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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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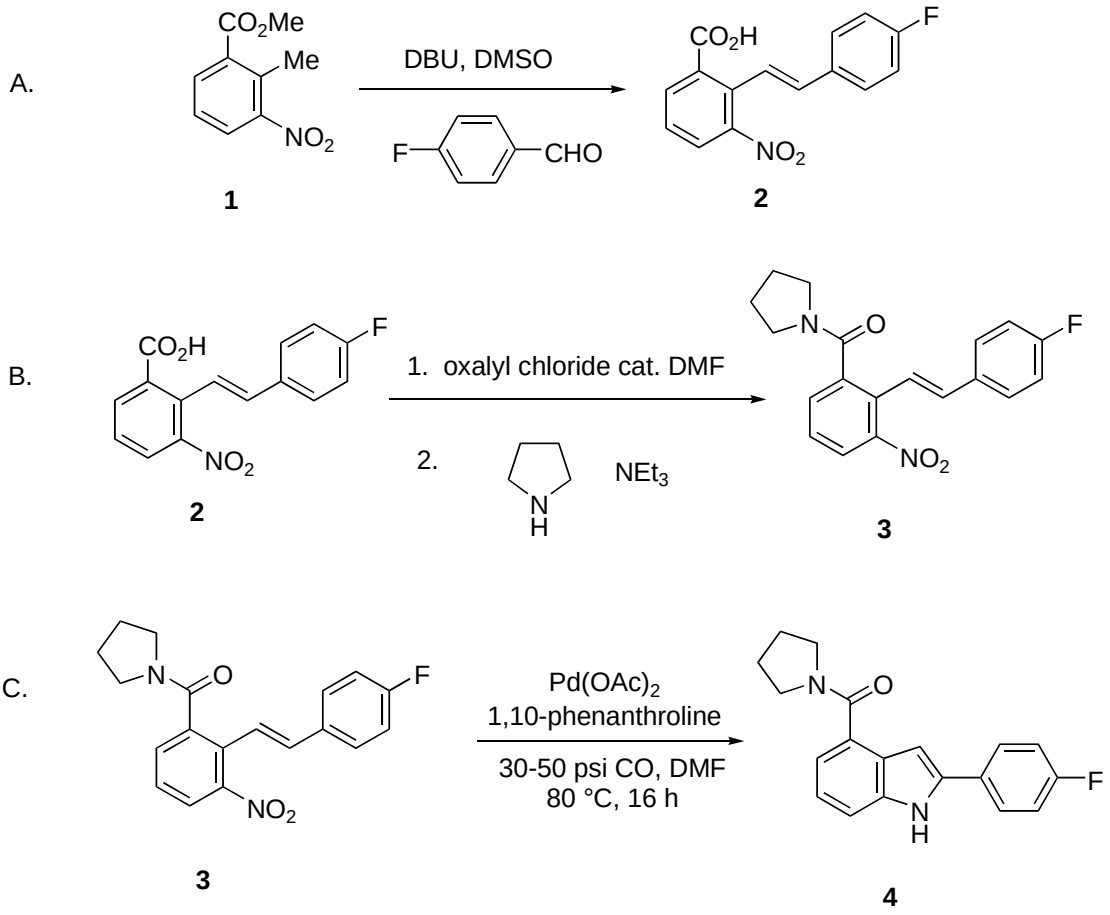
SYNTHESIS OF 2-ARYLINDOLE-4-CARBOXYLIC AMIDES: [2-(4-FLUOROPHENYL)-1*H*-INDOL-4-YL]-1-PYRROLIDINYLMETHANONE



Submitted by Jeffrey T. Kuethe[1] and Gregory L. Beutner.
Checked by Scott E. Denmark and Joseck M. Muhuhi.

1. Procedure

A. 2-[trans-2-(4-Fluorophenyl)vinyl]-3-nitrobenzoic Acid **2.** A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, a nitrogen inlet, a rubber septum, and a temperature probe is charged with methyl 2-methyl-3-nitrobenzoate **1** (7.50 g, 37.3 mmol) (Note 1) and anhydrous DMSO (52.5 mL) (Note 2). To the resulting mixture is charged sequentially 4-fluorobenzaldehyde (6.00 mL, 6.94 g, 1.5 equiv) (Note 3) and DBU (11.24 mL, 11.35 g, 2.00 equiv) (Note 4). The homogeneous, brown solution is then stirred at room temperature for 20 h

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and then heated to an internal temperature of 55 °C for 4 h (Notes 5 and 6). The reaction mixture is then allowed to cool to room temperature. In a separate 500-mL, three-necked flask equipped with a magnetic stirring bar and a temperature probe is added water (100 mL) and MTBE (100 mL) (Note 7) and this biphasic mixture is cooled in an ice bath to 0 – 5 °C. The above reaction mixture is then transferred to a 125-mL pressure-equalizing addition funnel and the reaction flask is rinsed with MTBE (15–25 mL). The crude reaction mixture is then added dropwise to the water/MTBE solution at such a rate that the internal temperature of the biphasic quench solution is maintained < 5 °C (Note 8). The mixture is then transferred to a 500-mL separatory funnel and the layers are allowed to separate. The organic layer is discarded. The yellow aqueous layer is washed with MTBE (60 mL). The aqueous layer is then made acidic (pH 1) by the addition of 6 N H_2SO_4 (15 mL, 2.40 equiv) (Note 9) and is extracted with EtOAc (100 mL). The aqueous layer is extracted with an additional portion of EtOAc (60 mL) and the combined organic extracts (Note 10) are concentrated by rotary evaporation (30 °C, 40 mmHg) to give a yellow oil. The oil is re-dissolved in MeOH (55 mL) (Note 11), a magnetic stir bar is placed in the flask and water (175 mL) is added dropwise to the stirred solution over 20 min. The yellow, crystalline slurry of the product is allowed to stir at room temperature for 45 min. The slurry is then filtered through a 150-mL fritted-glass funnel of medium porosity. The wet solid is washed with water (60 mL) and then dried under a vacuum/N_2 sweep (Note 12) for 8 h to provide 2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrobenzoic acid **2** as a bright yellow powder (8.89–9.21 g, 83–86%) (Notes 13, 14).

B. {2-[trans-2-(4-Fluorophenyl)vinyl]-3-nitrophenyl}-1-pyrrolidinylmethanone **3**. A single-necked, 500-mL round-bottomed flask equipped with a magnetic stirring bar is charged 2-[*trans*-2-(4-fluorophenyl)vinyl]-3-nitrobenzoic acid (**2**) (8.50 g, 29.6 mmol) and CH_2Cl_2 (65 mL) (Note 15). The flask is closed with a rubber septum and placed under nitrogen by piercing the septum with an 18-gauge needle. Oxalyl chloride (3.37 mL, 4.88 g, 38.5 mmol, 1.30 equiv) (Note 16) is added via syringe through the septum followed by the addition of 2 drops of DMF (Note 17). The resulting mixture is stirred at room temperature for 1.5 h and then concentrated by rotary evaporation (23 °C, 40 mmHg). To the resulting crude, yellow acid chloride is added CH_2Cl_2 (25 mL) and the solution is concentrated by rotary evaporation (23 °C, 40 mmHg). In a separate 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring

bar, a nitrogen inlet, a rubber septum, 125-mL pressure-equalizing addition funnel, and a temperature probe is charged CH_2Cl_2 (50 mL), triethylamine (6.20 mL, 4.49 g, 44.4 mmol, 1.5 equiv) (Note 18), and pyrrolidine (3.18 mL, 2.74 g, 38.5 mmol, 1.30 equiv) (Note 19) and the mixture is cooled in an acetone/ice bath to an internal temperature of < 5 °C. The crude acid chloride is dissolved in CH_2Cl_2 (45 mL) and this solution is transferred to the addition funnel. The acid chloride is added dropwise to the stirred pyrrolidine solution at such a rate that the internal temperature is maintained < 23 °C. Upon completion of the addition of the acid chloride solution, the mixture is stirred at room temperature for 30 min (Note 5). The mixture is then diluted with 2 N HCl (60 mL) (Note 20) and is transferred to a 500-mL separatory funnel and the layers separated. The organic layer is washed with brine (60 mL) and is then concentrated under reduced pressure (23 °C, 40 mmHg) (Note 10), diluted with MeOH (60 mL) and re-concentrated under reduced pressure (23 °C, 40 mmHg) to give a crude, yellow solid. The solid is slurried in MeOH (150 mL) and water (300 mL) is added dropwise over 20 min (Note 21). The slurry is stirred at room temperature for 1 h and then is filtered through a 150-mL fritted-glass, medium porosity funnel. The wet solid is washed with water (60 mL) and dried under a vacuum/N_2 sweep (Note 11) for 8 h to provide {2-[*trans*-2-(4-fluorophenyl)vinyl]-3-nitrophenyl}-1-pyrrolidinyl-methanone (**3**) as a yellow, crystalline solid or a yellow powder (9.90-10.0 g, 98-99%) (Notes 22, 23).

C. Caution! Due to the toxicity of carbon monoxide and the potential risk associated in handling pressurized glassware, it is recommended that this transformation be carried out in a well vented fume hood with a blast shield and the hood sash down or preferably conducted in an autoclave or metal reaction vessel. Users should exercise extreme caution at all times.

[2-(4-Fluorophenyl-1H-indol-4-yl]-1-pyrrolidinylmethanone **4**. To a 1-liter glass-lined pressure tube was added sequentially {2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrophenyl}-1-pyrrolidinylmethanone **3** (8.00 g, 23.5 mmol), $Pd(OAc)_2$ (54 mg, 0.235 mmol, 0.01 equiv) (Note 24), 1,10-phenanthroline (300 mg, 1.65 mmol, 0.07 equiv) (Note 25), and DMF (80 mL) (Note 16). The resulting reaction vessel is inserted into a Rocker Assembly (Note 26) and purged with N_2 (60 psi) three times (Note 27). The mixture is then purged with CO (60 psi) three times, (Note 28) and the final pressure set to 50 psi at continuous flow. The mixture is then heated to a jacket temperature of 80 °C and stirred at this temperature for 16 h (Note 5).

The reaction mixture is allowed to cool to room temperature and the system is vented to atmospheric pressure. The vessel is pressurized with N_2 (60 psi) and vented three times to remove all residual amounts of CO. The reaction mixture is then filtered through 10 grams of Celite (Note 29) in a 150-mL fritted-glass funnel of medium porosity into a single-necked flask rinsing both the reaction flask and the filter cake with DMF (60 mL). To the yellowish-orange filtrate is added a stir bar and the flask is equipped with a 250-mL pressure-equalizing addition funnel. The addition funnel is charged with 1 M H_3PO_4 (225 mL, Note 30) and 75 mL of this solution is added to the DMF solution over 15 min (Note 31), at which point the solution becomes turbid and the product begins to crystallize. The resulting slurry is stirred for 30 min and the remaining 1 M H_3PO_4 (150 mL) is added over 15 min. The slurry of the product is stirred an additional 30 min and is filtered through a 150-mL, medium-porosity fritted-glass funnel. The wet solid is washed with water (2 x 100 mL) and then is dried under a vacuum/N_2 sweep (Note 12) for 8 h to provide [2-(4-fluorophenyl-1*H*-indol-4-yl]-1-pyrrolidinylmethanone **4** as an off-white crystalline solid (6.92 g, 96%) (Notes 32, 33).

2. Notes

1. Methyl 2-methyl-3-nitrobenzoate **1** (97%) was purchased from Aldrich Chemical Company, Inc. and used as received.

2. Anhydrous DMSO was purchased from Aldrich Chemical Company, Inc. and was used as received.

3. 4-Fluorobenzaldehyde (98%) was purchased from Aldrich Chemical Company, Inc. and was purified by distillation (175-177 °C, atmospheric pressure under nitrogen) prior to its use in order to eliminate any traces of 4-fluorobenzoic acid.

4. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene (98%)) was purchased from Aldrich Chemical Company, Inc. and used as received.

5. All reactions were monitored by TLC using Merck silica gel 60 F_{254}, 250 μ, 1 × 10 cm, TLC plates using hexane/EtOAc, 1:1 as the eluent. The following R_f values were obtained: compound **1** (0.76), compound **2** (0.13), compound **3** (0.18), compound **4** (0.26). The submitters used reverse phase HPLC employing the following conditions: Zorbax Eclipse Plus C18 Rapid Resolution HT column (4.6 x 50 mm, 1.8-micron, Agilent part number: 959941-902) with a standard gradient of 10:90 MeCN/0.1% H_3PO_4

to 95:5 MeCN/0.1% H_3PO_4 over 5 min and hold at 95:5 MeCN/0.1% H_3PO_4 for 1 min, then back to 10:90 MeCN/0.1% H_3PO_4 at 8 min, detection at 210 nm. Retention times are as follows: compound **1** (3.78 min), compound **2** (3.92 min), compound **3** (4.03 min), compound **4** (3.73 min).

6. Typical conversion after 20 h was 80% by HPLC analysis. Heating for 4 h drives the conversion to > 90% by HPLC analysis.

7. Methyl *tert*-butyl ether was purchased from Aldrich Chemical Company, Inc. and was used as received.

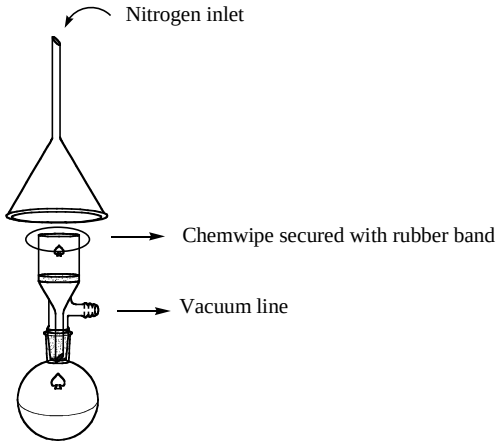
8. The temperature should be maintained below 5 °C in order to avoid hydrolysis of any remaining methyl 2-methyl-3-nitrobenzoate **1** to 2-methyl-3-nitrobenzoic acid which will contaminate the product. Under these conditions, no hydrolysis occurs. The third neck is left open.

9. 6 N H_2SO_4 was prepared from 12 N HCl purchased from Fisher Scientific.

10. The organic extracts will likely contain some water; however, there is no need to dry the extracts over any drying agent such as $MgSO_4$.

11. Methanol was purchased from Aldrich Chemical Company, Inc. and was used as received.

12. The product is dried under vacuum/N_2 sweep under house vacuum with house nitrogen at full flow using the apparatus below for the indicated time. Alternatively, the solid can be dried in a vacuum oven (10–25 mmHg, 35 °C) for the same amount of time.



13. Product **2** displayed the following physicochemical properties: bright yellow solid; mp 166–168 °C (sealed tube); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.49 (d, *J* = 16.5 Hz, 1 H), 7.03 (tt, *J* = 8.9, 2.5 Hz, 2 H), 7.42 (dt, *J* = 6.1, 2.5 Hz, 2 H), 7.45 (d, *J* = 16.5 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.94 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1 H), 11.7 (br s, 1 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 115.7 (d, *J* = 21.2 Hz), 122.3 (d, *J* = 2.8 Hz), 127.7, 127.9, 128.5 (d, *J* = 8.3 Hz), 131.1, 132.5 (d, *J* = 3.7 Hz), 133.1, 134.1, 134.3, 150.9, 162.8 (d, *J* = 246.6 Hz), 171.5; ^{19}F NMR ($CDCl_3$, 500 MHz) δ: –113.9. Anal. Calcd. For $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.32; H, 3.45; N, 4.87.

14. The submitters reported the mp at 156–157 °C, 10 ˚C lower than that of the checkers. As both samples passed elemental analysis, the discrepancy most likely arises from two different crystal forms.

15. Methylene chloride was purchased from Aldrich Chemical Company, Inc. and was used as received.

16. Oxalyl chloride (98%) was purchased from Aldrich Chemical Company, Inc. and was used as received.

17. Anhydrous DMF was purchased from Aldrich Chemical Company, Inc. and was used as received.

18. Triethylamine (99.5%) was purchased from Aldrich Chemical Company, Inc. and was used as received.

19. Pyrrolidine (99%) was purchased from Aldrich Chemical Company, Inc. and was used as received.

20. 2 N HCl was prepared from 12 N HCl purchased from Fisher Scientific.

21. The submitters used MeOH (60 mL) and water (120 mL), which the checkers found gave a yellow powder. When checkers used MeOH (150 mL) and water (300 mL) the product obtained was a yellow, crystalline solid. The extra MeOH helps in forming more fine particles.

22. Product **3** displayed the following physicochemical properties: yellow powder or yellow crystalline solid; mp 123–124 °C (sealed tube); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.78 (m, 4 H), 3.05 (t, *J* = 6.3 Hz, 2 H), 3.52 (t, *J* = 6.5 Hz, 2 H), 6.91 (d, *J* = 16.5 Hz, 1 H), 7.03 (tt, *J* = 8.9, 2.5 Hz, 2 H), 7.24 (d, *J* = 16.5 Hz, 1 H), 7.42 (tt, *J* = 7.3, 2.5 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.59 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.94 (dd, *J* = 8.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 24.3, 25.8, 45.8, 47.7, 115.8 (d, *J* = 22.1 Hz), 120.1 (d, *J* = 2.8 Hz), 124.9, 128.2, 128.5 (d, *J* = 8.3 Hz), 12.2, 131.5, 132.5 (d, *J* = 3.7 Hz), 135.3, 139.2, 148.6, 162.9 (d, *J* = 248.6 Hz), 167.4; ^{19}F NMR ($CDCl_3$, 500 MHz) δ: –113.5. Anal. Calcd. For $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.99; H, 5.05; N, 8.19.

23. The submitters reported the mp at 94–95 °C, 30 °C lower than that of the checkers. As both samples passed elemental analysis, the discrepancy most likely arises from two different crystal forms.

24. Palladium (II) acetate (min. 98%) was purchased from Strem Chemicals, Inc. and was used as received.

25. 1,10-Phenanthroline (99%) was purchased from Aldrich Chemical Company, Inc. and was used as received.

26. Submitters used a 4300 mL Fluitron Rocker Assembly, while the checker's rocker assembly was purchased from American Instruments CC Inc. A similar type reaction apparatus may be utilized for this transformation, see Söderberg, B. C.; Shriver, J. A.; Wallace, J. M. *Org. Synth.* **2003**, *80*, 75-84; however, it is strongly recommended that the reaction be conducted in an autoclave or metal reaction vessel with glass liner as described in this procedure. http://www.fluitron.com/vessels.html

27. Submitters evacuated the reaction vessel under reduced pressure (10-30 mm Hg).

28. Carbon monoxide was purchased from Matheson Trigas Co. and was used as received. Submitters used CO (30 psi) while checkers used CO (30 psi) for small-scale reaction (4.7 mmol) and CO (50 psi) for the full scale runs.

29. Celite® 545 coarse was purchased from Aldrich Chemical Company, Inc. and was used as received.

30. 1 M H_3PO_4 was prepared by dilution with water of 85% *o*-H_3PO_4 (115.3 g, Fisher Scientific, HPLC grade) to a final volume of 250 mL.

31. The addition of 75 mL of 1 M H_3PO_4 to the DMF filtrate is slightly exothermic from room temperature to 35–40 °C, but is not detrimental to the crystallization of the product.

32. Compound **4** displayed the following physicochemical properties: off-white to slight yellow crystalline solid: mp 184–185 °C (sealed tube); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.84 (q, *J* = 6.6 Hz, 2 H), 1.98 (q, *J* = 7.0 Hz, 2 H), 3.39 (t, *J* = 6.8 Hz, 2 H), 3.76 (t, *J* = 7.3 Hz, 2 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 7.00 (tt, *J* = 8.8, 2.3 Hz, 2 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 7.16 (dd, *J* = 7.5, 0.5 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 7.56 (tt, *J* = 7.3, 2.3 Hz, 1 H), 9.43 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 24.6, 26.2, 45.9, 49.0, 98.7, 112.6, 115.7 (d, *J* = 22.1 Hz), 118.5, 121.3, 126.3, 127.1 (d, *J* = 7.4 Hz), 128.4 (d, *J* = 3.7 Hz), 128.6, 137.4, 138.3, 162.3 (d, *J* = 247.6 Hz), 170.1; ^{19}F NMR ($CDCl_3$, 500 MHz) δ: –115.0. Anal. Calcd. For $C_{19}H_{17}FN_2O$: C, 74.01; H, 5.56; N, 9.07. Found: C, 74.11; H, 5.61; N, 9.08.

33. The submitters reported the mp at 130–131 °C, over 50 °C lower than that of the checkers. As both samples passed elemental analysis, the discrepancy most likely arises from two different crystal forms.

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.

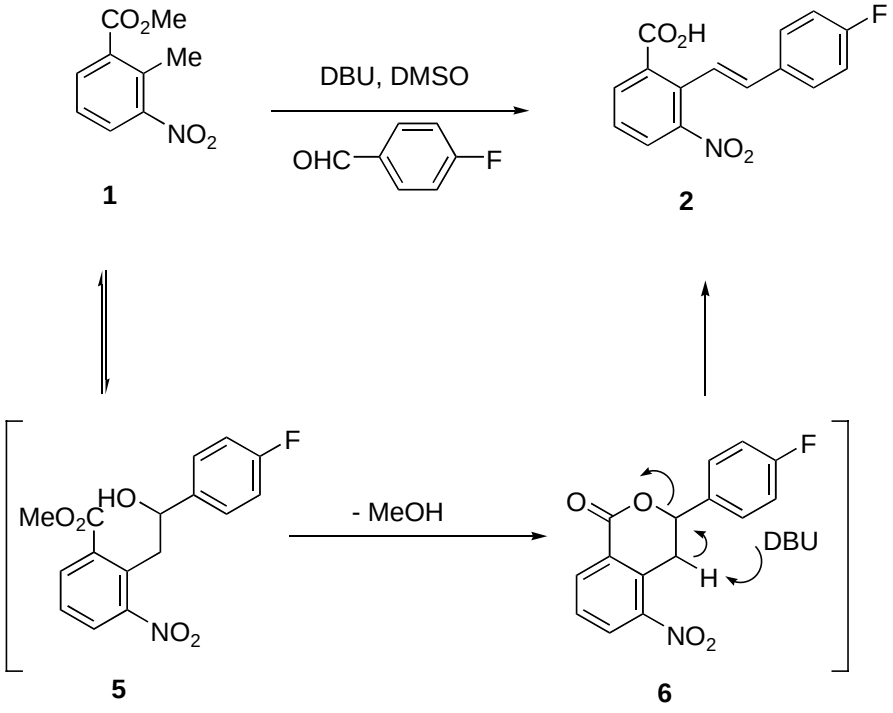
3. Discussion

The palladium-catalyzed reductive cyclization of aromatic nitrostyrene compounds employing carbon monoxide as the stoichiometric reductant has recently emerged as a highly versatile method for the construction of indoles due to superior yields, diminished amounts of reaction by-products, functional group compatibility, and favorable environmental impact.[2,3] The widespread use of *ortho*-nitrostyrenes as indole precursors has been limited by available methods for their preparation. Traditional approaches have relied on Wittig reactions of either 2-nitrobenzaldehydes or 2-nitrophosphonium and phosphonate salts.[4] Alternatively, cross-coupling approaches involving 2-halonitrobenzenes or 2-nitrophenylstannanes have received considerable attention as an attractive method for the preparation of a range of *ortho*-nitrostyrenes.[2] While each of these approaches offer certain advantages, they often require multiple steps for the construction of the appropriate starting materials and generally require purification by chromatography. These strategies also have a high environmental burden since they suffer from poor atom economy and generate a significant amount of phosphorous or tin byproducts. We have demonstrated that reactions of 2-nitrotoluenes or 2-trimethylsilylmethylnitrobenzenes with aromatic aldehydes via an addition/elimination protocol is an effective, high yielding method for the construction of *ortho*-nitrostyrenes and their subsequent conversion to indoles.[5]

The procedure described herein illustrates the concise preparation of [2-(4-fluorophenyl)-1*H*-indol-4-yl]-1-pyrrolidinylmethanone **4** in 75% overall yield from commercially available methyl 2-methyl-3-nitrobenzoate **1**.[6] Reaction of **1** with 4-fluorobenzaldehyde in the presence of DBU in DMSO is reversible leading to intermediate **5** (Scheme 1). Based on the juxtaposition of the methyl ester with the reacting center and its capacity to serve as an intramolecular trap, cyclization to lactone intermediate **6** occurs. In the presence of a second equivalent of DBU, deprotonation followed by elimination of the carboxylate anion furnishes nitrosytrene benzoic acid **2.**

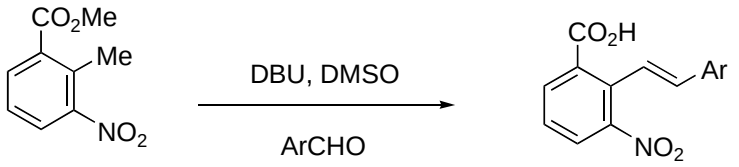
After an extractive work up to remove excess 4-fluorobenzaldehyde, the product **2** is obtained in 84% isolated yield after crystallization from MeOH/water. The reaction sequence is general and allows for the preparation of an array of structurally diverse nitrostyrene benzoic acids in good to excellent yield (Table 1). Substrates containing electron donating (entries 1- 4) or electron withdrawing groups (entry 5) participate equally as well. In all cases, the *trans*-nitrostyrene benzoic acids were the exclusive products.

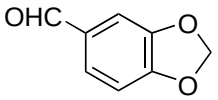
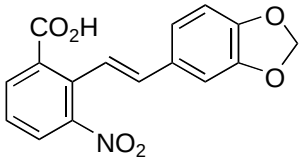
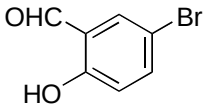
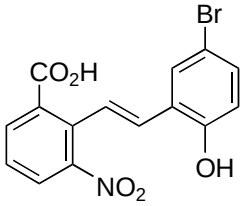
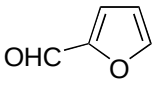
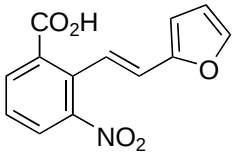
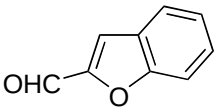
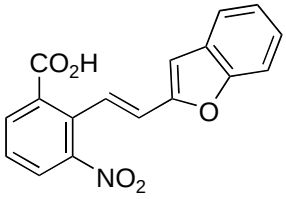
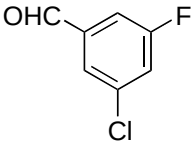
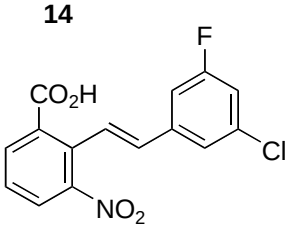
Scheme 1.



The preparation of 2-arylindole-4-carboxylic amide **4** involved conversion of **2** to the corresponding acid chloride with oxalyl chloride followed by reaction with pyrrolidine to give amide **3** followed by reductive cyclization. Reductive cyclization was carried out in the presence of 1 mol% $Pd(OAc)_2$, 7 mol% 1,10-phenanthroline, in DMF at 80 °C under an atmosphere of 30 psi CO for 16 h to give the desired product. Isolation of the product is accomplished by filtration through Celite and addition of the crude DMF filtrate to a solution of 1 M H_3PO_4, which precipitated the product in analytically pure form and in excellent overall yield. The sequence whereby the appropriately substituted nitrostyrene carboxylic acid was converted to the required amide followed by reductive cyclization provided an excellent, high yielding means of preparing the highly

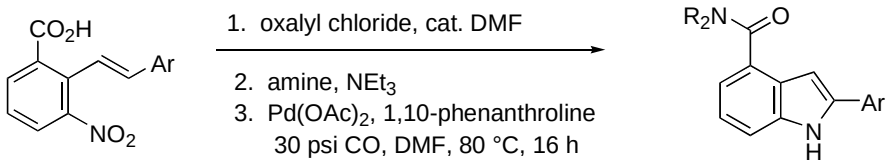
Table 1. Synthesis of Nitrostyrene Benzoic Acids

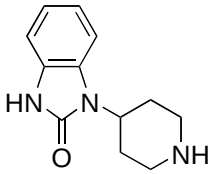
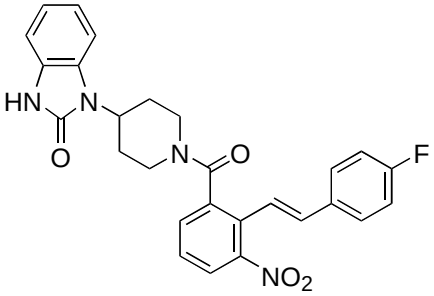
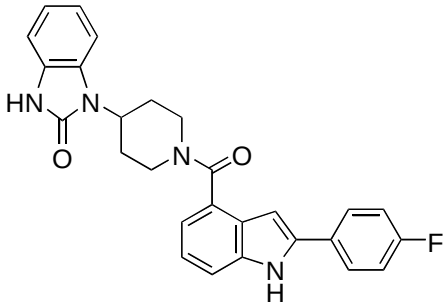
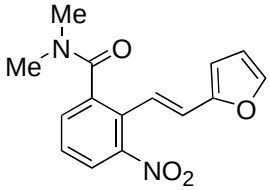
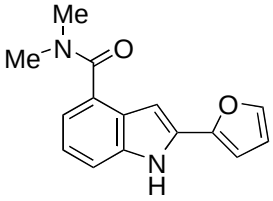
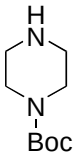
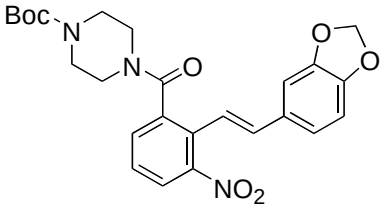
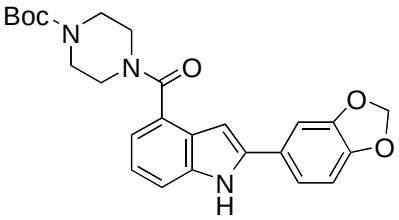
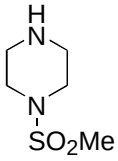
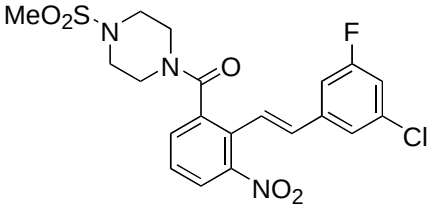
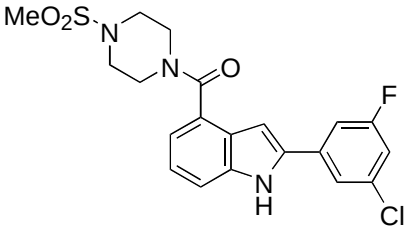
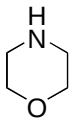
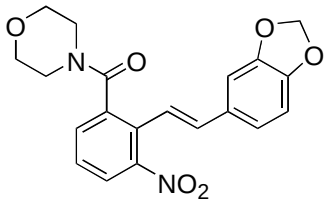
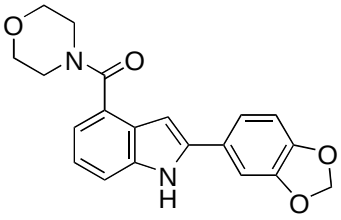


entry	aldehyde	nitrostyrene benzoic acid	Yield
1	 **7**	 **8**	68%
2	 **9**	 **10**	79
3	 **11**	 **12**	90
4	 **13**	 **14**	82
5	 **15**	 **16**	88

functionalized derivatives shown in Table 2. The use of 1M H_3PO_4 for the isolation of the product aided in the removal of trace amounts of 1,10-phenanthroline from the product and was mild enough that sensitive functionalities such as a Boc-protecting group were preserved (see entry 3, Table 2).

Table 2. Synthesis of Nitrostyrene Amides and Reductive Cyclization to 2-Arylindole-4-carboxylic amides.



amine	amide (isolated yield)	2-arylindole-4-carboxylic amide (isolated yield)
 **17**	 **18** (96%)	 **19** (94%)
Me_2NH **20**	 **21** (99%)	 **22** (91%)
 **23**	 **24** (98%)	 **25** (95%)
 **26**	 **27** (98%)	 **28** (94%)
 **29**	 **30** (97%)	 **31** (92%)

1. Department of Process Research, Merck & Co., Inc., Rahway, NJ, 07065, USA. E-Mail: Jeffrey_Kuethe@merck.com.
2. For leading references, see: (a) Dantale, S. W.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 5507-5514; (b) Scott, T. L.; Söderberg, D. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621-1624; (c) Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838-5845; (d) Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657-3660.
3. Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425-6437.
4. (a) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604-3610.; (b) Sundberg, R. J.; Yamazaki, T. *J. Org. Chem.* **1967**, *32*, 290-294. (c) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron* **2001**, *57*, 6197-6202.
5. (a) Kuethe, J. T.; Wong, A.; Davies, I. W.; *Org. Lett.* **2003**, *5*, 3721-3723. (b) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975-3978. (c) Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761-7764. (d) Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J. H.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555-2567.
6. For a complete account of our work in this area, see: Kuethe, J. T.; Davies, I. W. *Tetrahedron* **2006**, *62*, 11381-11390.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Methyl 2-methyl-3-nitrobenzoate; (59382-59-1)
4-Fluorobenzaldehyde; (459-57-4)
2-[*trans*-2-(4-Fluorophenyl)vinyl]-3-nitrobenzoic Acid; (917614-64-3)
{2-[*trans*-2-(4-Fluorophenyl)vinyl]-3-nitrophenyl}-1-pyrrolidinylmethanone; (917614-83-6)
1,10-Phenanthroline; (66-71-7)
$Pd(OAc)_2$: Palladium acetate; (3375-31-3)
[2-(4-Fluorophenyl-1*H*-indol-4-yl]-1-pyrrolidinylmethanone; (917614-84-7)

Jeff Kuethe was born in Cincinnati, Ohio in 1965. He studied chemistry at Middle Tennessee State University where he received in Bachelor of Science in 1993. He then joined the group of Professor Albert Padwa at Emory University in Atlanta, Georgia where he received a Ph.D. in 1998. He continued as a postdoctoral fellow in the group of Professor Daniel Comins at North Carolina State University before joining the Department of Process Research at Merck & Co., Inc., Rahway, New Jersey in 2000. His research interests include Process Research, synthetic methodology, heterocyclic chemistry, alkaloid and natural product synthesis, and tandem transformations.

Gregory L Beutner was born in Malden, Massachusetts in 1976. He graduated in 1998 with a Bachelor of Science in chemistry from Tufts University where he worked with Professor Arthur Utz and Professor Marc d'Alarcao. He completed his Ph.D studies under the supervision of Professor Scott E. Denmark at the University of Illinois in May 2004. He continued as an NIH postdoctoral fellow in the laboratories of Professor Robert H. Grubbs at the California Institute of Technology. He is currently working in the Department of Process Research at Merck & Co., Inc., Rahway, New Jersey. His research interests include Process Research, synthetic methodology development, and asymmetric catalysis.

Joseck Muhuhi graduated with a B.Sc. in Chemistry from the University of Nairobi, Kenya, in 1997, and after working in industry for 3 years, joined Wayne State University in 2000, for graduate education under the guidance of Dr. Mark Spaller. His doctoral research study was on mechanistic study of the aza-Diels-Alder reaction in the synthesis of anticancer heterolignans, synthesis of reduced peptides, and *E*-alkene dipeptide isosteres that target HIV-1 protease enzyme and PDZ domain proteins respectively. In December 2006, he joined the Denmark group as a visiting postdoctoral research associate to work on the development of tandem ring-closing metathesis/ silicon cross-coupling reactions and total synthesis of oximidine natural products. Dr. Muhuhi is a recipient of a NIH postdoctoral research fellowship.

2

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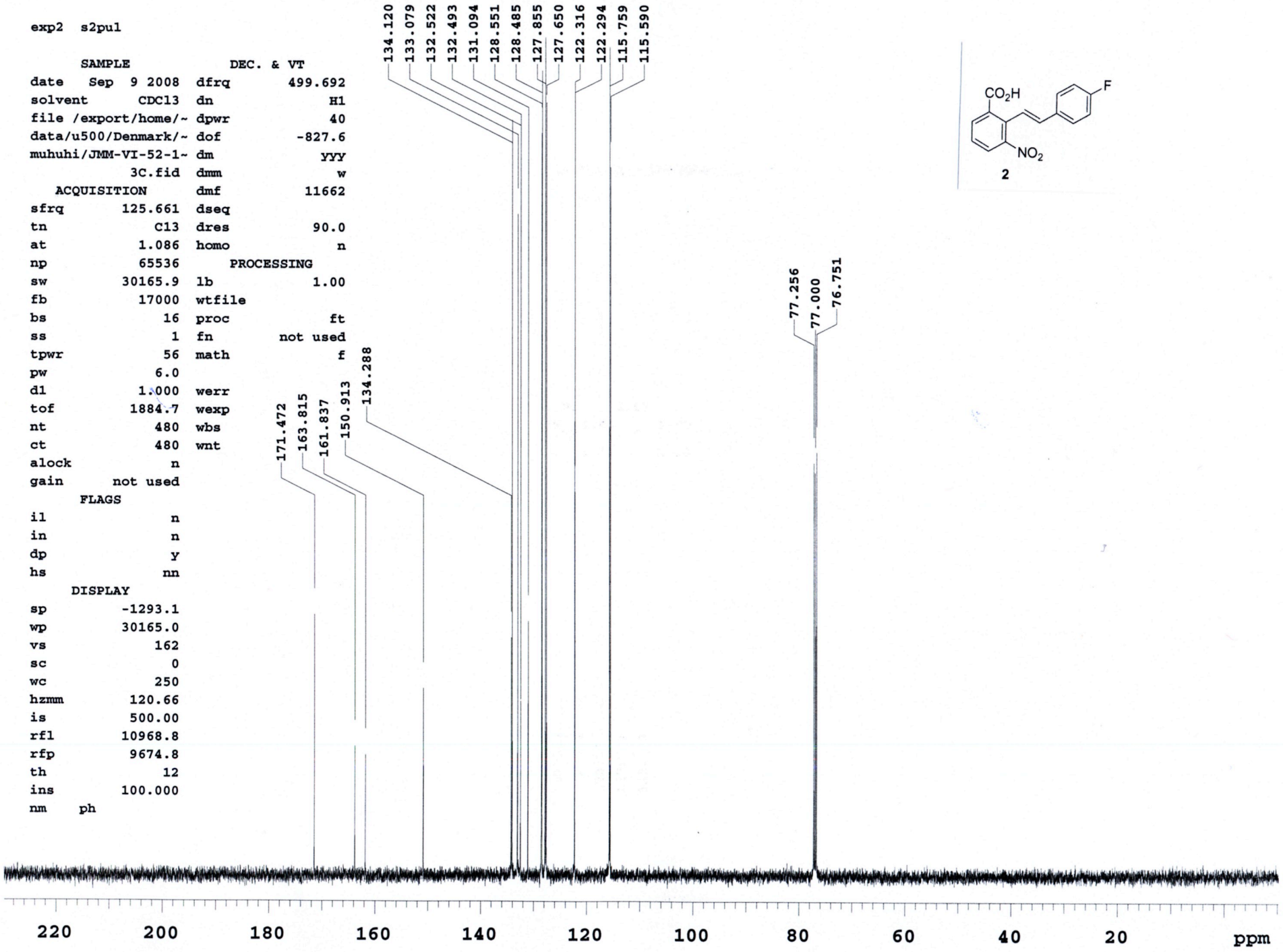

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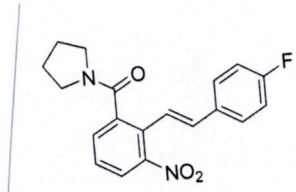

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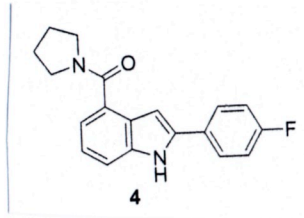

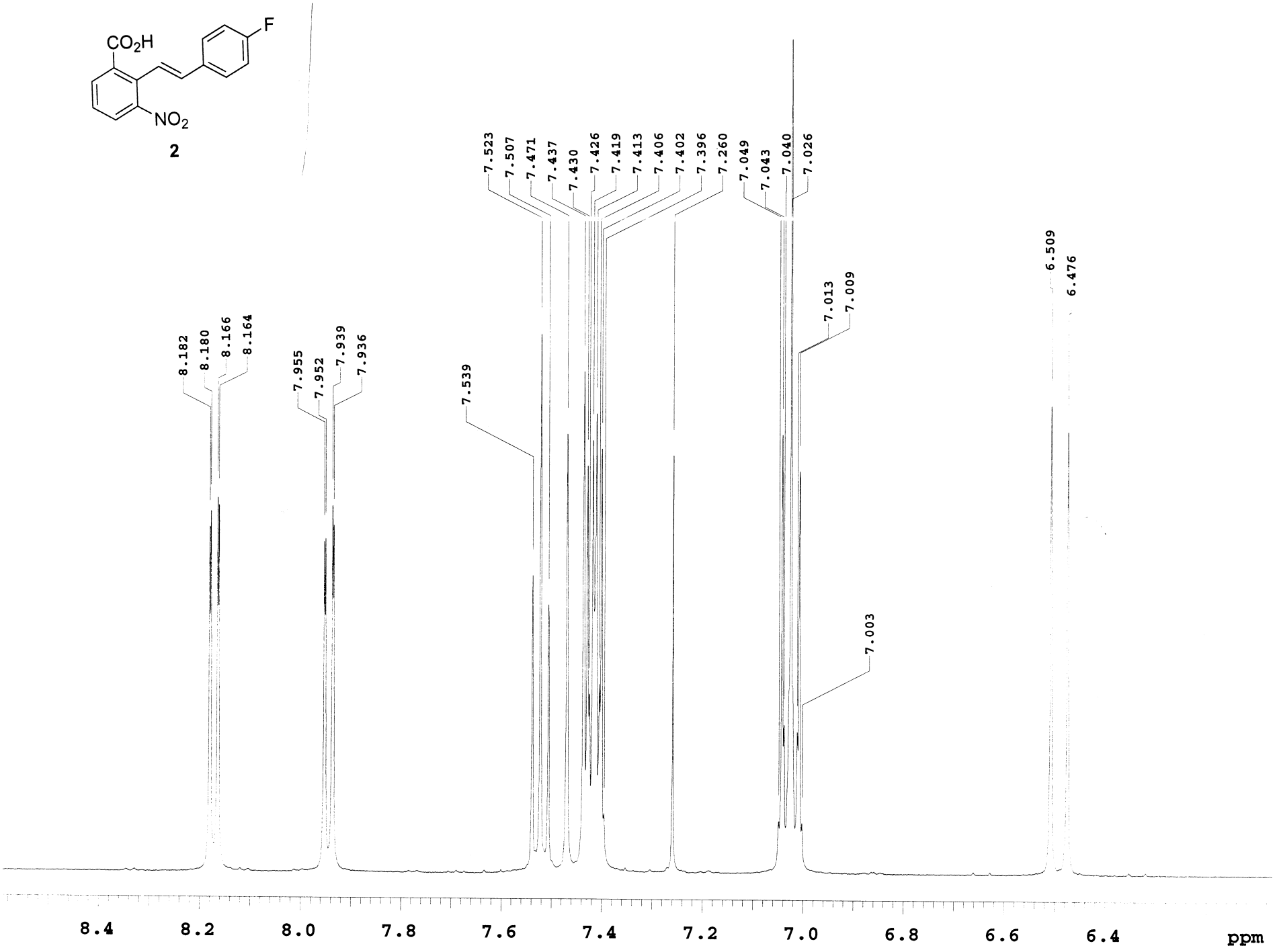
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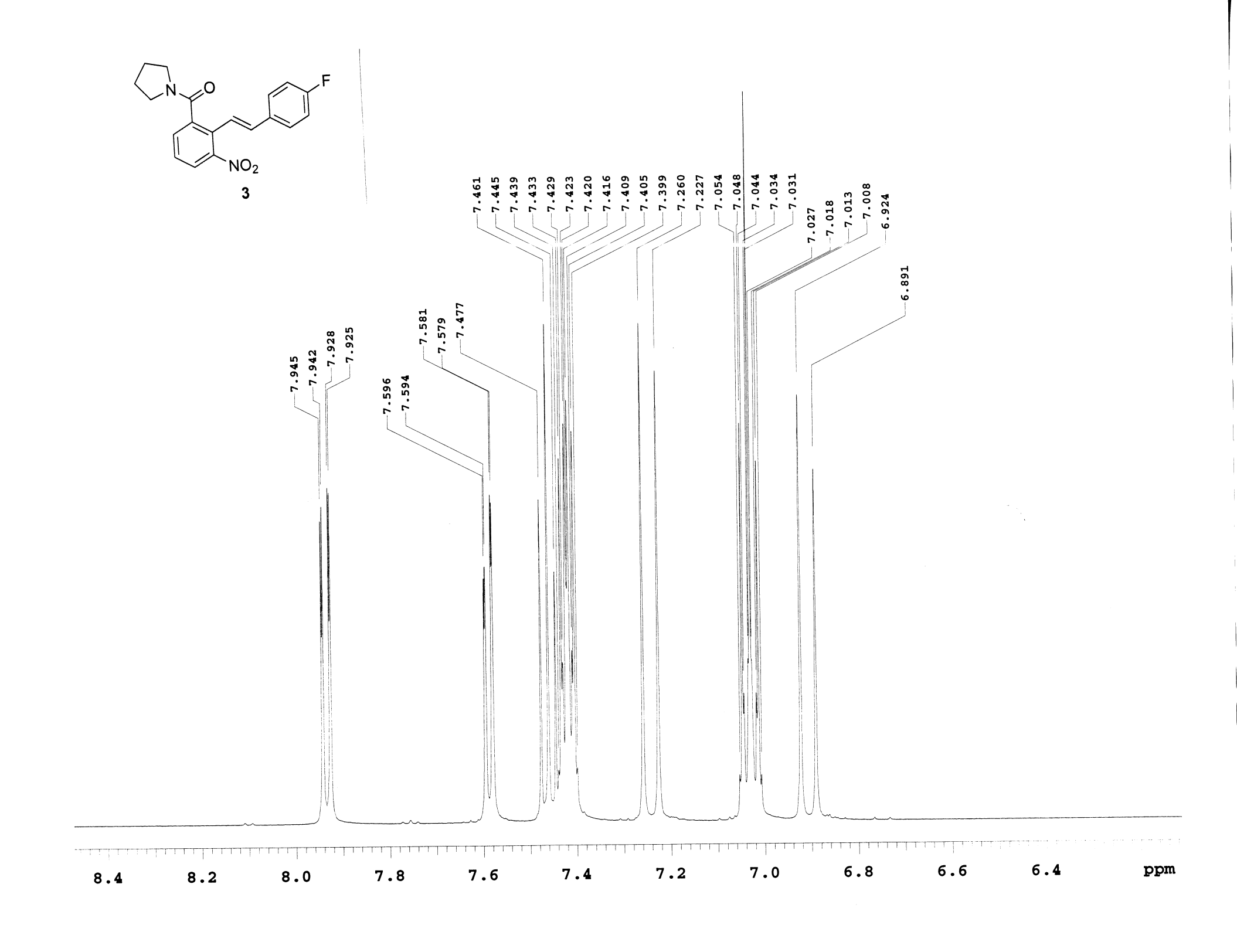
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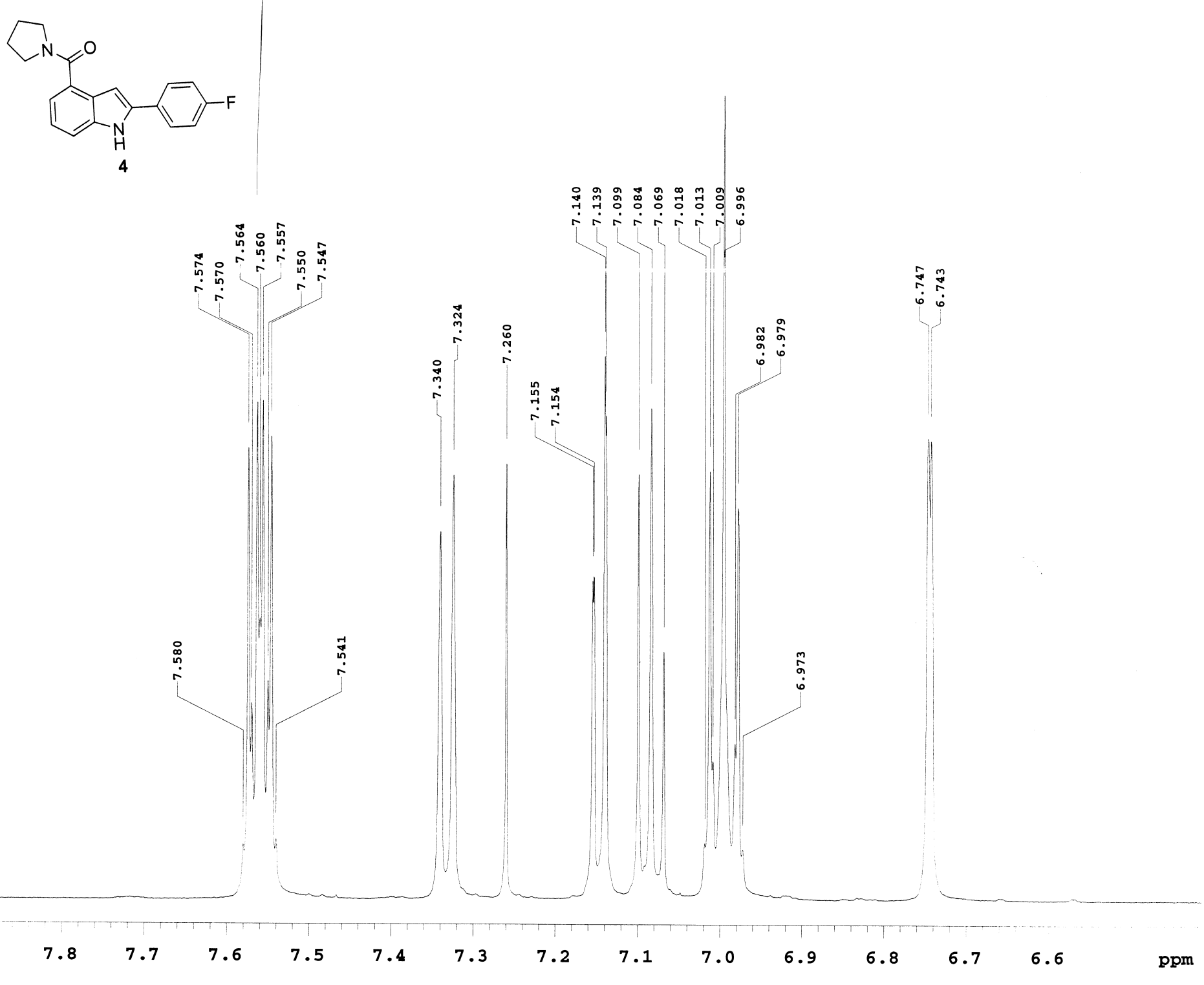
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