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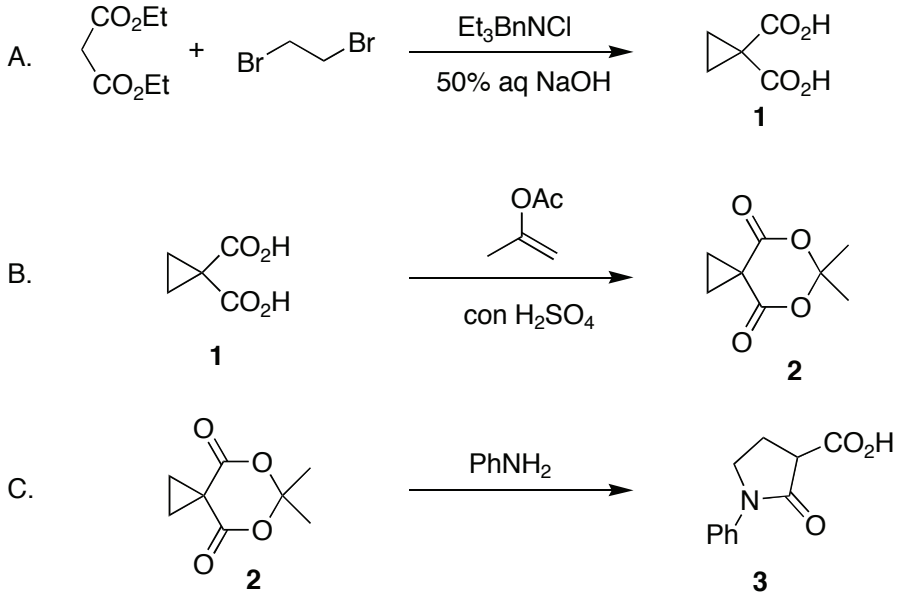
Homoconjugate Addition of Nucleophiles to Cyclopropane-1,1-Dicarboxylate Derivatives: 2-Oxo-1-Phenyl-3-Pyrrolidinecarboxylic Acid
[3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl-]



Submitted by Rajendra K. Singh and Samuel Danishefsky.[1]
Checked by M. R. Czarny and M. F. Semmelhack.
Rechecked by Stephanie Tumidajski and Rick L. Danheiser.

1. Procedure

A. *Preparation of cyclopropane 1,l-dicarboxylic acid* (**1**). To a 1-L solution of aqueous 50% sodium hydroxide (Note 1), mechanically stirred in a 2-L, three-necked flask, is added, at 25 °C, 114.0 g (0.5 mol) of triethylbenzylammonium chloride (Note 2). To this vigorously stirred suspension is added a mixture of 80.0 g (0.5 mol) of diethyl malonate and 141.0 g (0.75 mol) of 1,2-dibromoethane all at once. The reaction mixture is vigorously stirred for 2 h (Note 3). The contents of the flask are transferred to a 4-L Erlenmeyer flask by rinsing the flask with three 75-mL portions of water. The mixture is magnetically stirred and cooled with an ice bath to 15 °C, and then carefully acidified by dropwise addition of 1 L of concentrated hydrochloric acid. The temperature of the flask is maintained between 15 and 25 °C during acidification. The aqueous layer is poured into a 4-L separatory funnel and extracted three times with 900 mL of ether. The

aqueous layer is saturated with sodium chloride and extracted three times with 500 mL of ether. The ether layers are combined, washed with 1 L of brine, dried ($MgSO_4$), and decolorized with activated carbon. Removal of the solvent by rotary evaporation gave 55.2 g of a semisolid residue. The residue is triturated with 100 mL of benzene. Filtration of this mixture gave 43.1–47.9 g (66–73%) of **1** as white crystals, mp 137–140 °C.

B. *6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione* (**2**). A suspension of 39.0 g (0.30 mol) of **1** and 33.0 g (0.33 mol) of freshly distilled isopropenyl acetate is stirred vigorously (magnetic stirrer). To this suspension is added dropwise over a period of 30 min, 0.5 mL of concentrated sulfuric acid. While being stirred for an additional 30 min, the solution became clear yellow, and then partly solidified after being kept at 5 °C for 24 h. After addition of 50 mL of cold water, the precipitated solid is filtered, washed with 10 mL of cold water, and air-dried to give 30.9 g of crude spiroacylal **2**. The filtrate is extracted three times with 50-mL portions of ether. The combined organic layers are carefully washed with 50 mL of brine, dried ($MgSO_4$), and decolorized with activated carbon. Evaporation of the solvent gave an additional 7.8 g of spiroacylal **2** as a yellow solid. The combined samples of crude spiroacylal (38.7 g) are recrystallized (Note 4) from 110 mL of hexane and 25 mL of benzene to give 28.7–31.5 g (55–61%) of **2** (Note 5) as colorless needles, mp 65–67 °C. Concentration of the above mother liquor to ca. 40 mL gave 0.80 g of a second crop of spiroacylal **2** as slightly yellow crystals, mp 58–60 °C.

C. 2-*Oxo-1-phenyl-3-pyrrolidinecarboxylic acid* (**3**) (Note 6). A 100-mL, round-bottomed flask equipped with an egg-shaped Teflon-coated magnetic stir bar (3 x 1 cm), rubber septum, and argon inlet needle is charged with spiroacylal **2** (5.10 g, 30 mmol, 1.0 equiv). Aniline (8.2 mL, 8.4 g, 90 mmol, 3.0 equiv) (Note 7) is added rapidly via syringe and the spiroacylal dissolved within 15 min to produce a pale yellow solution. The reaction mixture is stirred at room temperature for 13 h and the resulting orange solution (Note 8) is diluted with 150 mL of chloroform, washed with three 10-mL portions of 10% hydrochloric acid solution and 20 mL of brine, dried over 5 g of $MgSO_4$, and filtered. The filtrate is decolorized by stirring for 5 min over 0.5 g of activated carbon which is then separated by suction filtration through 1-inch of Celite in a Büchner funnel with the aid of 30 mL of chloroform. Concentration by rotary evaporation (25 °C, 20 torr) afforded 6.18 g of a light brown solid. This material is dissolved completely in 52 mL of chloroform (60 °C) and then hexanes (15 mL) are slowly added

until the solution became turbid. Hot chloroform (3 mL) is added until the solution became clear and then the solution is allowed to cool slowly to 0 °C over 2 h during which time white crystals began to form. The flask is capped and allowed to stand in a freezer at –25 °C for 16 h. The resulting crystals are collected by suction filtration on a Büchner funnel, washed with 20 mL of ice-cold hexanes, and transferred to a 50-mL, round-bottomed flask and dried overnight at 0.05 mmHg to provide 4.06 g pyrrolidinone **3** as a white solid. The filtrate is concentrated to a brown solid, dissolved in 8 mL of hot chloroform (60 °C), and then 3 mL of hexanes are added until the solution became turbid. An additional 4 drops of chloroform is added until the solution became clear and the hot solution is allowed to cool to rt over 2 h at which time a seed crystal is added. The flask is cooled at 0 °C for 1 h and then -25 °C for an additional 14 h. The resulting crystals are collected by suction filtration on a Büchner funnel, washed with 10 mL of ice-cold hexanes, and transferred to a 50-mL, round-bottomed flask and dried overnight at 0.05 mmHg to provide 0.933 g of **3** as a white solid. The two crops are combined to afford 4.99 g (81%) of **3** as a white solid.

2. Notes

1. Aqueous 50% sodium hydroxide was prepared by dissolving 500 g of sodium hydroxide pellets in water and diluting to 1 L.

2. This compound is commercially available from Aldrich Chemical Company, Inc. Alternatively, it can be made very cheaply and simply by mixing benzyl chloride (1 equiv) with triethylamine (2.5 equiv). The mixture is allowed to stand for 4–7 days at room temperature. Filtration of the solid and drying in vacuum give triethylbenzylammonium chloride suitable for use in nearly quantitative yield.

3. Some exothermicity results on mixing, causing the temperature to rise to ca. 65 °C.

4. The second checkers recrystallized the crude product from benzene-hexanes at 45 °C according to the following procedure. The crude product (15.7 g) was taken up in 0.3 mL of water and 10 ml of benzene at 45 °C. Hexanes (8 mL) were then added slowly until the solution became cloudy. An addition 4 mL of benzene was then added dropwise at 45 °C until the solution became clear. The solution was allowed to cool and let stand at 15 °C for 3 h. The resulting colorless crystals were filtered on a Buchner funnel washing with ca. 14 mL of cold hexanes. The hexane-benzene filtrate

was concentrated to provide a mother liquor for further crystallization. The crystals collected by the filtration were found to be contaminated with unreacted cyclopropane-1,1-dicarboxylic acid, which was removed by washing with 100 mL of ice-cold water, leaving 6.40 g of pure **2**. The filtrate was extracted with three 30-mL portions of Et_2O, concentrated, and then washed further with 40-mL of ice-cold water to afford an additional 1.12 g of **2**. A second crop of product (2.33 g) was obtained by applying a similar procedure to the mother liquor. Total yield: 9.85 g (56%) of **2**. Due to volatility, the product should be air-dried and not exposed to high vacuum.

5. Analytical data for **2**: mp = 64-65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 4 H), 1.82 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 105.4, 27.8, 24.4, 24.1; IR (KBr) 3484, 3113, 3018, 2938, 1739, 1362, 1042, 970, 727, 621, and 491 cm^{-1}; Anal. calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92; found: C, 56.38; H, 5.74.

6. The originally published procedure for Step C contained several errors with regard to the amounts of reactants. This procedure was rechecked and a revised procedure was published in August, 2012.

7. Aniline 99+% was purchased from Alfa Aesar and used as received.

8. The authors report that they obtained a crystalline mass after stirring overnight.

9. Analytical data for **3**: mp = 144 -145 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (br s, 1 H) 7.58 (app d, J = 7.5 Hz, 2 H), 7.43 (app t, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 1 H), 3.89-3.99 (m, 2 H), 3.67 (t, J = 10.5 Hz, 2 H), 2.47-2.64 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.6, 138.1, 129.4, 126.4, 120.8, 47.8, 47.3, 21.1; IR (KBr) 3233, 2939, 2585, 1724, 1679, 1401, 1167, 753, and 660 cm^{-1}. The authors report that at the melting point, after a few minutes, the lactam acid **3** suffers smooth decarboxylation to afford *N*-phenyl-2-pyrrolidinone. Alternatively, the acid can be esterified (methanol-hydrochloric acid), and the resulting 1-phenyl-3-carbomethoxypyrrolidin-2-one can be used for the introduction of other functionality at the 3-position.

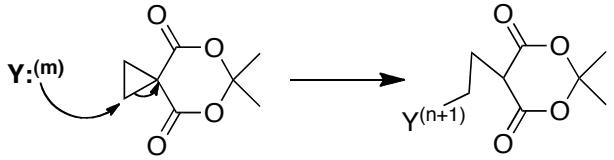
3. Discussion

Previously cyclopropane-1,1-dicarboxylic acid had been prepared[2,3,4] by hydrolysis of the corresponding diester. The preparation of 1,1-dicarboalkoxycyclopropanes by a conventional double alkylation of diethyl malonate with 1,2-dibromoethane was severely complicated by the recovery

of unreacted diethylmalonate. This required a rather difficult distillation to separate starting material and product. In fact, many commercially offered lots of cyclopropane diester contain extensive amounts of diethyl malonate. Furthermore, preparation of the diacid required a separate and relatively slow saponification of the diester.[5]

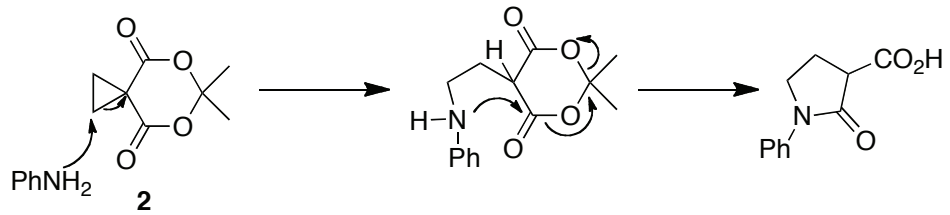
The procedure described here for compound **1** is a scale-up of a published method.[6] Phase-transfer catalysis[7] and concentrated alkali are used to effect a one-pot conversion of diethyl malonate to the cyclopropane diacid, which is easily obtained by crystallization. Apparently alkylation of the malonate system occurs either at the diester or monocarboxylate, monoester stage since the method fails when malonic acid itself is used as the starting material. This method of synthesizing doubly activated cyclopropanes has been extended to the preparation of 1-cyanocyclopropanecarboxylic acid (86%) by the use of ethyl cyanoacetate and 1-acetylcyclopropanecarboxylic acid (69%) by use of ethyl acetoacetate.[6]

The spiroacylal **2** is potentially a valuable agent in organic synthesis.[8] It is readily attacked by a variety of nucleophiles, including pyridine, to give ring-opened products bearing a stabilized carbanion. It is thus seen to be a synthetic equivalent of CH_2-CH_2-$CH(CO_2H)_2$ and $CH_2(CH_2)_2$-CO_2H, i.e., a



2

homo-Michael acceptor. The general reaction is where Y = aniline, piperidine, pyridine, mercaptide, enolate, etc. Spiroacylal **2** was designed under the rationale that the constraint of the carbonyl groups into a conformation in which overlap of their π-orbitals with the "bent bonds" of the cyclopropane is assured should dramatically increase the vulnerability of the cyclopropane toward nucleophilic attack.[8] Experimental support for this notion is abundant.[8] Spiroacylal **2** is considerably more reactive than 1,1-dicarbethoxycyclopropane in such reactions. For instance, reaction of **2** with piperidine occurs at room temperature. The corresponding reaction in the case of the diester is conducted at 110 °C.[5] Reactions with enolates also occur under mild conditions.[8] Compound **2** reacts with the weak nucleophile pyridine at room temperature to give a betaine.[8] An illustrative mechanism for the reaction of the acylal **2** with aniline to afford 2-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (**3**) is



The synthesis of the spiroacylal **2** from the diacid **1** follows a procedure used by Scheuer in a different context.[9]

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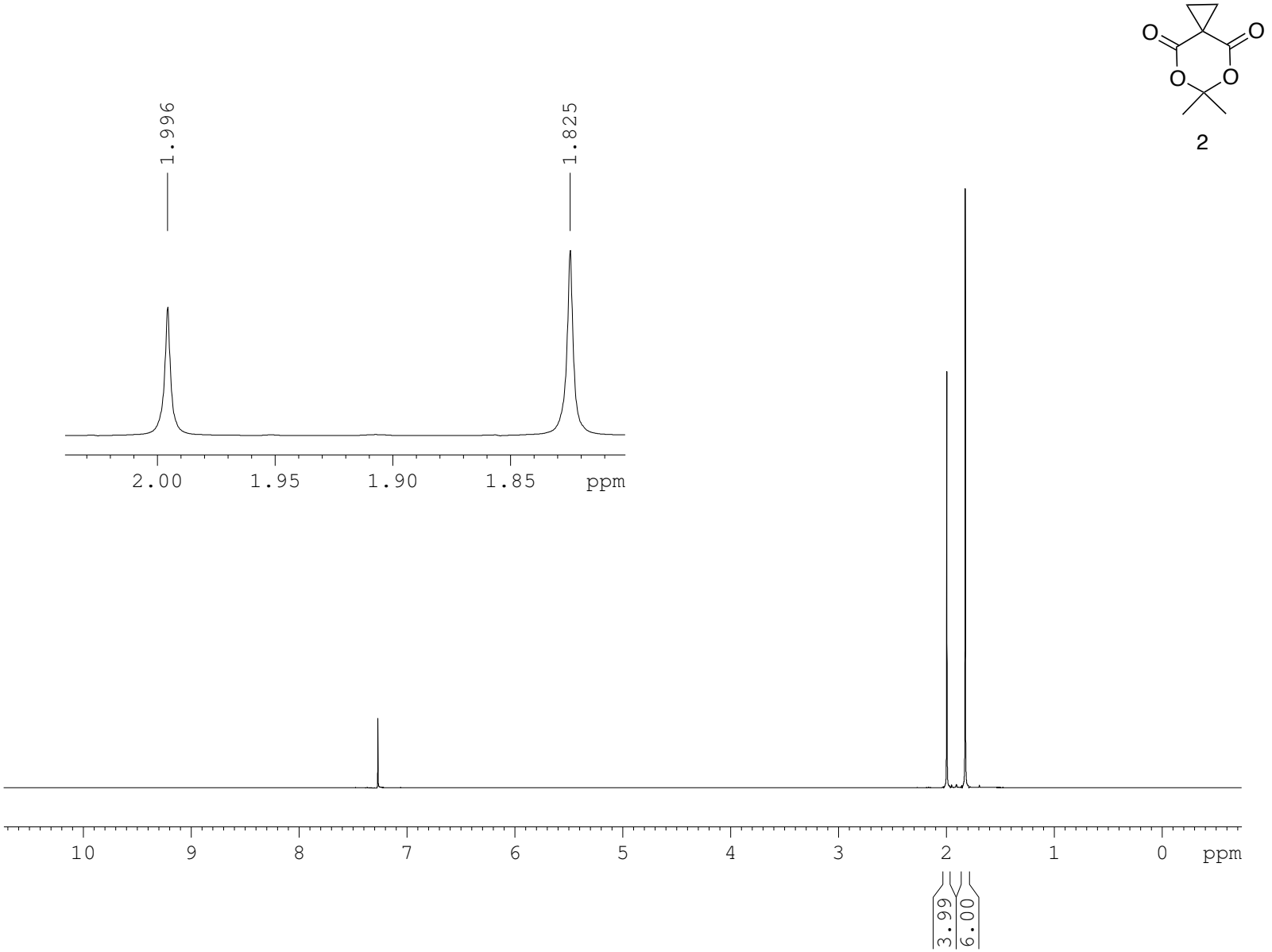
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

1,2-Dibromoethane (106-93-4)
Ethyl cyanoacetate (105-56-6)
Ethyl acetoacetate (141-97-9)
Diethyl malonate (105-53-3)
Isopropenyl acetate (108-22-5)
Cyclopropane-1,1-dicarboxylic acid (598-10-7)
Triethylbenzylammonium chloride (56-37-1)
2-Oxo-1-phenyl-3-pyrrolidinecarboxylic acid, 3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl- (56137-52-1)
6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (5617-70-9)
1-Phenyl-3-carbomethoxypyrrolidin-2-one
1-Cyanocyclopropanecarboxylic acid (6914-79-0)
1-Acetylcyclopropanecarboxylic acid
1,1-Dicarbethoxycyclopropane (1559-02-0)
N-Phenyl-2-pyrrolidinone (4641-57-0)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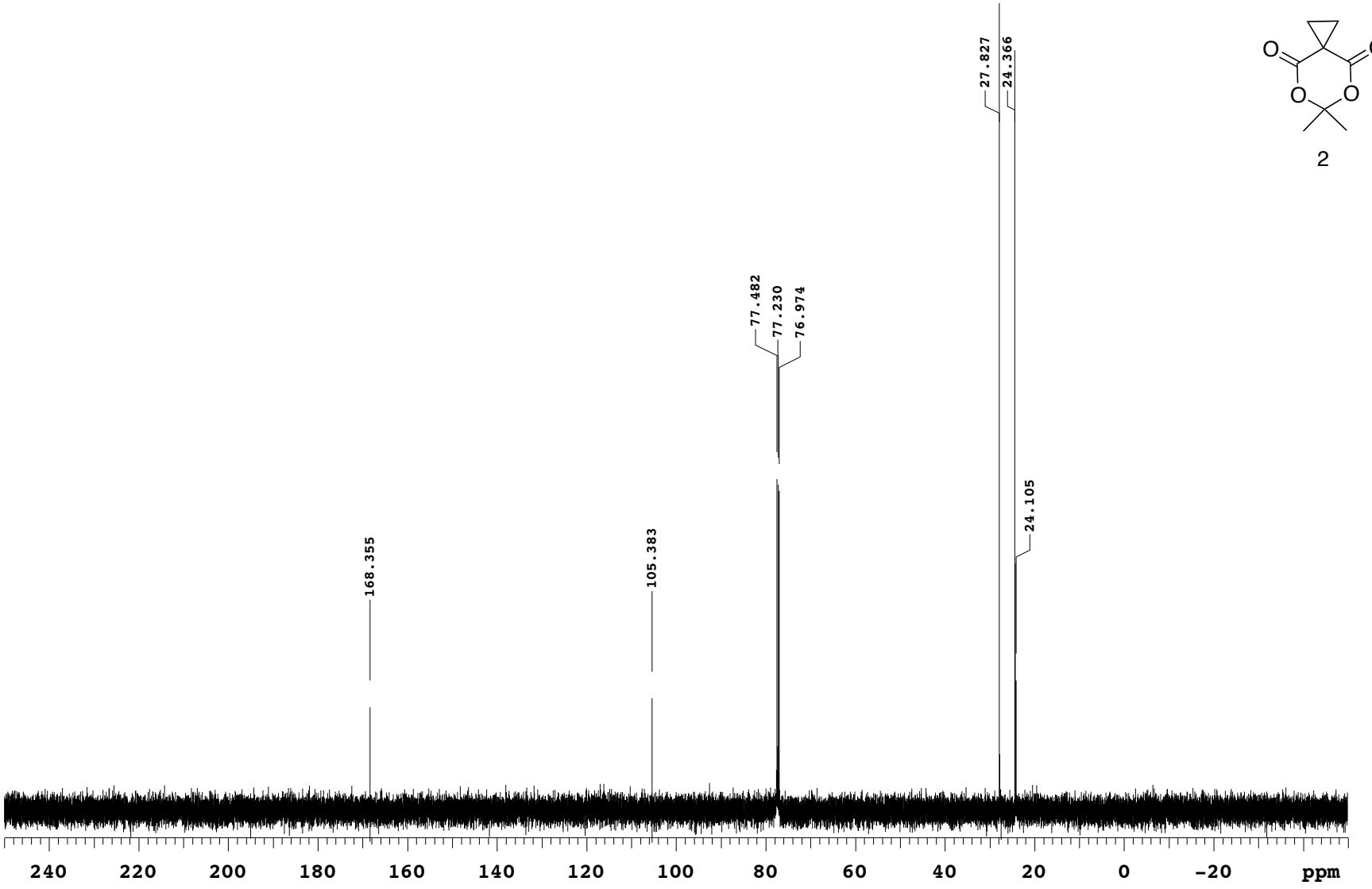
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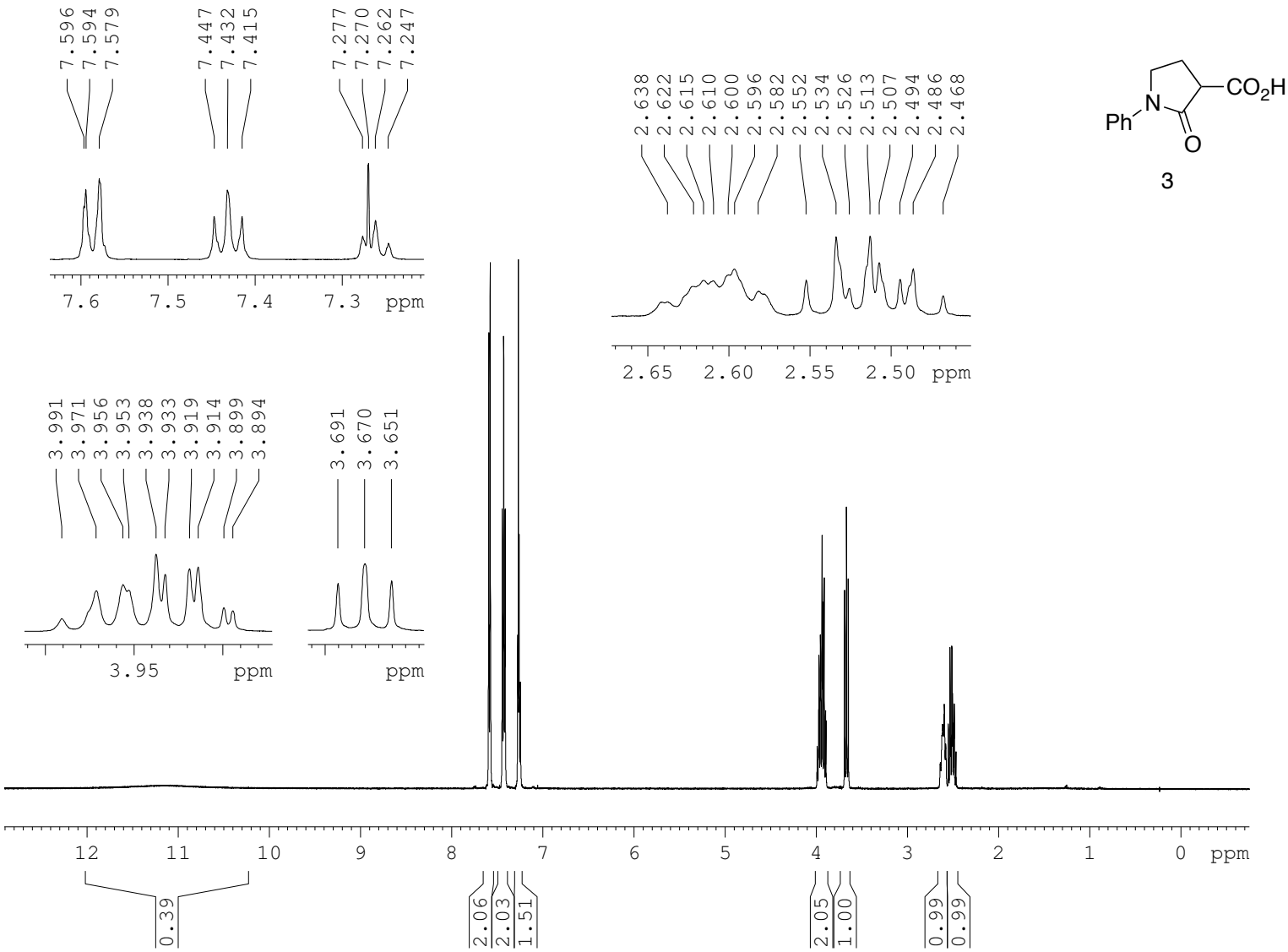
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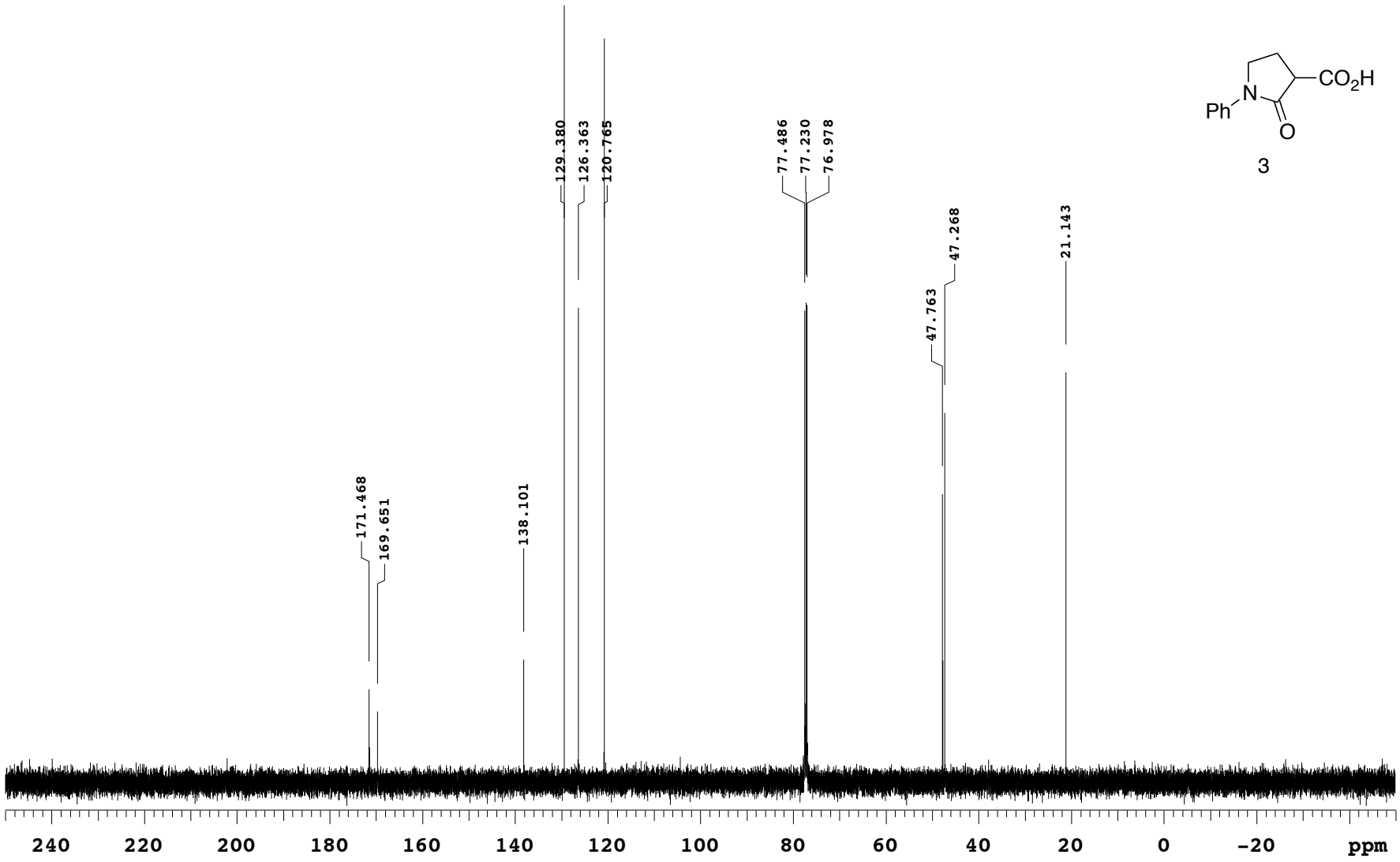
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