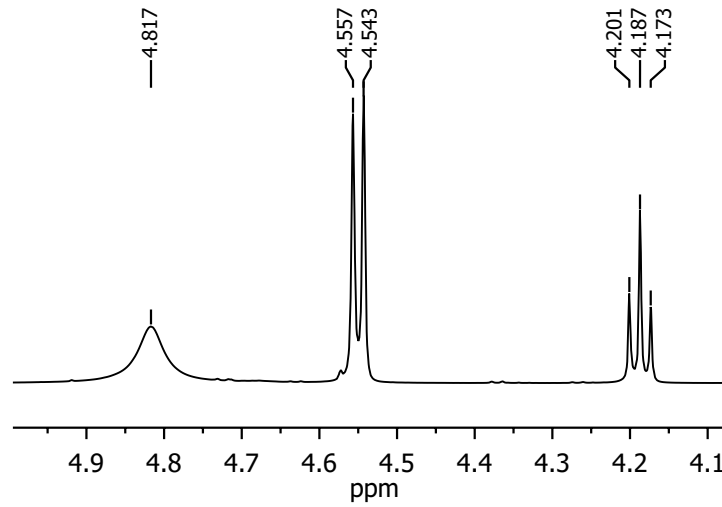
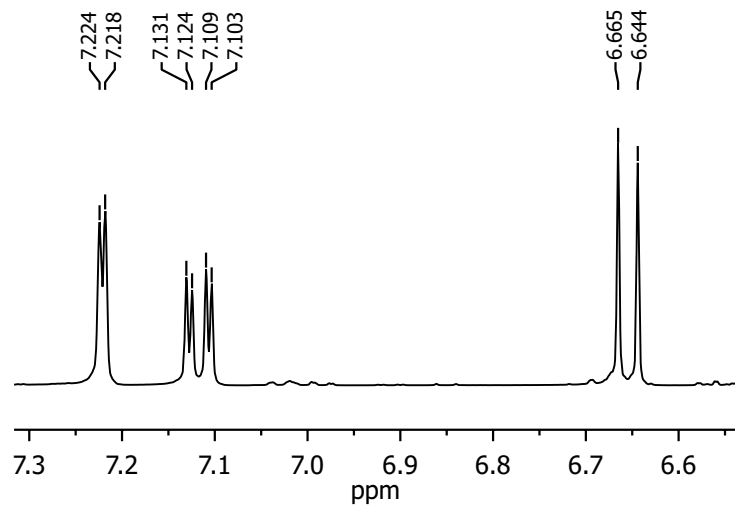
in acetone-d6

7.224  
7.218  
7.131  
7.124  
7.109  
7.103  
6.665  
6.644

4.817  
4.557  
4.543  
4.201  
4.187  
4.173

2.853

2.061  
2.056  
2.050  
2.045



206.201  
206.191  
206.182  
206.174  
206.165  
206.155  
206.143

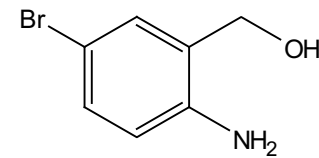
146.845

131.288  
131.130  
128.690

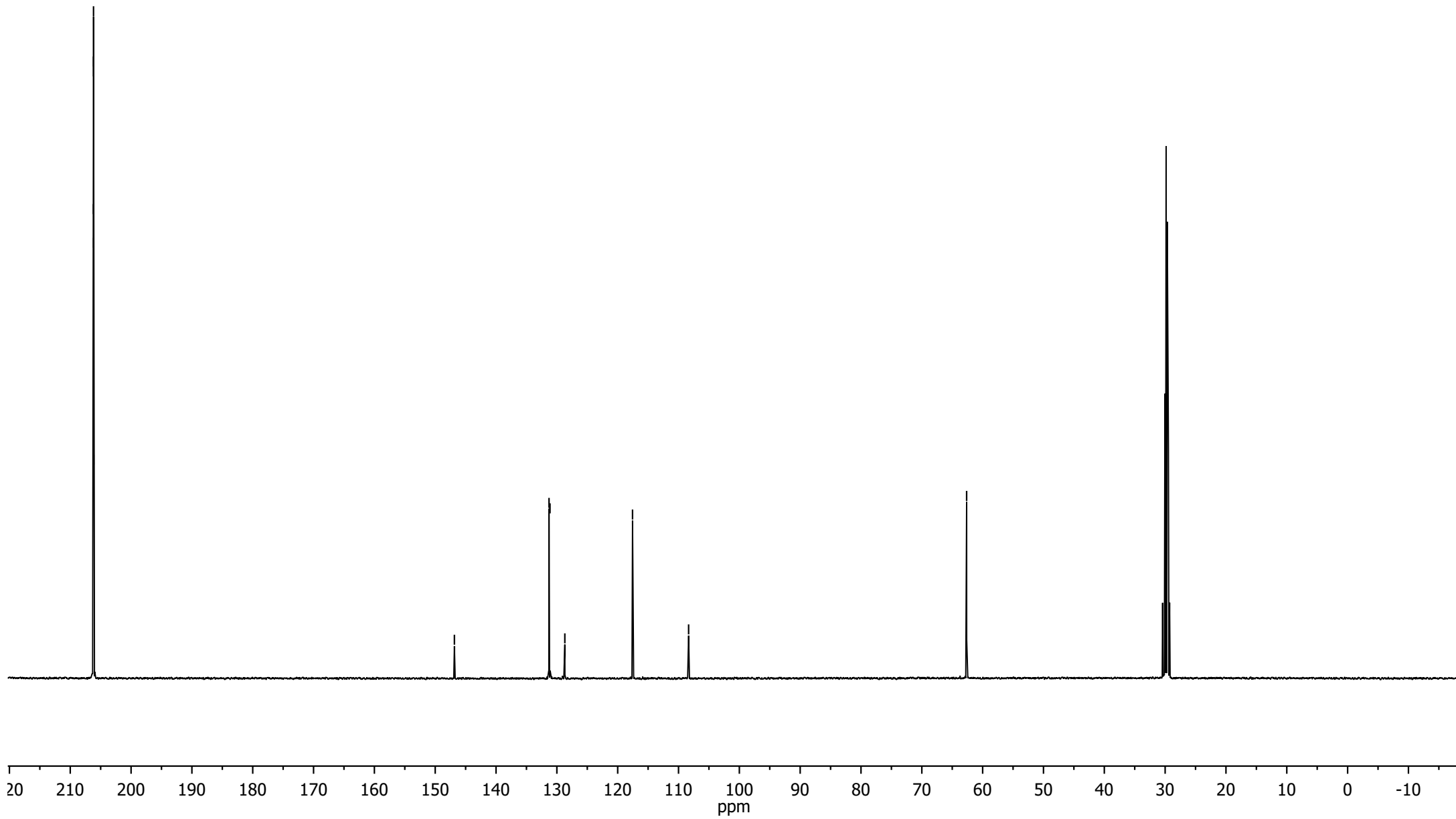
117.560

108.340

62.634



in acetone-d6

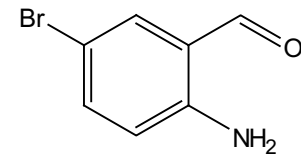


—9.792

7.578  
7.572  
7.379  
7.373  
7.357  
7.351  
7.260

6.574  
6.552

—6.142



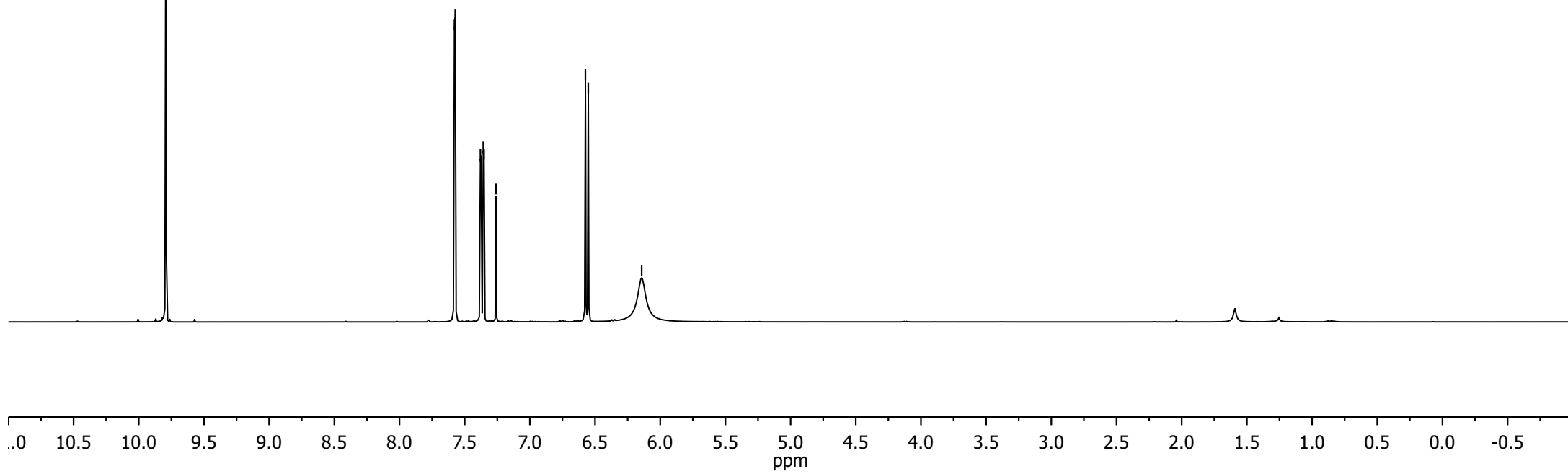
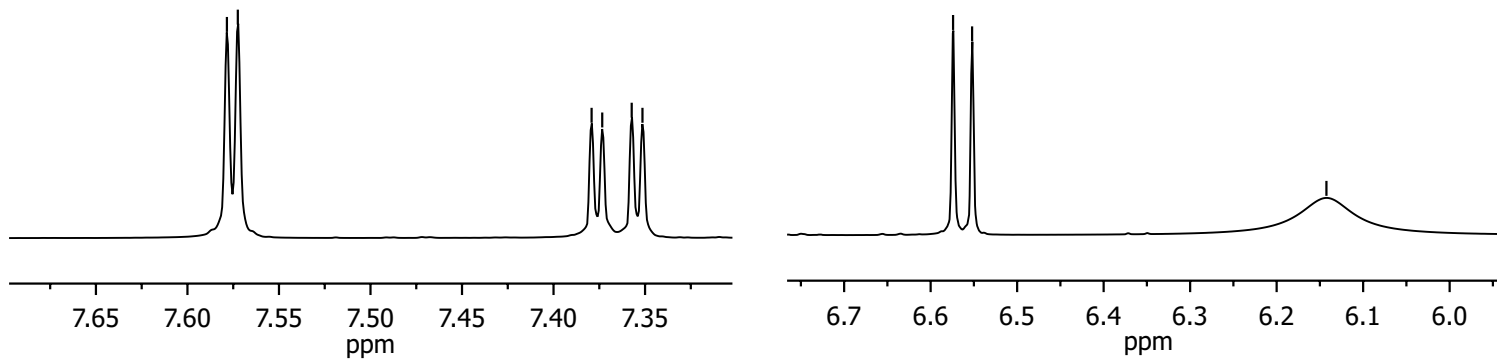
in chloroform-d

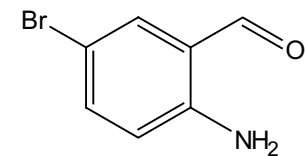
7.578  
7.572

7.379  
7.373  
7.357  
7.351

6.574  
6.552

—6.142





in chloroform-d

