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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.

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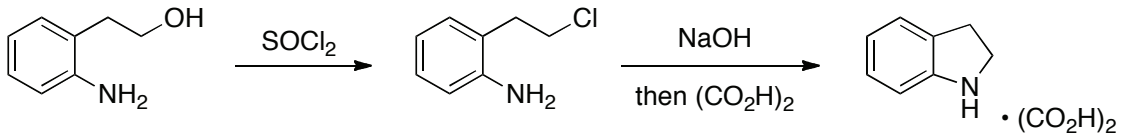
One-Pot Preparation of Cyclic Amines from Amino Alcohols



Submitted by Feng Xu[1] and Bryon Simmons.
Checked by Tomoaki Maehara and Tohru Fukuyama.

1. Procedure

Indoline oxalic acid salt. A 500-mL, 3-necked, round-bottomed flask equipped with a septum through which is inserted a thermocouple probe, an overhead stirrer with a paddle size of 5 cm, and a 50-mL pressure-equalizing addition funnel fitted with a nitrogen inlet, is charged with anhydrous DME (80 mL) (Note 1) and $SOCl_2$ (6.2 mL, 0.087 mol, 1.2 equiv) (Note 2) at ambient temperature. A solution of 2-aminophenethyl alcohol (10.0 g, 0.070 mol, 1.0 equiv) (Note 3) in DME (20 mL) is added dropwise to the stirred solution via the additional funnel over 1–1.5 h, maintaining the internal temperature at 20–30 °C with an external cooling bath (Notes 3 and 4). After addition, the batch is further stirred for 6–7 h at ambient temperature (Note 5). Sodium hydroxide (2.5 N, 128 mL, 0.32 mol, 4.4 equiv), followed by water (16 mL), is added to the reaction mixture via the addition funnel over 30 min, maintaining the internal temperature at <35 °C with an ice/water cooling bath (Note 6). The reaction mixture is then warmed to 60 °C and stirred for 10 h (Note 7). The reaction mixture is cooled to ambient temperature and transferred to a 1-L separatory funnel. *tert*-Butyl methyl ether (MTBE, 100 mL) and water (56 mL) (Note 8) are added. The organic phase is retained and the separated aqueous phase is back extracted with MTBE (56 mL) (Note 9). The combined organic phase is washed with brine (43 mL) (Note 10), dried over sodium sulfate (Notes 11 and 12), and concentrated by rotary evaporation to dryness under reduced pressure (35 °C bath, 60 mmHg). The resulting crude product is dissolved with ethyl acetate (ca. 90 mL) to a volume of 100 mL (Note 13).

A 500-mL, 3-necked, round-bottomed flask equipped with a septum through which is inserted a thermocouple probe, an overhead stirrer with a paddle size of 5 cm, and a 100-mL pressure-equalizing addition funnel fitted

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with a nitrogen inlet, is charged with oxalic acid dihydrate (9.3 g, 0.073 mol, 1.04 equiv) (Note 14) and methanol (14 mL). The resulting stirred solution is warmed to ambient temperature (Note 15). About 30 mL of the above crude product solution in ethyl acetate is added dropwise via the additional funnel at ambient temperature over 15 min. The batch is seeded with crystalline product (3 mg) (Note 16) and stirred for 30 min to form a seed bed slurry. Then, the rest of the product solution in ethyl acetate is added dropwise over 2 h. The slurry is stirred at ambient temperature for 15 h, then filtered through a 100-mL sintered glass funnel (Note 17). The wet cake is washed with 10% methanol in ethyl acetate (2 x 15 mL). Air suction drying affords the oxalic acid salt of indoline (12.0–12.1 g, 79%) as a white crystalline solid (Note 18).

2. Notes

1. Anhydrous 1,2-dimethoxyethane (DME) was obtained from Sigma–Aldrich and used as received. All solvents (*tert*-butyl methyl ether, ethyl acetate, methanol) were obtained from Fisher Scientific and used as received.

2. Thionyl chloride was obtained from Sigma–Aldrich and used as received.

3. 2-Aminophenethyl alcohol (97%) was obtained from Sigma–Aldrich and used as received.

4. The addition of 2-aminophenethyl alcohol was mildly exothermic. A cold water bath was used to maintain the internal temperature between 20–30 °C.

5. Typically, a slurry forms within 1–2 h after addition of thionyl chloride. The submitters report that the reaction progress can be monitored by HPLC. After stirring the reaction mixture for 6–7 h, >99% conversion was achieved as determined by HPLC analysis: YMC Pro Pack C18 column, 4.6 x 250 mm, 5 μm particle size, 40 °C, mobile phase: MeCN/10 mM, pH 6.5 phosphate buffer; MeCN increased from 30% to 70% over 18 min. Flow rate: 1.0 mL/min; UV detector at 210 nm. Retention times: 2-aminophenethyl alcohol, 4.5 min; 2-(2-chloroethyl)aniline, 12.7 min.

6. The addition of NaOH was mildly exothermic. The pH of the quenched solution containing 2-(2-chloroethyl)aniline was ~13–14.

7. By HPLC analysis, >99% of 2-(2-chloroethyl)aniline was converted to the desired cyclized product, indoline. Retention time of

indoline: 9.4 min. The aqueous phase pH decreased to ~9 as HCl formed during the cyclization neutralized a portion of the excess NaOH.

8. The addition of 56 mL water dissolved the precipitated inorganic salts.

9. By HPLC analysis, the product loss to the first aq. phase (~280 mL) was ~5%; the loss to the back-extracted aq. phase was <0.5%.

10. The HPLC assay yield of the final organic phase (~230 mL) was 95%. No product was lost to the brine wash.

11. Anhydrous sodium sulfate was obtained from Sigma–Aldrich and used as received.

12. Sodium sulfate was filtered through a medium porosity sintered glass funnel.

13. Alternatively, the wet organic phase after aqueous workup could be azeotropically dried and solvent-switched to ethyl acetate under reduced pressure.

14. Oxalic acid dihydrate was obtained from Fisher Scientific and used as received.

15. Dissolution of oxalic acid dihydrate in methanol was endothermic.

16. It is recommended to seed the batch to relieve super saturation for a robust crystallization. The seed could be prepared by subdividing 1.6 mL of the crude indoline solution in EtOAc used for salt formation, which is then mixed with a solution of oxalic acid dihydrate (0.15 g) in MeOH (1.6 mL). The mixture is concentrated by rotary evaporation to dryness under reduced pressure (35 °C bath, 60 mmHg). The resulting crude product is triturated with 3.2 mL of 20% MeOH in EtOAc at ambient temperature to give the crystalline indoline oxalic acid salt, which can be used 'as is' to seed the batch or can be filtered and air-suction dried.

17. Typical supernatant concentration of indoline free base: 7–8 mg/mL by HPLC analysis.

18. Indoline oxalic acid salt has the following physical and spectroscopic properties: 99.5% purity (HPLC conditions in note 5, retention times: oxalic acid, 2.2 min; indoline, 9.4 min); mp = 128–129 °C (Lit.[2] mp = 128 °C); ^{1}H NMR (500 MHz, d_6-DMSO) δ: 2.90 (t, J = 8.3 Hz, 2 H), 3.40 (t, J = 8.3 Hz, 2 H), 6.55 (m, 2 H), 6.91 (m, 1 H), 7.03 (m, 1 H), 10.91 (s, br, 1.5 H); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 29.1, 46.0, 110.4, 119.1, 124.3, 126.9, 129.9, 149.3, 161.6; Anal. Calcd for $C_{10}H_{11}ClNO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.37; H, 5.28; N, 6.67.

Handling and Disposal of Hazardous Chemicals

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3. Discussion

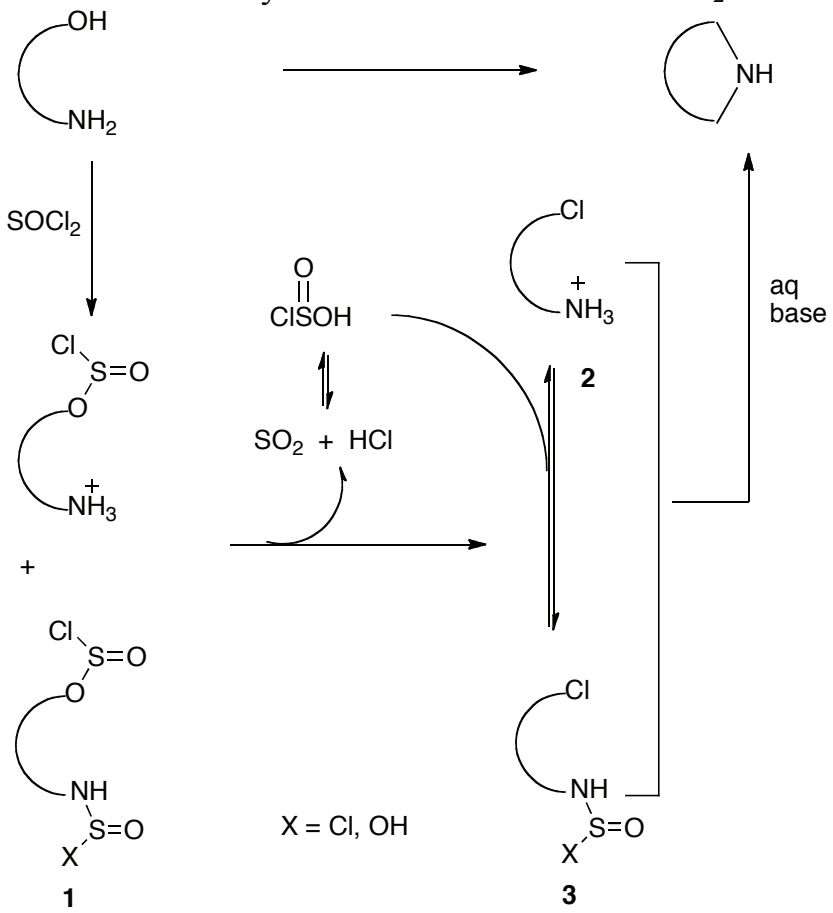
Many methods[3,4] have been developed to prepare cyclic amines through cyclodehydration of amino alcohols. Classical indirect cyclodehydration of amino alcohols typically involves a tedious sequence of protection/activation/cyclization/deprotection. Although commonly implemented,[3,4] these indirect approaches require multiple chemical steps that reduce the overall efficiency of the transformation.

Direct cyclodehydration of amino alcohols is one of the most straight-forward approaches to prepare cyclic amines.[5-9] However, direct chlorination of an amino alcohol free base with $SOCl_2$, which was discovered several decades ago, has not been well studied.[10] Its application to prepare cyclic amines is underutilized due to the expected competition[10] between *N*- and *O*-sulfinylation and subsequent 'inevitable' side reactions. Low yields are typically an issue for this reaction[12-14] when $SOCl_2$, as reported,[13,14] is typically added to a solution of the amino alcohol in the presence or absence of a base.

The development of the one-pot process described here is based on a rational mechanistic understanding of the chlorination pathway (Scheme 1), which is further confirmed by NMR studies.[15] Unlike the prevailing literature procedure, a clean cyclodehydration transformation is achieved by 'inverse' addition of a solution of the free amino alcohol in an appropriate

solvent (such as DME, *i*-PrOAc, and CH_2Cl_2) to a solution of $SOCl_2$. As such, the amino alcohol becomes instantly protonated upon contact with HCl as it is generated in the $SOCl_2$ solution. Because the amino alcohol is added slowly to keep a low concentration of its protonated salt in the reaction mixture, the protonated amino alcohol would be expected immediately to react with excess $SOCl_2$ and to retain a kinetically favorable, homogenous reaction solution before it could crystallize.[12,15] Thus, complete conversion could be achieved. In addition, the minor *N*-sulfinylated intermediates (such as sulfamic chloride **1**) that could be formed by reacting with $SOCl_2$ are also preserved and further converted to the corresponding chlorides (such as **2** and **3**, X = Cl) in the acidic inverse-addition reaction media, because the nucleophilic amine species that could react with these *N*-sulfinylated intermediates are either quenched by HCl or converted to sulfamic acids with $ClSO_2H$.

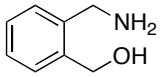
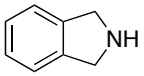
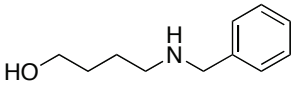
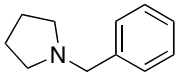
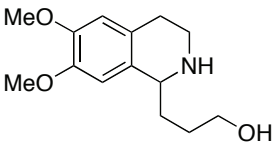
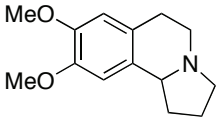
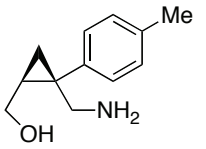
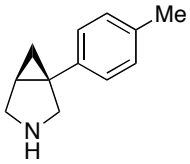
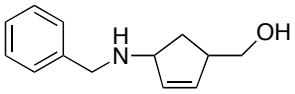
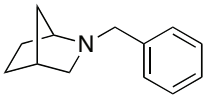
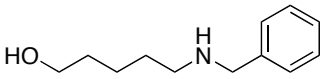
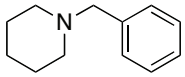
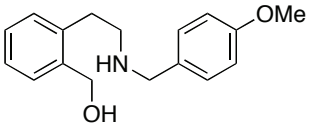
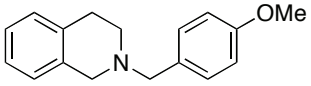
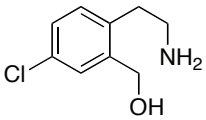
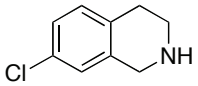
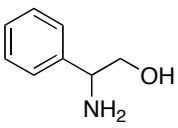
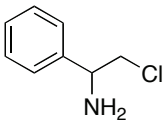
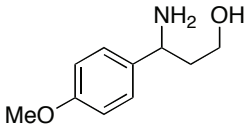
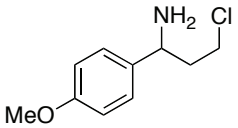
Scheme 1. Reaction Pathways for Chlorination with $SOCl_2$



The examples shown in Table 1 illustrate the scope of this simple, practical one-pot process. We were gratified to observe that all of the amino

alcohols examined were cleanly and efficiently converted to the

Table 1. Direct Chlorination/Cyclization of Amino Alcohols

		Conditions[a]			
Entry	Starting Material	Chlorination	Cyclization	Product	Yield (%)[b]
1		$(MeOCH_2)_2$ rt	rt		83[c]
2		$(MeOCH_2)_2$ rt	rt		94
3		CH_2Cl_2 40 °C	$(MeOCH_2)_2$ 40 °C, 3 h		95
4		*i*-PrOAc rt	rt		92[c]
5		CH_2Cl_2 rt	$(MeOCH_2)_2$ 40 °C, 3 h		90
6		$(MeOCH_2)_2$ rt	rt		92[c]
7		$(MeOCH_2)_2$ rt	40 °C		96[c]
8		$(MeOCH_2)_2$ rt	rt		79
9		$(MeOCH_2)_2$ rt			99
10		$(MeOCH_2)_2$ 40 °C			99

[a] Unless otherwise noted, the cyclization was carried out in the same solvent as the chlorination. [b] Unless otherwise noted, isolated yield through SiO_2 column chromatography purification. [c] Isolated as its HCl salt.

corresponding chloroamine in nearly quantitative yield. Full conversion to the desired chloride was observed within 5 h for most examples; however, some substrates (for example**,** Table 1, entries 3 and 10) required heating at 40 °C for several hours to achieve complete conversion. For a direct cyclodehydration transformation, the crude chloroamine intermediates were then treated with base. The intramolecular cyclization rate is dependent on the substrates as expected. Attempts to cyclize the readily formed 1,2- and 1,3-chloroamines **(**Table 1, entries 9 and 10) even at elevated temperatures resulted in complicated mixtures containing only small amounts of desired cyclized product.[16]

1. Department of Process Chemistry, Merck Research Laboratory, Rahway, NJ 07065, USA. E-mail: feng_xu@merck.com

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9. For reviews on application of the Appel reaction and its variants, see: (a) Castro, B. R. *Org. Reactions* **1983**, *29*, 1. (b) Appel, R. *Angew. Chem.*, *Int. Ed. Engl.* **1975**, *14*, 801.

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16. For examples of relative rates of cyclization as a function of ring size: see (a) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1. (b) Winnik, M.A. *Chem. Rev.* **1981**, *81*, 491. (c) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

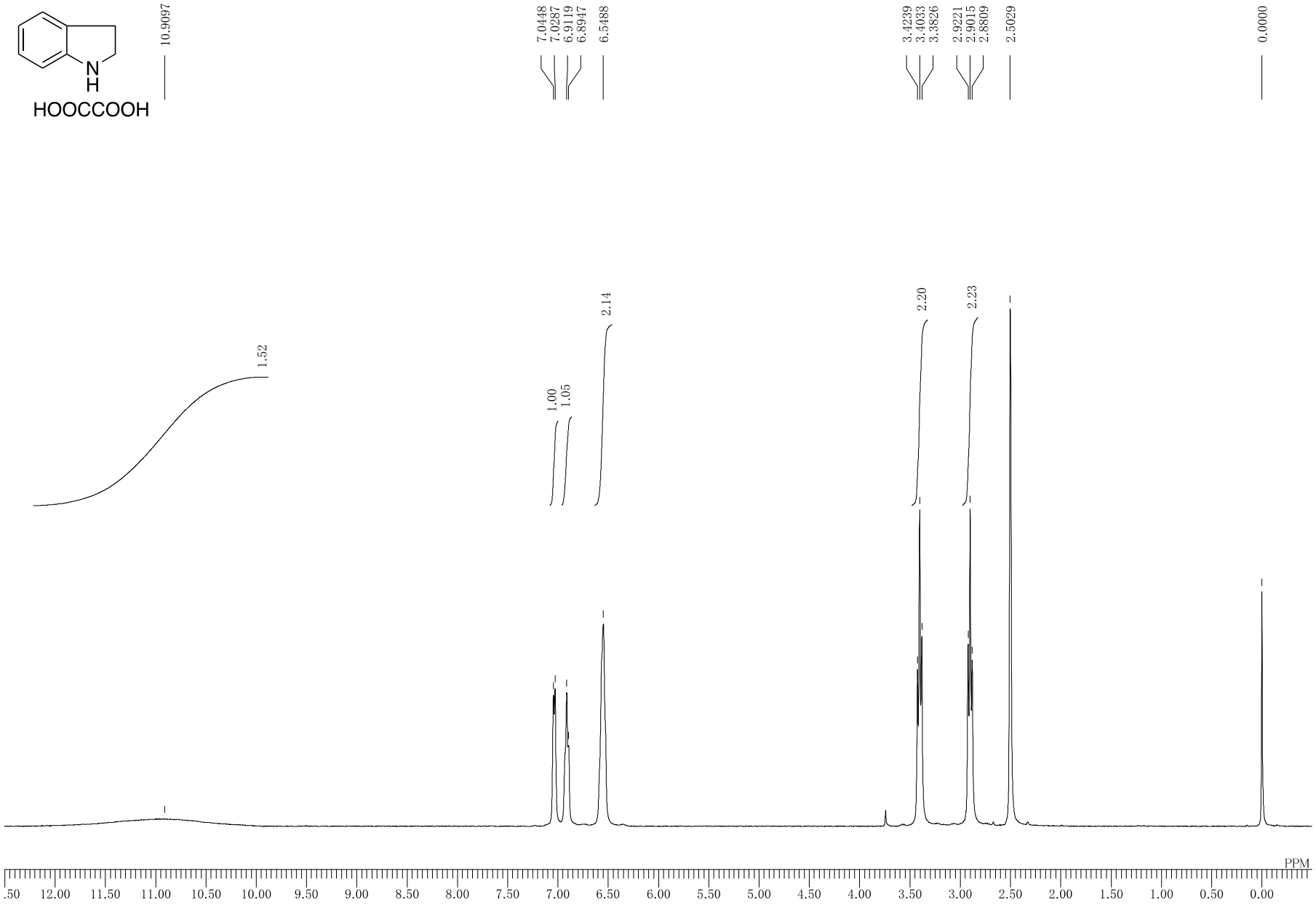
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Thionyl chloride; (7719-09-7)
2-Aminophenethyl alcohol; (5339-85-5)
2-(2-Chloroethyl)aniline; (762177-99-1)
Oxalic acid dihydrate; (6153-56-6)
Indoline; (486-15-1)

Dr. Feng Xu obtained his Ph.D. at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences in 1989 where he worked on the total synthesis of complex natural products. He joined SIOC before moving to the USA. After he undertook a postdoctoral fellow with Professors Martin Kuehne and James Dittami, and completed the total syntheses of several complex indole alkaloids, he joined Merck Process Research Department in 1996.

Dr. Bryon Simmons received a B.S. degree in chemistry in 2002 from Brigham Young University and a Ph.D. degree in 2010 with Professor David W. C. MacMillan at Princeton University. He currently works at Merck in the Process Research Department.

Tomoaki Maehara was born in Shizuoka, Japan in 1989. He received his B.S.in 2012 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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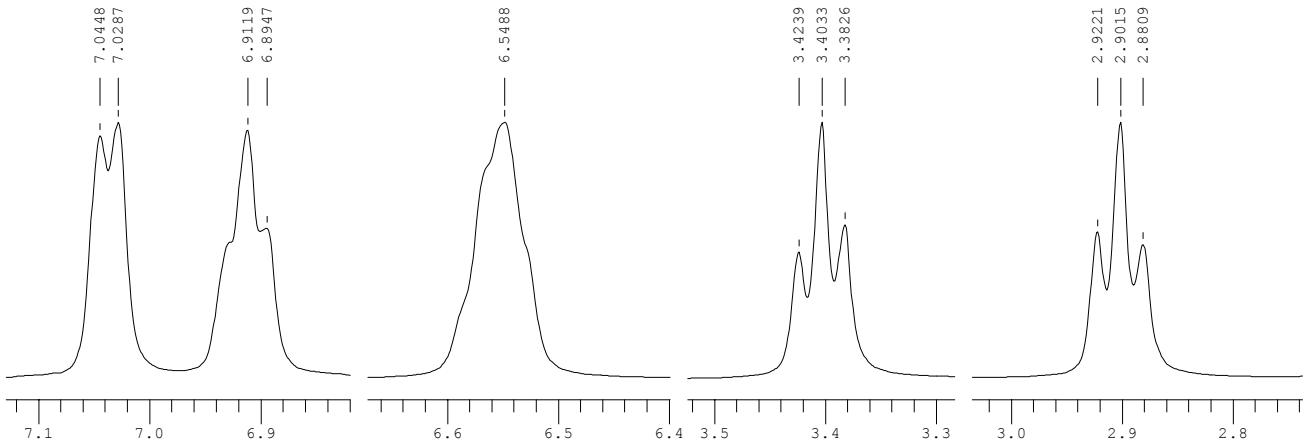
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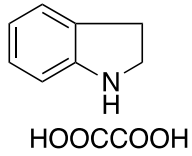
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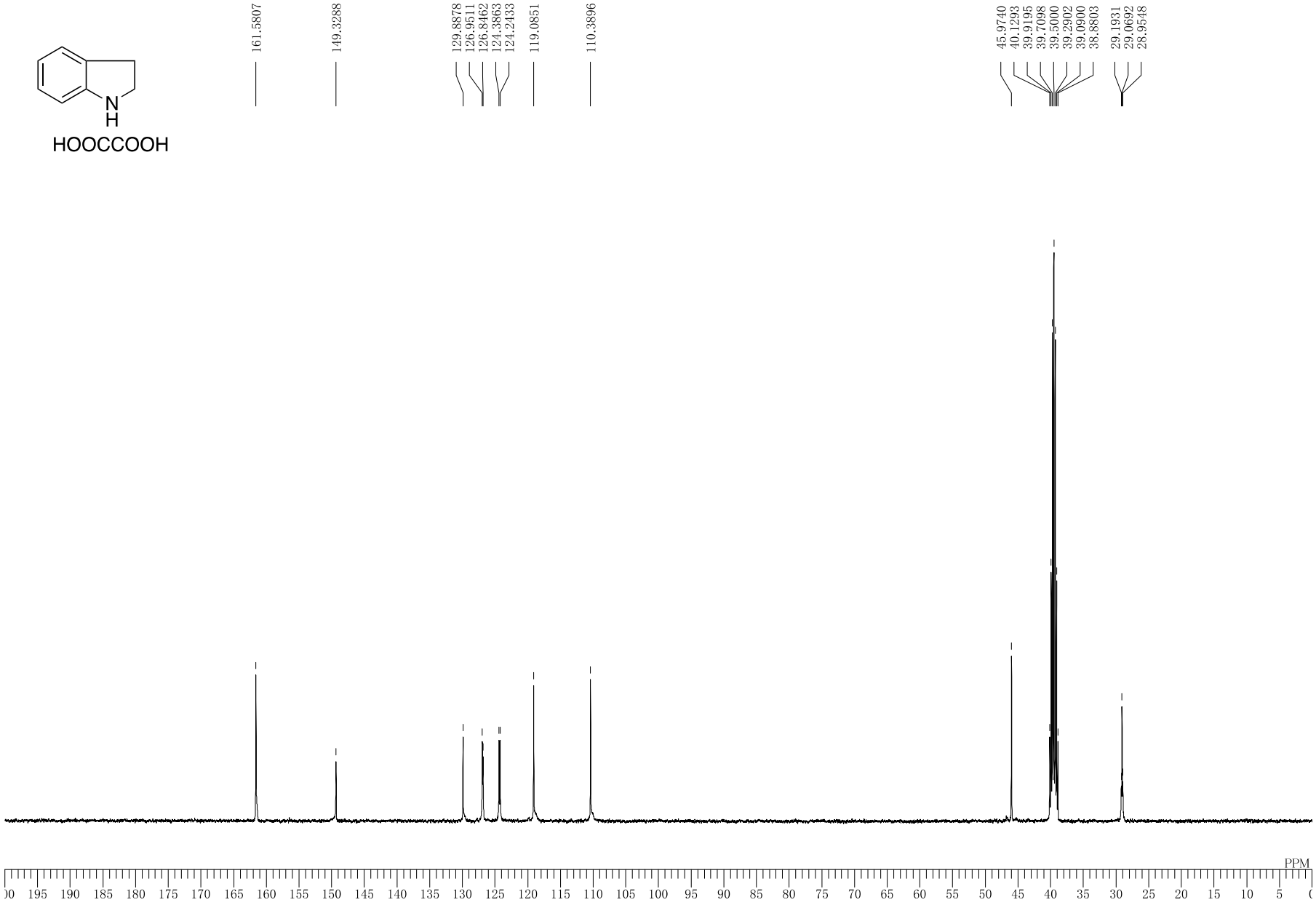
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