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.

Organic Syntheses

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Working with Peroxy Compounds

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added April 2018].

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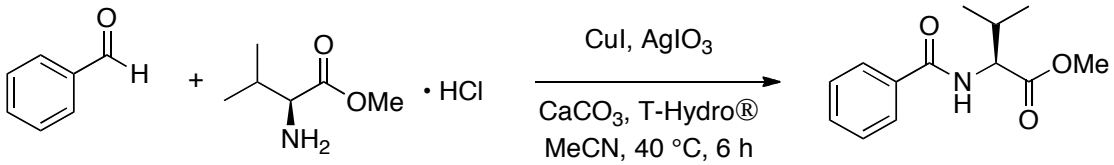
THE PREPARATION OF AMIDES BY COPPER-MEDIATED OXIDATIVE COUPLING OF ALDEHYDES AND AMINE HYDROCHLORIDE SALTS



Submitted by Maxime Giguère-Bisson, Woo-Jin Yoo and Chao-Jun Li.[1]
Checked by Melissa J. Leyva and Jonathan A. Ellman.

1. Procedure

All the following manipulations are performed in air.

A mechanical stir paddle (60 mm in diameter) is fitted to an oven-dried 100-mL, 2-necked round-bottomed flask (24/40 joint). Copper (I) iodide (0.047 g, 0.25 mmol, 0.01 equiv) (Note 1), $AgIO_3$ (0.070 g, 0.25 mmol, 0.01 equiv) (Note 2), L-valine methyl ester hydrochloride (6.19 g, 36.9 mmol, 1.5 equiv) (Note 3) and $CaCO_3$ (2.10 g, 21.0 mmol, 0.9 equiv) (Note 4) are added sequentially to the reaction flask, and the mixture is stirred at the maximum rate (the submitters stirred at 230 rpm). Acetonitrile (5.5 mL) (Note 5) is added in one portion using a syringe under constant stirring. A white opaque mixture is obtained at the end of this step. Benzaldehyde (2.50 mL, 24.6 mmol, 1.0 equiv) (Note 6) is added over 15 seconds using a syringe under constant stirring, and upon addition the reaction mixture becomes an opaque yellow. A *tert*-butyl hydroperoxide solution (4.00 mL, 28.0 mmol, 1.1 equiv) (Note 7) is added using a syringe under constant stirring and the mixture turns green. The reaction flask is then placed in an oil bath at 40 °C for 6 h under constant stirring.

After placing the reaction flask in the oil bath, the reaction mixture gradually becomes a clear orange-gold solution. The reaction flask is taken out of the oil bath and is placed in an ice-bath. Upon cooling, the reaction mixture becomes a thick, opaque mustard-yellow. Hydrochloric acid (1.6 M, 7.5 mL) is added dropwise (ca. 4 drops per second) under constant stirring. Upon neutralization, the reaction mixture turns green. The reaction flask is taken out of the ice-bath and ethyl acetate (25 mL) (Note 8) and distilled water (20 mL) are added. The organic layer is light green and the aqueous layer white-blue and opaque. If left overnight at room temperature, the

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organic layer may turn orange. The mixture is transferred to a 250-mL separatory funnel. The 100-mL round-bottomed flask is rinsed with ethyl acetate (15 mL) and distilled water (15 mL). The rinsings are transferred to the separatory funnel. Brine (15 mL) is added to the separatory funnel to obtain a better phase separation. The two layers are separated and transferred into 250-mL Erlenmeyer flasks. The aqueous layer is then transferred back to the separatory funnel and extracted with ethyl acetate (3 x 25 mL). Brine (3 x 15 mL) is added to facilitate every extraction. The organic layers are combined and washed with a saturated solution of $NaHCO_3$ (25 mL) and poured into a 250-mL Erlenmeyer flask. Anhydrous magnesium sulfate (4.0 g) (Note 9) is added. The solution is filtered under vacuum using a 30-mL suction funnel equipped with a medium porosity fritted-disc into an oven-dried, 500-mL round-bottomed flask. The magnesium sulfate in the frit is washed with two portions of ethyl acetate (2 x 10 mL), and the combined filtrate is concentrated under vacuum (40 °C and 21 mmHg) to provide a white-beige solid. Dichloromethane (20 mL) (Note 10) is added to the round-bottomed flask. The flask is sonicated for 30 seconds resulting in a green brown solution. Silica gel (5.0 g) (Note 11) is added to the flask and the solvent is evaporated using a rotary evaporator at 55–60 °C (21 mmHg). Flash column chromatography is performed using a 5-cm-wide, 45-cm-high column packed with 230 g of silica gel. The column is packed with silica gel, flushed with 1000 mL of the eluent (hexanes: ethyl acetate = 3:2) (Note 12). The eluent level is adjusted to the upper level of the silica gel. The silica gel containing the compound is then loaded on the column and column chromatography is then performed (1.7 L of eluent is used). The collected fractions (15 mL each) are analysed using TLC (eluting with hexanes: ethyl acetate =3:2) and the spots are visualized using a UV lamp (254 nm) (Note 13). The fractions (41 to 92) containing the desired compound are combined and evaporated to dryness using a rotary evaporator. The product is further dried under reduced pressure (0.01 mmHg) for 2 h to give (*S*)-methyl-2-benzamido-3-methylbutanoate (4.91 g, 20.9 mmol, 85% yield) (Note 14).

2. Notes

1. Copper (I) iodide was obtained from Aldrich and used as received.
2. Silver iodate was obtained from GFS Chemicals and used as received.
3. L-Valine methyl ester hydrochloride 99% was obtained from

Aldrich and used as received.

4. Calcium carbonate A.C.S reagent was obtained from Aldrich and used as received.

5. Acetonitrile A.C.S. Grade was obtained from Fisher Scientific and used as received.

6. Benzaldehyde ReagentPlus ≥99% was obtained from Aldrich and used as received.

7. *tert*-Butyl hydroperoxide, T-hydro solution, 70 wt. % in water was obtained from Aldrich and used as received.

8. Ethyl acetate HPLC Grade was obtained from Fisher Chemicals and used as received.

9. Anhydrous magnesium sulfate was obtained from Fisher Chemicals and used as received.

10. Dichloromethane A.C.S. Reagent was obtained from ACP Chemicals and used as received.

11. Silica gel MP Silitech 32-63 D 60 Å was used as received.

12. Hexanes HPLC Grade was obtained from Fisher Chemicals and used as received.

13. The reaction and column fractions were monitored by TLC using Dynamic Adsorbents, Inc. glass plates coated with 250 mm F-254 silica gel: Hexanes:ethyl acetate (3:2). The benzaldehyde starting material has an R_f of 0.65, and the product (*S*)-methyl-2-benzamido-3-methylbutanoate has an R_f of 0.45.

14. The product is obtained as a white (slightly yellow) flaky solid and has the following physical and spectroscopic properties: Melting point: 108-109 °C, IR (neat): 3347, 2967, 1736, 1640, 1518, 1490, 1202, 1151, 994, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.96 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J*= 7.0 Hz, 3 H), 2.25 (m, 1 H), 3.74 (s, 3 H), 4.74 (dd, *J*= 5.2, 8.4 Hz, 1 H), 6.64 (d, *J*= 8.4 Hz, 1 H), 7.39 (m, 2 H), 7.48 (m, 1 H), 7.77 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.1, 19.2, 31.8, 52.4, 57.6, 127.2, 128.8, 131.9, 134.3, 167.5, 172.9. MS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{18}NO_3$: 236.128. Found: 236.128. HPLC (Daicel Chiral AD-H, hexanes/isopropanol=95:5, flow rate 1.0 mL/min) t_R = 20.556 min (major), < 99.9 % ee. Submitters provided checkers with racemic product, t_R = 15.150 min (minor). Anal. calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.38; H, 7.44, N, 5.85. Specific rotation, $[\alpha]_D^{20}$ +34.0° (c = 0.1, CH_2Cl_2)

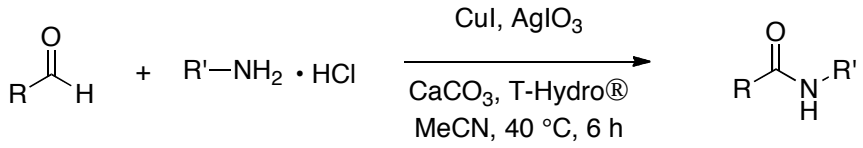
Safety and Waste Disposal Information

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

The amide functional group is ubiquitous in organic chemistry and is an important motif in polymers, natural products, and pharmaceuticals.[2] The most prevalent strategy for amide bond formation relies heavily upon the interconversion of activated carboxylic acid derivatives with an amine.[3] However, due to the lability of activated carboxylic acid derivatives, alternative strategies toward the synthesis of amides have been explored. Examples include the utilization of azides as amine equivalents in the modified Staudinger reaction,[4] hydrative amide syntheses with alkynes,[5] and thio acid/ester ligation methods.[6] Transition-metal-catalyzed carbonylation of alkenes,[7] alkynes,[8] and haloarenes[9] with amines has also been employed for amide synthesis. Finally, the direct coupling of aldehydes with amines under oxidative conditions can also serve as an attractive entry into amides.[10] This methodology has been hampered thus far by the need for expensive transition-metal catalysts and poor substrate scope. We previously reported a copper-catalyzed stereoselective oxidative esterification of aldehydes with β-dicarbonyl compounds using *tert*-butyl hydroperoxide (TBHP) as an oxidant.[11] In light of our success in that oxidative esterification reaction, we turned our attention to the much more challenging amidation reaction of simple aldehydes and amines. Subsequently, we developed a simple methodology[12] using CuI as catalyst, an aqueous solution of *tert*-butyl hydroperoxide as an oxidant, as well as $AgIO_3$ as an additive. This paper describes the scale up of this methodology. The specific reaction shown in this paper is the oxidative amidation of benzaldehyde with the hydrochloride salt of L-valine methyl ester. The CuI/TBHP/$AgIO_3$ methodology has also been used successfully on a smaller scale with other aldehydes and amine hydrochloride salts as shown in the following table.

Table 1. Copper Catalyzed Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts[a,b]



Entry	R	R'	Isolated yield(%)
1	Ph	Et	91
2	Ph	Bn	71
3	Ph	CH_2Bn	89
4	Ph	*c*-C_6H_{11}-	73
5	Ph	*t*-Bu	39
6	Ph	CH_2CH_2Cl	89
7	Ph	CH_2CO_2Et	91
8	4-Me-C_6H_4	CH_2CO_2Et	91
9	4-MeO-C_6H_4	CH_2CO_2Et	78
10	4-Cl-C_6H_4	CH_2CO_2Et	81
11	4-NO_2-C_6H_4	CH_2CO_2Et	49
12	*c*-C_6H_{11}	CH_2CO_2Et	39

[a] See reference 12; [b] 0.9 mmol scale

1. Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, QC H3A 2K6, Canada. Email: cj.li@mcgill.ca.
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

L-Valine methyl ester hydrochloride: (*S*)-2-amino-3-methylbutanoate hydrochloride; (6306-52-1)

Silver iodate: iodic acid (HIO_3), silver(1+) salt (1:1); (7783-97-3)

Calcium carbonate: carbonic acid, calcium salt (1:1); (471-34-1)

tert-Butyl hydroperoxide: 1,1-dimethylethyl hydroperoxide; (75-91-2)

Benzaldehyde: benzenecarboxaldehyde; (100-52-7)

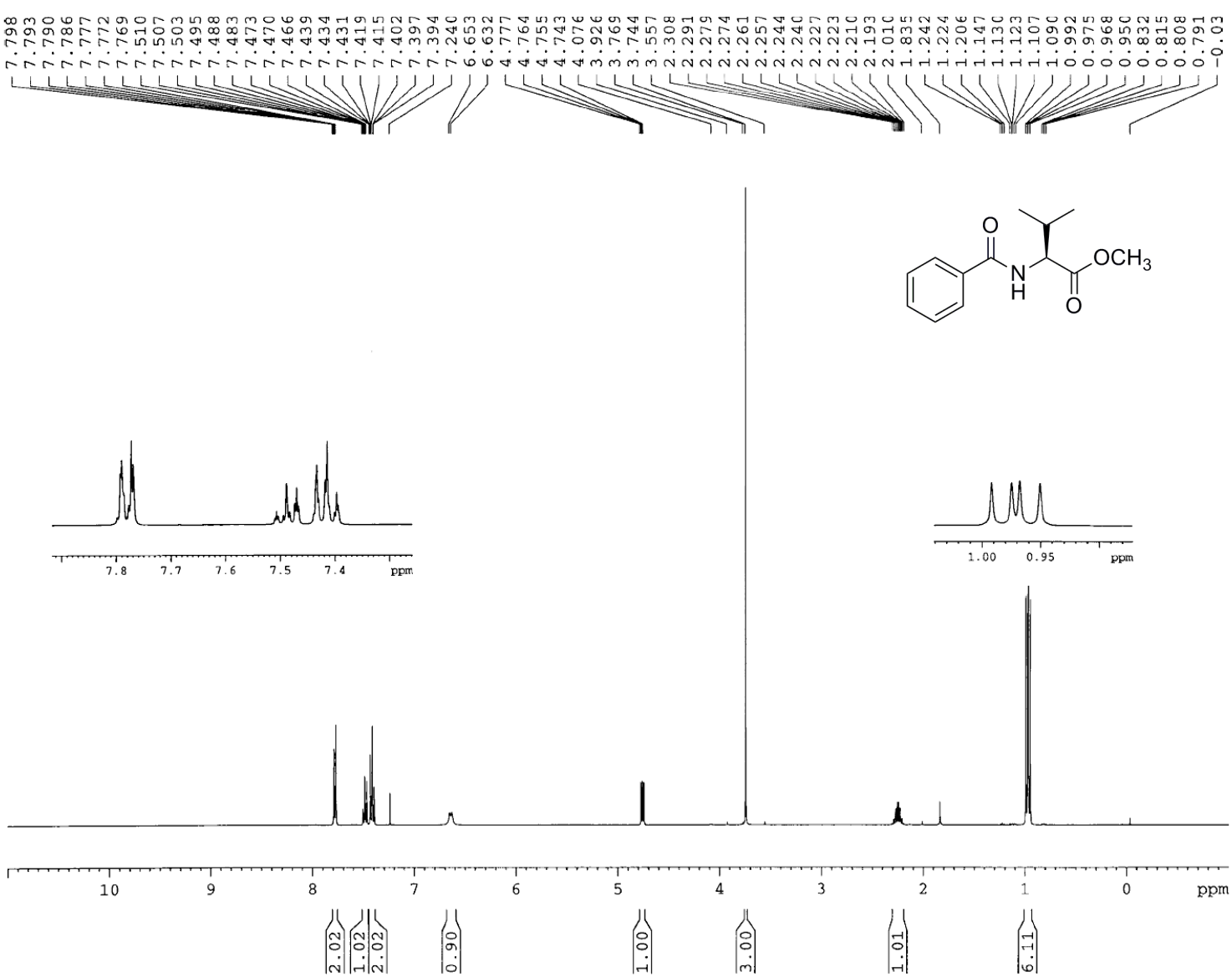
(*S*)-Methyl-2-benzamido-3-methylbutanoate: L-Valine, *N*-benzoyl-, methyl ester; (10512-91-1)

Chao-Jun Li (born in 1963) received his Ph.D at McGill University (1992). After a two year NSERC Postdoctoral position at Stanford University, he became Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000) at Tulane University. In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor (E. B. Eddy Chair Professor since 2010) of Chemistry at McGill University in Canada. Currently, he serves as the Co-Chair of the Canadian Green Chemistry and Engineering Network, Director of CFI Facility for Green Chemistry and Green Chemicals, and Co-Director for FQRNT Center for Green Chemistry and Catalysis. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and have high synthetic efficiency.

Maxime Giguère-Bisson was born in 1986 in Grand-Mère (Canada). He obtained his B. Sc. Degree in Chemistry Honours in 2008 from McGill University. He is currently doing his Masters in Chemistry under the supervision of Dr. Chao-Jun Li. His current research focuses on Asymmetric A^3-Coupling.

Woo-Jin Yoo (born in 1978) received his B.Sc. degree from the University of Guelph in 2003. In 2005, he received his M.Sc. degree from the University of Guelph under the supervision of William Tam, where he studied metal-catalyzed cross-coupling reactions and Diels-Alder cycloadditions. He then joined the research group of Chao-Jun Li at McGill University and studied copper-catalyzed oxidative coupling reactions and multicomponent coupling reactions. He obtained his Ph.D. degree in 2009 and is currently a postdoctoral fellow with Shū Kobayashi at The University of Tokyo. He has been the recipient of the Alexander Graham Bell Canada Graduate Scholarship (Ph.D.), an NSERC Postdoctoral Fellowship (declined), and a JSPS Postdoctoral Fellowship for Foreign Researchers.

Melissa J. Leyva was born in El Paso, Texas in 1982. She received her B.S. degree in Chemistry at the University of Texas, El Paso in 2005. She then began her doctoral studies at the University of California, Berkeley under the direction of Professor Jonathan A. Ellman. Her graduate research has focused on the identification of novel inhibitors for therapeutically important proteases.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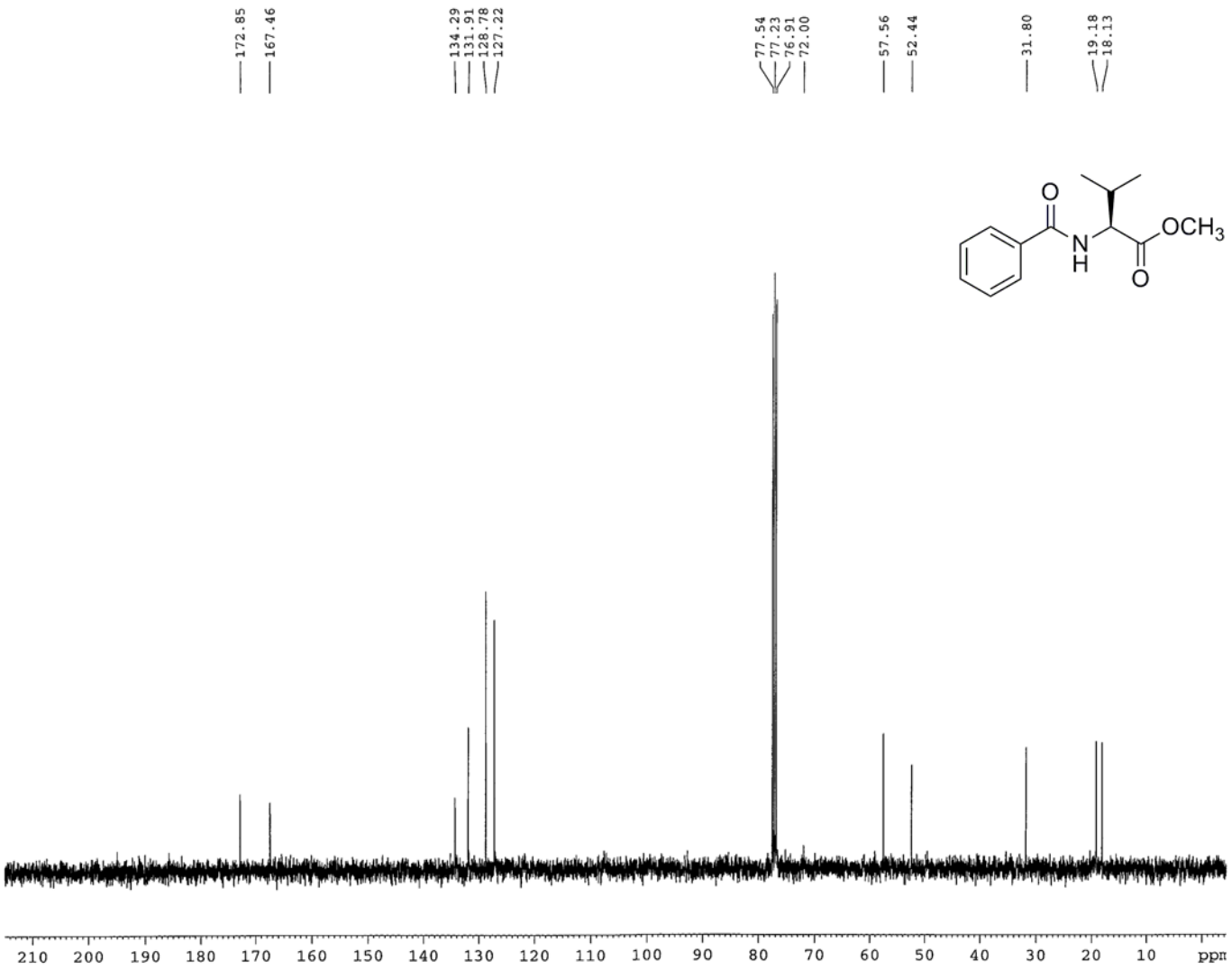
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