A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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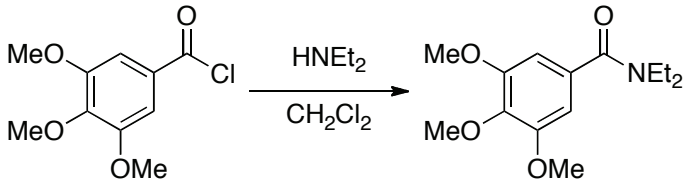
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

MILD CONVERSION OF TERTIARY AMIDES TO ALDEHYDES USING $Cp_2Zr(H)Cl$ (SCHWARTZ'S REAGENT)

A.



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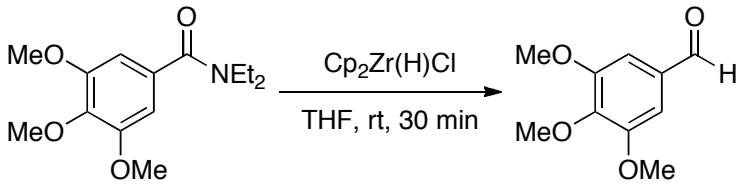
B.



2 3

Submitted by Matthew W. Leighty, Jared T. Spletstoser, and Gunda I. Georg.[1]
Checked by Hirotatsu Umihara and Tohru Fukuyama.

1. Procedure

A. N,N-Diethyl-3,4,5-trimethoxybenzamide. A 300-mL, three-necked, round-bottomed flask equipped with a 4.5-cm rod-shaped, Teflon-coated, magnetic stir bar, an internal thermocouple temperature probe, a calcium chloride drying tube, and a 50-mL pressure-equalizing dropping funnel sealed with a rubber septum is charged with 3,4,5-trimethoxybenzoyl chloride **1** (20.0 g, 86.7 mmol, 1 equiv) under ambient atmosphere (Notes 1 and 2). The acid chloride is dissolved in anhydrous CH_2Cl_2 (120 mL), and the resulting solution is stirred (500 rpm) in an ice-water bath while diethylamine (18.8 mL, 182 mmol, 2.1 equiv) is added dropwise from the dropping funnel over 15 min, such that the internal temperature does not exceed 15 °C (Notes 3 and 4). The reaction mixture is warmed to room temperature and stirred for 15 min at which time TLC analysis shows that no acid chloride **1** remains (Note 5). The reaction mixture is diluted with 2.7 M aqueous HCl (100 mL), and the resulting mixture is transferred to a 500-mL separatory funnel containing CH_2Cl_2 (50 mL) and 2.7 M aqueous HCl (50 mL) (Note 6). The layers are separated, and the aqueous phase is extracted with CH_2Cl_2 (50 mL). The combined organic layers are washed with

saturated aqueous $NaHCO_3$ (100 mL), and the aqueous layer is extracted with CH_2Cl_2 (50 mL). The combined organic layers are dried over Na_2SO_4, filtered into a 1-L one-necked, round-bottomed flask and concentrated on a rotary evaporator (30 °C, 40 mmHg) (Note 7). The residue is purified by silica gel column chromatography (elution with ethyl acetate/*n*-hexane, 3/1) (Note 8). The combined eluates are concentrated on a rotary evaporator (30 °C, 40 mmHg) and then dried overnight at 20 mmHg at room temperature to afford 22.1 g of amide **2** as a white solid in 95% yield (Note 9).

B. 3,4,5-Trimethoxybenzaldehyde. A 300-mL, three-necked, round-bottomed flask equipped with a 4.0-cm rod-shaped, Teflon-coated, magnetic stir bar, an internal thermocouple temperature probe, an argon flowing tube, and a rubber septum is charged with amide **2** (10.7 g, 40.0 mmol, 1 equiv). Tetrahydrofuran (THF, 100 mL) is added to the flask, and the resulting mixture is stirred (300 rpm) until homogenous, and then the flask is covered with aluminum foil (Note 10). The rubber septum is briefly removed and Schwartz's reagent (10.8 g, 42 mmol, 1.05 equiv) is added directly to the vigorously stirring solution in one portion followed by recapping the reaction flask with the rubber septum (Notes 11 and 12). An additional 30 mL of THF is added to rinse the reagent on the inside of the flask into the reaction mixture, ensuring complete addition of the zirconium reagent. The suspension is stirred for 30 min. The reaction mixture becomes slowly homogeneous during the course of the reaction at which time TLC analysis shows that no amide **2** remains (Notes 13 and 14). Silica gel (70 g) is added in one portion, and the mixture is stirred (1350 rpm) for one minute under ambient atmosphere (Note 15). The heterogeneous mixture is filtered over a silica plug (10 g) eluting with ethyl acetate (500 mL). The resulting filtrate is then added to a 2-L separatory funnel containing *n*-hexane (200 mL) and H_2O (400 mL) (Notes 16 and 17). The layers are separated, and the aqueous layer is extracted twice with ethyl acetate (400 mL) and *n*-hexane (160 mL). The combined organic layers are dried over Na_2SO_4 and concentrated on a rotary evaporator (35 °C, 30 mmHg). The residue is purified by silica gel column chromatography (elution with ethyl acetate/*n*-hexane, 1/4) (Note 18). The combined eluents are concentrated on a rotary evaporator (35 °C, 30 mmHg) and then dried overnight at 20 mmHg at room temperature to afford 7.20 g of aldehyde **3** as an off-white solid in 92% yield (Note 19).

2. Notes

1. All glassware was flame-dried immediately before use.

2. 3,4,5-Trimethoxybenzoyl chloride (98%) was purchased by the submitters and checkers from Aldrich Chemical Company, Inc. and used as received.

3. The submitters obtained dry CH_2Cl_2 by passing the solvent through an activated alumina column under a nitrogen atmosphere. The checkers followed the same method. Freshly distilled CH_2Cl_2 can also be used.

4. Diethylamine (99.5%) was purchased by the submitters and checkers from Aldrich Chemical Company, Inc. and was used as received. Slow addition allows for minimal heat fluctuation as the amine is added. The reaction mixture becomes slightly heterogeneous during the course of the reaction.

5. TLC analysis was conducted on Merck silica gel 60 F_{254} plates (0.25 mm, glass-backed, visualized with 254 nm UV lamp and stained with *p*-anisaldehyde) using 50% *n*-hexane in ethyl acetate as an eluent. Acid chloride **1** had an $R_f = 0.69$ and 0.13 (UV active, dark purple after staining) and amide **2** had an $R_f = 0.17$ (UV active, white after staining).

6. CH_2Cl_2 (ACS grade) used for workup was purchased by the submitters from Fisher Scientific and used as received. The checkers purchased CH_2Cl_2 (ACS grade) from Wako Pure Chemical Industries, Ltd., and used as received.

7. The submitters purchased Na_2SO_4 (anhydrous, ≥99%) from Mallinckrodt and used as received. The checkers purchased Na_2SO_4 (anhydrous, ≥98.5%) from Nacalai Tesque, Inc. and used as received.

8. Silica gel (acidic) was purchased from Kanto Chemical Co., Inc. (40-100 μm). The crude material was dissolved in the eluent (20 mL), and the solution was then charged onto a column (diameter = 7.5 cm) of 80 g of silica gel. The column was eluted with *n*-hexane/EtOAc, 1:3, and 100-mL fractions were collected. Fractions 3-16 were collected.

9. Physical characteristics of amide **2**: mp (uncorr.) 59–60 °C, (submitter: 60–62 °C); IR (thin film) 2971, 1632, 1458, 1333, 1236, 1127, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (6 H, br s), 3.31 (2 H, br s), 3.53 (2 H, br s), 3.85 (3 H, s), 3.88 (6 H, s), 6.60 (2 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.06, 13.53, 38.52, 42.60, 55.30, 59.88, 102.74, 131.90, 137.77, 152.41, 169.99. MS (ESI-MS) *m/z*: (M+H) calcd. for $C_{14}H_{22}NO_4$, 268.33; Found 268.35 (100%); (HR-ESI) *m/z*: (M+H) calcd. for $C_{14}H_{22}NO_4$,

268.1549; Found 268.1539. The submitters evaluated **2** for purity by LCMS employing a reversed phase HPLC column (ACQUITY UPLC BEH C18 Column (2.1 x 30 mm)), using 95% water/5% MeCN with 0.1% formic acid (solvent A) and 95% MeCN/5% water with 0.1% formic acid (solvent B). A linear gradient of 5% to 95% solvent B in solvent A over 4.5 min was used at a flow rate of 0.25 mL/min; t_R = 3.63 min. The purity was determined to be >98% at 220 nm. The checkers evaluated **2** for purity by elemental analysis. Anal. calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.74; H, 7.95; N, 5.22.

10. The submitters obtained dry THF by passing the solvent through an activated alumina column under a nitrogen atmosphere. The checkers followed the same method. Freshly distilled THF can also be used.

11. $Cp_2Zr(H)Cl$ (95%) was obtained by the submitters and the checkers from Alfa Aesar and used as received. Although this reagent is commercially available from other vendors, the Alfa Aesar reagent appears to be of superior quality. This reagent can also be prepared using a literature procedure.[3]

12. $Cp_2Zr(H)Cl$ is sensitive to prolonged contact to air and light, therefore the reagent was used with minimal exposure to air and light. Before storage, the reagent bottle was flushed briefly with argon, sealed with parafilm, and stored at 0 °C.

13. The reaction was monitored by TLC analysis on Merck silica gel 60 F_{254} plates (0.25 mm, glass-backed, visualized with 254 nm UV lamp and stained with Ce-PMA) using 50% *n*-hexane in ethyl acetate as an eluent. Amide **2** had an R_f = 0.17 (UV active, pale blue after staining) and aldehyde **3** had an R_f = 0.63 (UV active, blue after staining).

14. The submitters reported that an additional portion of $Cp_2Zr(H)Cl$ (2.06 g, 7.99 mmol, 0.2 equiv) was sometimes needed 25 min after the first addition in order for the reaction to reach completion. This is ascribed to variations in the quality of the $Cp_2Zr(H)Cl$.

15. Quenching with silica gel serves to break down the stable zirconacycle intermediate into the aldehyde as well as to destroy any remaining hydride. The use of water to quench the reaction can result in hard to break emulsions.

16. Leaving the aldehyde in contact with the silica gel for prolonged periods can result in a bright yellow or orange-red impurity that is difficult to separate from the product. This impurity is presumed to be a consequence of further reaction of the aldehyde with the zirconium by-products and the

silica gel. Thus, care should be taken to avoid prolonged exposure of the product to the zirconium entities and silica gel after the quench.

16. Ethyl acetate and *n*-hexane used for extraction was purchased by the checkers from Wako Pure Chemical Industries, Ltd., and was used as received.

17. The use of *n*-hexane as a co-solvent for extraction prevented the formation of emulsions.

18. Silica gel (acidic) was purchased from Kanto Chemical Co., Inc. (40–100 μm). The crude material was dissolved in CH_2Cl_2 (15 mL) and then was charged onto a column (diameter = 7.5 cm) of 90 g of silica gel. The column was eluted with *n*-hexane/EtOAc, 4:1, and 100-mL fractions were collected. Fractions 9–24 were collected.

19. Physical characteristics of aldehyde **3**: mp (uncorr.) 72–73 °C (submitter: 75–77 °C); IR (thin film) ν 2971, 1686, 1588, 1459, 1332, 1234, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94 (6 H, s), 3.95 (3 H, s), 7.14 (2 H, s), 9.88 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.86, 60.57, 106.29, 131.40, 143.14, 153.27, 190.71. MS (ESI-MS) *m/z*: (M+H) calcd. for $C_{10}H_{13}O_4$, 197.1; Found 197.0 (100%); MS (HR-ESI) *m/z*: (M+H) calcd. for $C_{10}H_{13}O_4$, 197.0814; Found, 197.0813. The submitters evaluated **3** for purity by LCMS using a reversed phase HPLC column (ACQUITY UPLC BEH C18 Column (2.1 x 30 mm)), using 95%water/ 5% MeCN with 0.1% formic acid (solvent A) and 95% MeCN/ 5% water with 0.1% formic acid (solvent B). A linear gradient of 5% to 95% solvent B in solvent A over 4.5 min was used at a flow rate of 0.25 ml/min; t_R = 3.58 min. The purity was determined to be >98% at 220 nm. The checkers evaluated **3** for purity by elemental analysis. Anal. calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.14; H, 6.10.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

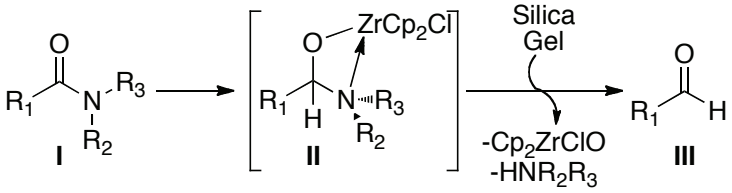
$Cp_2Zr(H)Cl$ (Schwartz's reagent) is an efficient reagent for the reduction of tertiary amides to aldehydes.[5] This reaction is conducted at

room temperature and is complete in short reaction times. Over-reduction to the alcohol is generally not observed, and the crude reaction mixture is clean enough to require only minimal purification.

One of the remarkable features of this reduction is that it works well on a variety of amide substrates including aromatic and aliphatic amides as well as *N*,*N*-dialkyl and *N*,*O*-dimethyl (Weinreb) amides. Many of the known methods for the *selective* reduction of amides to aldehydes are substrate specific, generally requiring specialized amide types for successful conversion to the aldehyde.[6] Most other existing methods tend to give over-reduction to the alcohol or amine products.[7] The described method is unique in that nearly all types of amide linkages are compatible substrates and the conditions are remarkably tolerant to a wide range of functional groups. Of considerable note is that the tertiary amide is *selectively* cleaved in the presence of the more easily reduced ester functional group.

Mechanistic evidence[5c] for the reduction suggests that after hydride delivery, the zirconium reagent forms a stable sp^3-hybridized, 18-electron complex with the amide **I** to yield intermediate **II** (Scheme 1). Silica gel addition to the reaction mixture breaks downs the intermediate into the desired aldehyde **III** and zirconium by-products. Therefore, only amides are reduced in the presence of esters and other potentially reducible moieties. Although most amides are reduced using this procedure, important to note is that very sterically-demanding amides generally afford lower yields of aldehyde. The low yields are presumably a consequence of poor hydride delivery/complex formation due to the bulky cyclopentadienyl groups encountering the sterically hindered amide, which results in lower yields. Rawal has developed modified reaction conditions to overcome this limitation.[8]

Scheme 1. Reduction Mechanism



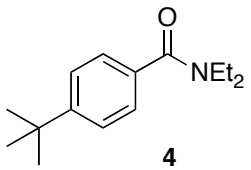
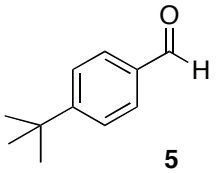
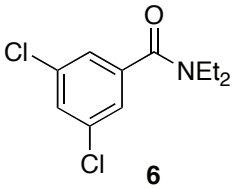
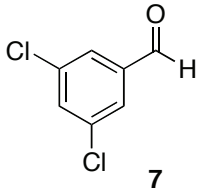
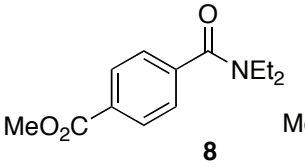
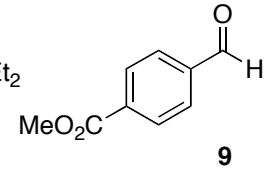
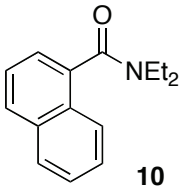
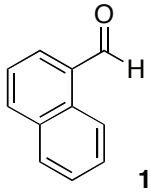
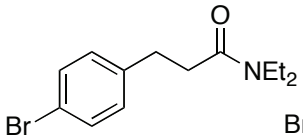
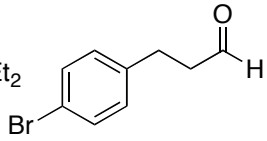
In this protocol, the addition of silica gel is in most cases the best workup procedure. The use of an aqueous quench generally affords problematic emulsions and/or the precipitation of a white solid (assumed to

be the zirconium oxide byproducts) that can be difficult to remove. The use of silica gel effectively cleaves the reaction intermediate to the product aldehyde while concomitantly destroying excess reagent and sequestering the zirconium byproducts. The use of an aqueous workup, after filtering off the silica gel, was implemented in order to ensure complete removal of these byproducts as unwanted side reactions were found to occur with prolonged exposure to the silica gel upon scale up. This procedure allows for a very facile and efficient workup procedure that provides a crude product that is easily purified by standard chromatography.

As is evident in Table 1, the reaction is tolerant to a variety of functionality. For example, both neutral and electron-deficient aromatic amides are readily reduced affording the corresponding aldehydes in good yields (entries 1 and 2). As demonstrated in entry 3, *selective* amide reduction occurs in the presence of an ester in good yield. In addition, bulky amides and non-aromatic amides can be reduced to the corresponding aldehydes in excellent yields (entries 4 and 5).

Presented is a mild and operationally simple method for the selective reduction of tertiary amides to aldehydes using $Cp_2Zr(H)Cl$. This method offers an alternative to known methods that are either substrate selective or can result in over-reduction products. In addition, this procedure can be conducted in the presence of esters and results in *selective* reduction of the amide to afford the corresponding aldehyde. Therefore, this procedure is a significant improvement over known amide reduction methods due to its mild and selective nature.

Table 1. Preparative Reduction of Tertiary Amides with $Cp_2Zr(H)Cl$[a]

Entry	Amide	Aldehyde	Scale (mmol)	Yield (%)
1	 **4**	 **5**	12.9	80
2	 **6**	 **7**	10.2	82
3	 **8**	 **9**	10.3	73
4	 **10**	 **11**	15.8	90
5	 **12**	 **13**	5.3	72

a) Each amide in the Table was prepared from the corresponding acid chloride or acid, which were purchased from either Aldrich Chemical Company, Inc. or TCI America and used as received. Amides **4**, **6**, **8**, and **10** were synthesized using the procedure described Step A. Amide **12** was prepared from the corresponding acid using standard coupling conditions. All reactions in the Table were conducted for 30 minutes at the indicated scale, using the procedure as described in Step B and purified using MPLC (silica gel) eluting with the appropriate ratio of hexanes and ethyl acetate. The pure aldehydes were characterized by standard methods and are consistent with the proposed structures.

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55414. E-mail: georg@umn.edu. Support is acknowledged from the University of Minnesota through the Vince and McKnight Endowed Chairs.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

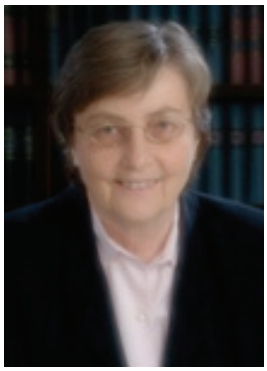
Diethylamine: Ethanamine, *N*-ethyl-; (109-89-7)

Zirconocene chloride hydride: Zirconium chlorobis(η^5-2,4-cyclopentadien-1-yl)hydro-; (37342-97-5)

3,4,5-Trimethoxybenzoyl chloride: Benzoyl chloride, 3,4,5-trimethoxy-; (4521-61-3)

3,4,5-Trimethoxybenzaldehyde; (86-81-7)

N,N-Diethyl-3,4,5-trimethoxybenzamide; (5470-42-8)

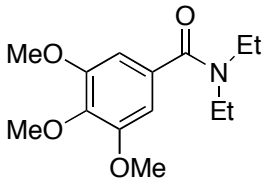


Gunda I. Georg obtained her doctoral degree from the University of Marburg in Germany. After postdoctoral studies at the University of Ottawa in Canada, and one year on the faculty at the University of Rhode Island, she joined the faculty of the Department of Medicinal Chemistry at the University of Kansas (1984). In 2007 she moved to the University of Minnesota as Head of the Department of Medicinal Chemistry. She holds the Robert Vince Endowed Chair and a McKnight Presidential Chair. She is the Founding Director of the Institute for Therapeutics Discovery and Development at the University of Minnesota.

Matthew W. Leighty (born 1979) graduated with a B.S. in chemistry from Alma College in 2001. He received his Ph.D. in 2009 from the University of Kansas under the guidance of Professor Gunda I. Georg working on the design and synthesis of biologically active compounds. Matthew is currently a postdoctoral research associate in the laboratories of Jeffrey N. Johnston.

Jared Spletstoser was born in Center, ND in 1976 and received his B.S. from the University of North Dakota. He received his Ph.D. in 2004 from the University of Kansas in the labs of Gunda Georg where he worked on Taxol photoprobes and brain delivery, the reduction of amides to aldehydes and the total synthesis of Oximidine II. He then joined the labs of James Leighton where he developed methods for the tandem silylformylation-crotylation of internal alkynes as an American Cancer Society postdoctoral fellow. He is currently a Principal Scientist at GlaxoSmithKline working in Infectious Diseases.

Hirotatsu Umihara was born in Kanagawa, Japan in 1988. He received his B.S. in 2011 from the University of Tokyo. In the same year, he began his graduate studies at the Graduate School of Pharmaceutical Sciences, the University of Tokyo, under the guidance of Professor Tohru Fukuyama. His research interests are in the area of the total synthesis of natural products.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MeO
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2

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6.5969
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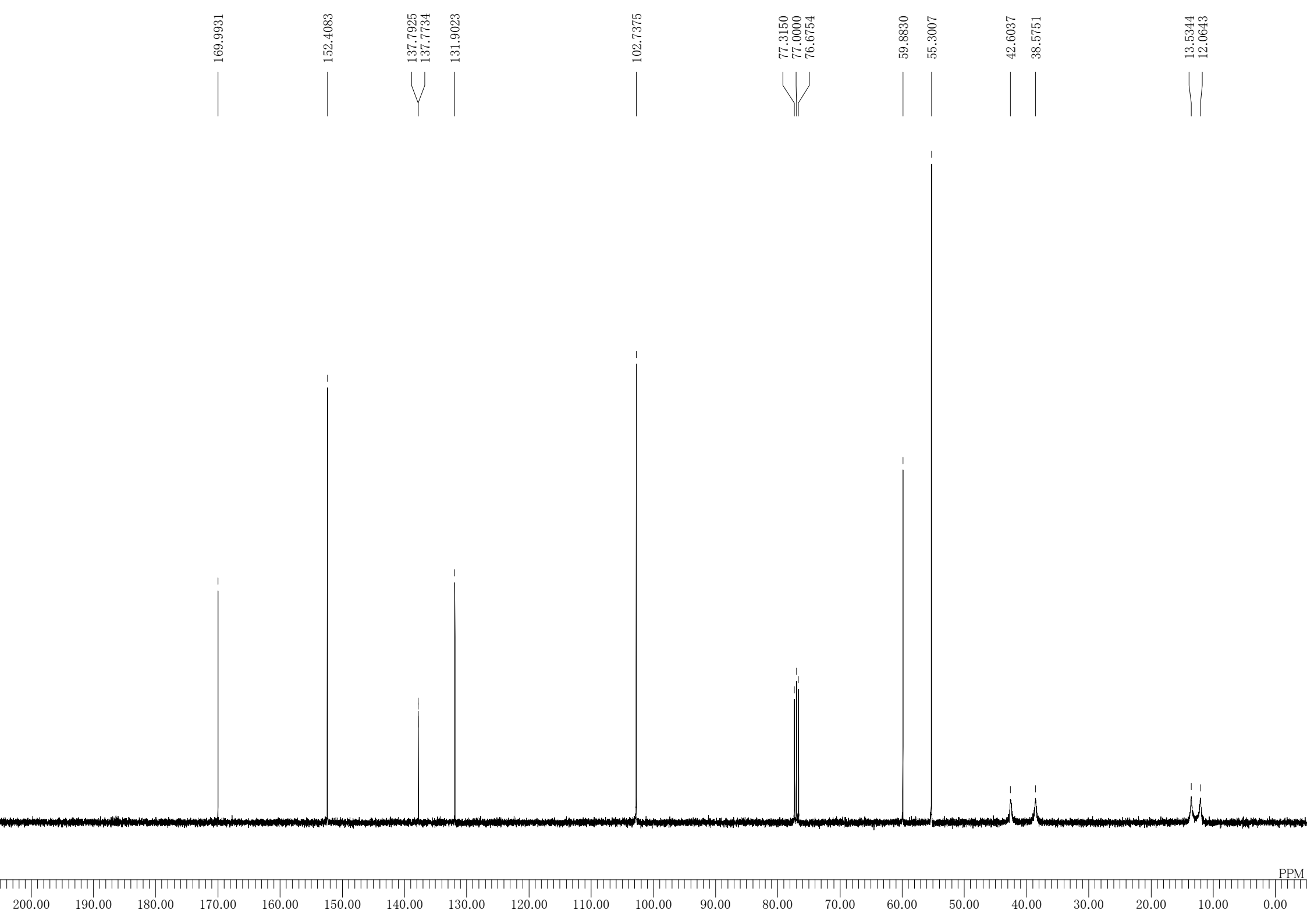
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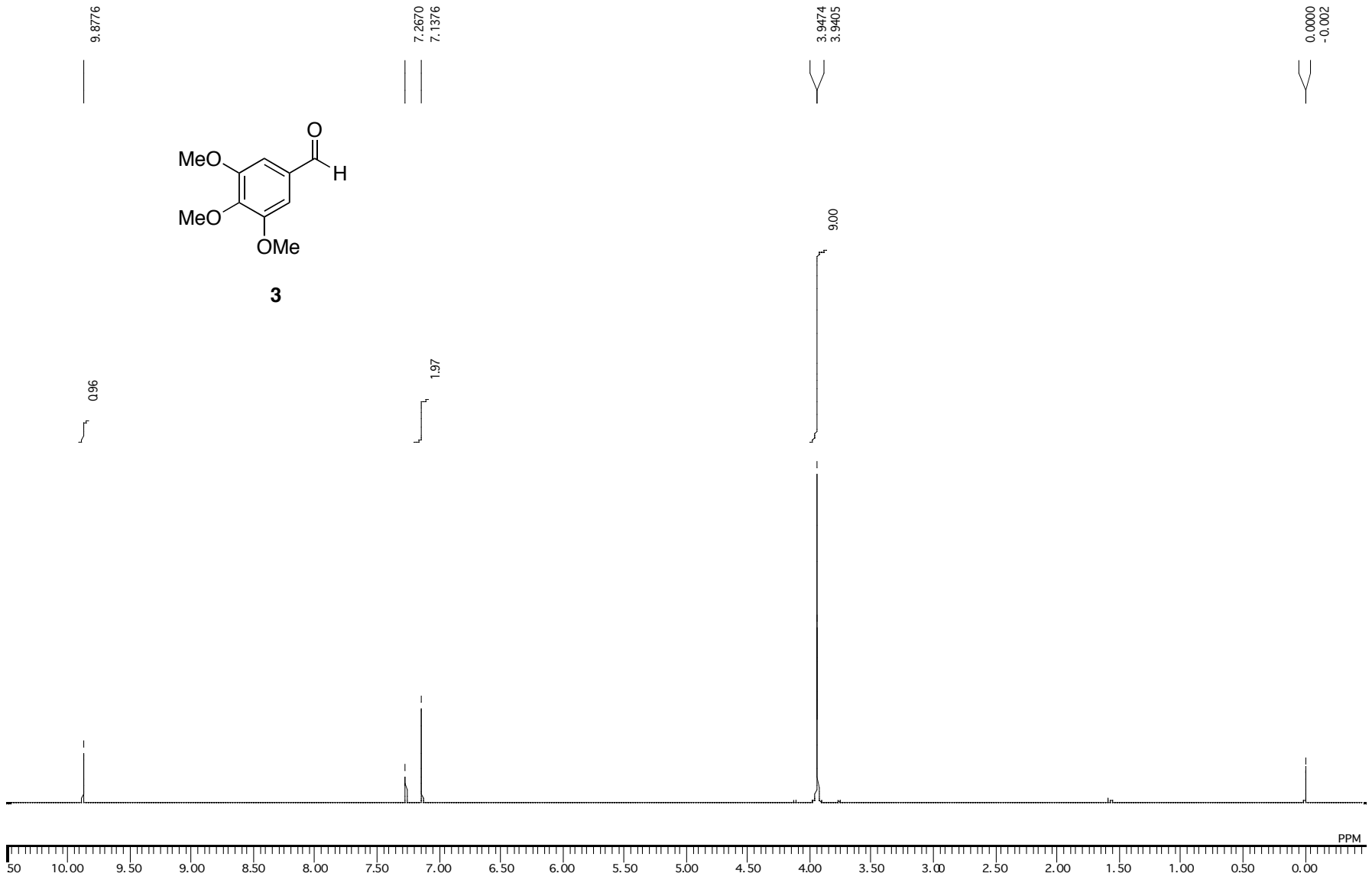
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