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for the Preparation
of Organic Compounds

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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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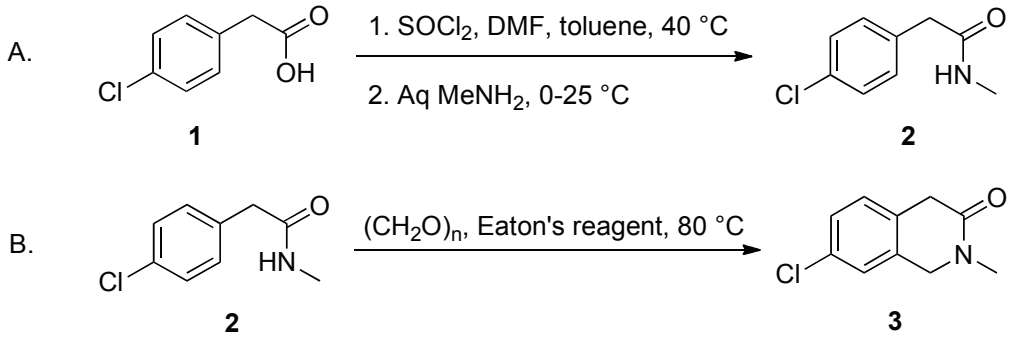
Preparation of Tetrahydroisoquinoline-3-ones Via Cyclization of Phenyl Acetamides Using Eaton's Reagent



Submitted by Qiang Yang, Luckner G. Ulysse, Mark D. McLaws, Daniel K. Keefe, Peter R. Guzzo, and Brian P. Haney.[1]
Checked by Andrew S. Cosbie and Margaret M. Faul.

1. Procedure

A. *2-(4-Chlorophenyl)-N-methylacetamide (**2**).* A three-necked, 500-mL round-bottomed flask is equipped with a 4-cm magnetic stir bar, a temperature probe, a 50-mL addition funnel, and a reflux condenser with a nitrogen gas inlet adaptor (Note 1). The apparatus is flushed with nitrogen for a minimum of 15 min and charged with 4-chlorophenyl acetic acid (50.0 g, 293 mmol) and 100 mL of anhydrous toluene (Note 2) under nitrogen. Anhydrous DMF (2.28 mL, 2.15 g, 29.3 mmol, 0.1 equiv) (Note 2) is added and the mixture is heated to 35 °C with a heating mantle. $SOCl_2$ (25.6 mL, 41.9 g, 352 mmol, 1.2 equiv) (Note 2) is added through the addition funnel over 30 min at such a rate that the internal temperature is maintained at <40 °C (Note 3). The resulting light brown solution is stirred at 40 °C and monitored by HPLC until the reaction is complete (Notes 4, 5, and 6).

A three-necked, 1-L round-bottomed flask is equipped with an 8-cm mechanical stirrer, a temperature probe, a 250-mL addition funnel, and a nitrogen gas inlet adaptor. The flask is charged with methylamine solution (40 wt% in water or 11.5M, 128 mL, 114 g, 1470 mmol, 5.0 equiv) (Note 7) and cooled to 5 °C with an ice bath.

The acid chloride solution is transferred from the 500-mL flask to the 250-mL addition funnel. The solution is added to the 1-L flask containing

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the methylamine solution over 45 min while maintaining the internal temperature at <25 °C with an ice bath (Note 8). *Caution! The reaction is exothermic* (Note 9). The resulting white suspension is stirred at ambient temperature for a minimum of 30 min and filtered through a Büchner funnel. The filter cake is washed with water (2 × 100 mL) and dried under vacuum (30 mmHg) at 40 °C for a minimum of 24 h to afford 50.9–51.5 g (95–96%) of the desired product **2** as a white crystalline solid (Notes 4 and 10).

B. *7-Chloro-2-methyl-1,4-dihydro-2H-isoquinolin-3-one (**3**).* A three-necked, 500-mL round-bottomed flask is equipped with a 3-cm magnetic stir bar, a temperature probe, a 50-mL addition funnel, and a reflux condenser with a nitrogen gas inlet adaptor (Note 1). The apparatus is flushed with nitrogen for a minimum of 15 min and charged with 50 mL of Eaton's reagent (Note 11). 2-(4-Chlorophenyl)-*N*-methylacetamide (10.0 g, 54.5 mmol) is charged in portions, resulting in an exotherm from 23 °C to 29 °C (Note 12). Paraformaldehyde (1.98 g, 65.3 mmol, 1.2 equiv) (Notes 13 and 14) is added and the reaction mixture is heated at 80 °C with a heating mantle for 2 h to afford a brown solution [*Caution! The reaction is exothermic* (Note 15)], at which point HPLC analysis indicates complete consumption of starting material **2** (Notes 4 and 16). The reaction mixture is cooled to 5 °C with an ice bath and water (50 mL) is added through the addition funnel over 30 min while maintaining the internal temperature at <25 °C. *Caution! The addition of water is exothermic.* Isopropyl acetate (IPAc) (50 mL) is added and the mixture is cooled to 5 °C with an ice bath. The pH of the mixture is adjusted to 8–8.5 using 19M NaOH solution (~48-49 mL) while maintaining the internal temperature at <25 °C with an ice bath. *Caution! The addition of NaOH is exothermic.* The solid precipitate is filtered off with a Büchner funnel. The filter cake is washed with IPAc (10 mL). The filtrate mixture is transferred to a 500-mL separatory funnel and the phases are separated. The aqueous phase is extracted with IPAc (50 mL) and the organic phases are combined. The combined organic phases are concentrated by rotary evaporation (35 °C, 30 mmHg) to afford a brown residue. The residue is dissolved in EtOAc (50 mL) and charged on a column (5 × 20 cm) of 200 g of silica gel (Note 17). The column is eluted with 1 L of EtOAc and fraction collection (50-mL fractions) is begun after 500 mL of solvent is eluted. Elution is continued with 1 L of 10% MeOH/EtOAc and the desired product is obtained in fractions 12-22 (Notes 18 and 19), which are concentrated by rotary evaporation (35 °C, 30 mmHg) to afford a yellow oil. The oil is dried under vacuum (30 mmHg) at ambient

temperature (20–25 °C) for a minimum of 24 h to afford 9.00-9.07 g (85%) of a light yellow solid (Notes 4, 20, and 21).

2. Notes

1. The glassware was oven-dried at 80 °C for a minimum of 24 h.

2. 4-Chlorophenyl acetic acid (99%), anhydrous toluene, anhydrous DMF, and thionyl chloride (Reagent grade) were purchased from Aldrich and used as received.

3. Vigorous off-gassing was observed during and after $SOCl_2$ was added. Sufficient ventilation should be employed to avoid pressure accumulation during the reaction. On large scale (e.g. >300 g scale) a caustic scrubber was used to sequester acidic off-gas.

4. Reaction progress and product purity were evaluated by HPLC analysis using a Waters Sunfire C18 3.5 μm column (150 mm × 4.6 mm) with mobile phases A (water + 0.05% TFA) and B (acetonitrile + 0.05% TFA) and detection at 220 nm; flow: 1.0 mL/min; temp. 25 °C; and gradient: 0 min: A = 95%, B = 5%; 20 min: A = 5%, B = 95%; 20.1 min: A = 95%, B = 5%; and 22 min: A = 95%, B = 5%.

5. The reaction conversion samples were prepared as follows: A sample of reaction mixture (25 μL) was quenched into 50 μL of 40 wt% aqueous $MeNH_2$ and shaken for 5 min. It was diluted with 1:1 acetonitrile/water to 2 mL and 5 μL of the resulting solution was injected on HPLC. The retention time for starting material **1** was 12.3 min, and the retention time of product **2** was 10.5 min under the HPLC conditions in Note 4. Alternatively, the reaction can be monitored by TLC. Silica plates with glass backing were used. The plates were developed in 3:1 EtOAc/Hexanes and visualized with UV light. The R_F value for starting material **1** was 0.47. The R_F value for product **2** was 0.31.

6. Generally the reaction should be complete within 30 min.

7. Methylamine solution (40 wt% in water or 11.5M) was purchased from Sigma Aldrich and used as received. A total of five equiv of $MeNH_2$ were used to quench excess $SOCl_2$ and acids generated during the reaction.

8. The methylamine solution was diluted with an equal volume of water in cases when a thick suspension formed and became difficult to stir.

9. Significant exotherm was observed during the addition of acid chloride solution to methylamine solution. The exotherm was controlled by the addition rate of acid chloride. As confirmed by safety assessment

evaluated by RC1 calorimetry, the heat output of the amide formation stayed constant during the addition of the acyl chloride, characteristic of a fast reaction with no potential for latent reaction.[2]

10. Physical properties and spectral data for **2** are as follows: mp 106–107 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.77 (d, J = 4.9 Hz, 3 H), 3.53 (s, 2 H), 5.43 (bs, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 26.5, 42.9, 129.1, 130.8, 133.3, 133.4, 170.9; IR (film) [cm^{-1}]: 3281, 1646, 1557, 1492, 1408, 1260, 1085, 1017, 806, 734; HRMS (ES+) calculated for $C_9H_{11}NOCl$ 184.05292, found 184.05252; HPLC >99% (t_R = 10.5 min).

11. Eaton's reagent was purchased from Aldrich (7.7 wt% of P_2O_5 in MsOH) and used as received. Alternatively, fresh Eaton's reagent was prepared in-house at a concentration of 7.5 wt% by adding P_2O_5 (12 g) to methanesulfonic acid (100 mL) at <25 °C. A slight exotherm occurred which was easily controlled by the rate of P_2O_5 addition. Once the addition was complete, the solution was stirred at ambient temperature for 18 h and then stored in airtight containers under nitrogen. Cleaner reaction profile was obtained when freshly prepared Eaton's reagent was used.

12. Safety assessment evaluated by RC1 calorimetry indicated that a mild thermal event took place upon addition of the phenyl acetamide (ΔH = −35 kJ/mol, ΔT_{ad} = 14 K) which rapidly subsided.[2]

13. Paraformaldehyde (95%) and sodium hydroxide solution (19M or 50 wt%) were purchased from Aldrich and used as received.

14. RC1 study revealed that addition of paraformaldehyde was marked by an initial endothermic event devoid of any significant thermal activity until the system was heated.[2]

15. The thermal profile observed during heating resulted in a net output of −120 kJ/mol (ΔT_{ad} = 43 K). Upon completion of the heat cycle, a decaying heat flow was observed which ended within an hour, indicating that no rapid temperature spike or uncontrollable heat accumulation occurred.[2]

16. The reaction progress was monitored using the HPLC method described in Note 4. The reaction conversion samples were prepared as follows: A sample of reaction mixture (25 μL) was quenched into 1 mL of water. It was diluted with acetonitrile to 2 mL and 5 μL of the resulting solution was injected on HPLC. The retention time for starting material **2** was 10.5 min, and the retention time of product **3** was 11.3 min under the HPLC conditions in Note 4.

17. Silica gel SiliaFlash® F60 (40–63 μm/230–400 mesh) was purchased from Silicycle.

18. The starting material **2** co-elutes with the product during column chromatography purification, thus it is necessary to ensure complete consumption of the starting material before work up.

19. The fractions were monitored by HPLC analysis for purity using the HPLC method described in Note 4. HPLC samples were prepared as follows: A sample of each fraction (100 μL) was evaporated under a flow of nitrogen to a residue and dissolved in 2 mL of 1:1 acetonitrile/water. The typical injection volume was 10 μL, but the volume was adjusted for some fractions based on the concentration of each fraction.

20. Physical properties and spectral data for **3** are as follows: mp 51–54 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.11 (s, 3 H), 3.58 (s, 2 H), 4.47 (s, 2 H), 7.09 (d, J = 8.2 Hz, 1 H), 7.17 (d, J = 1.9 Hz, 1 H), 7.23 (dd, J = 8.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 34.4, 36.3, 52.4, 125.2, 127.7, 128.7, 130.7, 132.3, 132.6, 168.2; IR (film) [cm^{-1}]: 1626, 1488, 1389, 1331, 1244, 1085, 902, 810; HRMS (ES+) calculated for $C_{10}H_{11}NOCl$ 196.05292, found 196.05257; HPLC 97.6-98.3% (t_R = 11.3 min).

21. The product needs to be stored under nitrogen at –20 °C as slow decomposition was observed when it was stored at ambient temperature (20–25 °C).

Safety and Waste Disposal Information

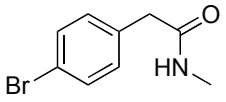
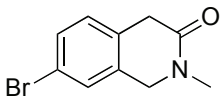
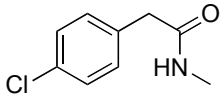
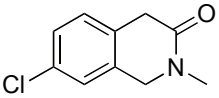
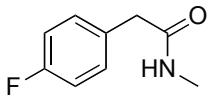
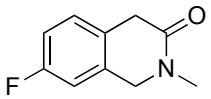
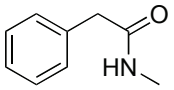
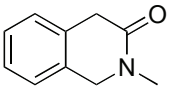
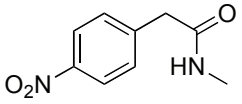
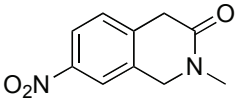
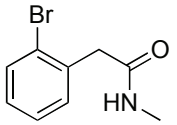
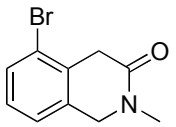
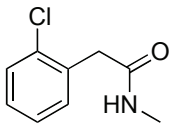
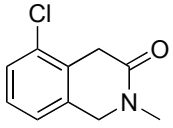
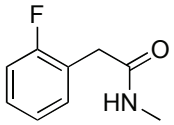
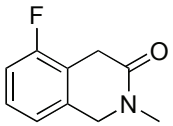
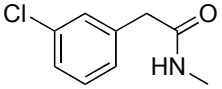
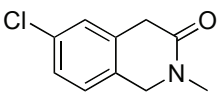
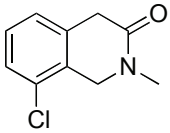
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

Tetrahydroisoquinoline is a ubiquitous structural framework present in numerous pharmacologically relevant molecules.[3,4] Such structural framework was envisioned to be achieved via the Pictet-Spengler cyclization;[5] however, conditions commonly used for the preparation of tetrahydroisoquinoline-3-ones required the use of polyphosphoric acid (PPA).[6] The high temperature requirement of this reaction coupled with the high viscosity associated with the PPA at 160 °C rendered this condition unattractive on scale.

The present procedure is a simple, efficient, and economical method for the preparation of tetrahydroisoquinoline-3-ones that can be easily scaled up. The safety concerns are minimized with the use of Eaton's reagent since the resultant mixtures are more mobile solutions with temperature requirements much lower than that of PPA. Although the use of Eaton's reagent as a dehydrating agent in various reactions is well documented, Eaton's reagent-mediated cyclization of phenyl acetamide derivatives with formaldehyde was not available in the literature[7-15]. Cyclization of phenyl acetamides using Eaton's reagent was broadened to understand the scope and limitation of the process. Some representative examples of tetrahydroisoquinoline-3-ones prepared by this method are compiled in Table 1. For the phenyl acetamides with electron-withdrawing groups on 2- or 4- positions, the desired cyclized products were isolated in excellent yield by neutralization of the reaction to pH 8.0 – 8.5 with sodium hydroxide (NaOH), followed by extraction of the product with isopropyl acetate (IPAc) and isolation by concentration. A ~2:1 mixture favoring 6-chloro-2-methyl-1,4-dihydro-2*H*-isoquinolin-3-one was obtained when 2-(3-chlorophenyl)-*N*-methylacetamide was subjected to this condition, as the formation of 8-chloro-2-methyl-1,4-dihydro-2*H*-isoquinolin-3-one was more hindered by the chloro group. Complicated results were afforded when phenyl acetamides with electron-donating groups were treated with Eaton's reagent under the same conditions.

Table 1. Scope of cyclization using Eaton's reagent

Phenyl acetamide	Product	Isolated yield (%)
		95[a]
		80[a]
		89[a]
		96[a]
		98[a]
		77[a]
		79[a]
		71[a]
		41[b]
		18[b]

[a] Crude yield; [b] Purified yield.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-Chlorophenylacetic acid: *p*-Chlorophenylacetic acid, PCPA; (1878-66-6)

Thionyl chloride: sulfur chloride oxide, sulfurous oxychloride, sulfinyl chloride, sulfurous dichloride, thionyl dichloride; (7719-09-7)

Methylamine: monomethylamine, aminomethane, carbinamine, mercurialin; (74-89-5)

2-(4-Chlorophenyl)-N-methylacetamide; (60336-41-6)

Eaton's reagent: Phosphorus pentoxide, 7.7 wt% solution in methanesulfonic acid; (39394-84-8)

Paraformaldehyde: Polyformaldehyde; Polyoxymethylene; Formaldehyde polymer; Polyoxymethylene glycol; Trioxymethylene; (30525-89-4)

Qiang Yang received his B.S. in Chemistry from Beijing Normal University in 1996 and M.S. in Organic Chemistry from Institute of Chemistry, the Chinese Academy of Sciences in 1999. Qiang completed his Ph.D. study under the direction of Prof. David C. Baker at the University of Tennessee, Knoxville in 2002. His Ph.D. research focused on the total synthesis of C-/O- and S-/O- linked oligosaccharide mimetics of Hyaluronic Acid (HA). Qiang joined the Chemical Development group at AMRI in 2003 focusing on route scouting, process development, and technology transfer of processes for pilot manufacture of Active Pharmaceutical Ingredients intended for toxicological and clinical evaluations.

Luckner G. Ulysse Jr. (born in 1970) started his academic studies at the University of Louvain la Neuve, in Belgium transferring later to Walsh University in Canton, OH obtaining his BS degree Magna Cum Laude in 1991. As an NIH pre-doctoral fellow, he completed his Doctoral studies from Purdue University in Chemistry, graduating Cum Laude under the direction of professor Jean Chmielewski (1996). He joined Advanced ChemTech (1996), working on unnatural amino acids, and in 1999 started at AMRI as a Senior Scientist. After nearly 10 years at AMRI working on process development of various APIs, Luckner headed the global chemical development/GMP group as its vice president. In 2010, he joined Cherokee Pharmaceuticals, LLC as Director-Head of Technical Operations overseeing a portfolio of commercial and late stage products.

Mark McLaws (born in 1972) received his B.A. degree in chemistry from Southern Utah University in 1997. He continued his studies under the mentorship of Gary Keck at the University of Utah where he obtained a Ph.D. in 2003. His graduate research included work towards the total synthesis of the natural products Dolabelide B and Rhizoxin D. Upon completing his graduate work, Mark moved to Albany, NY and joined the Chemical Development at AMRI.

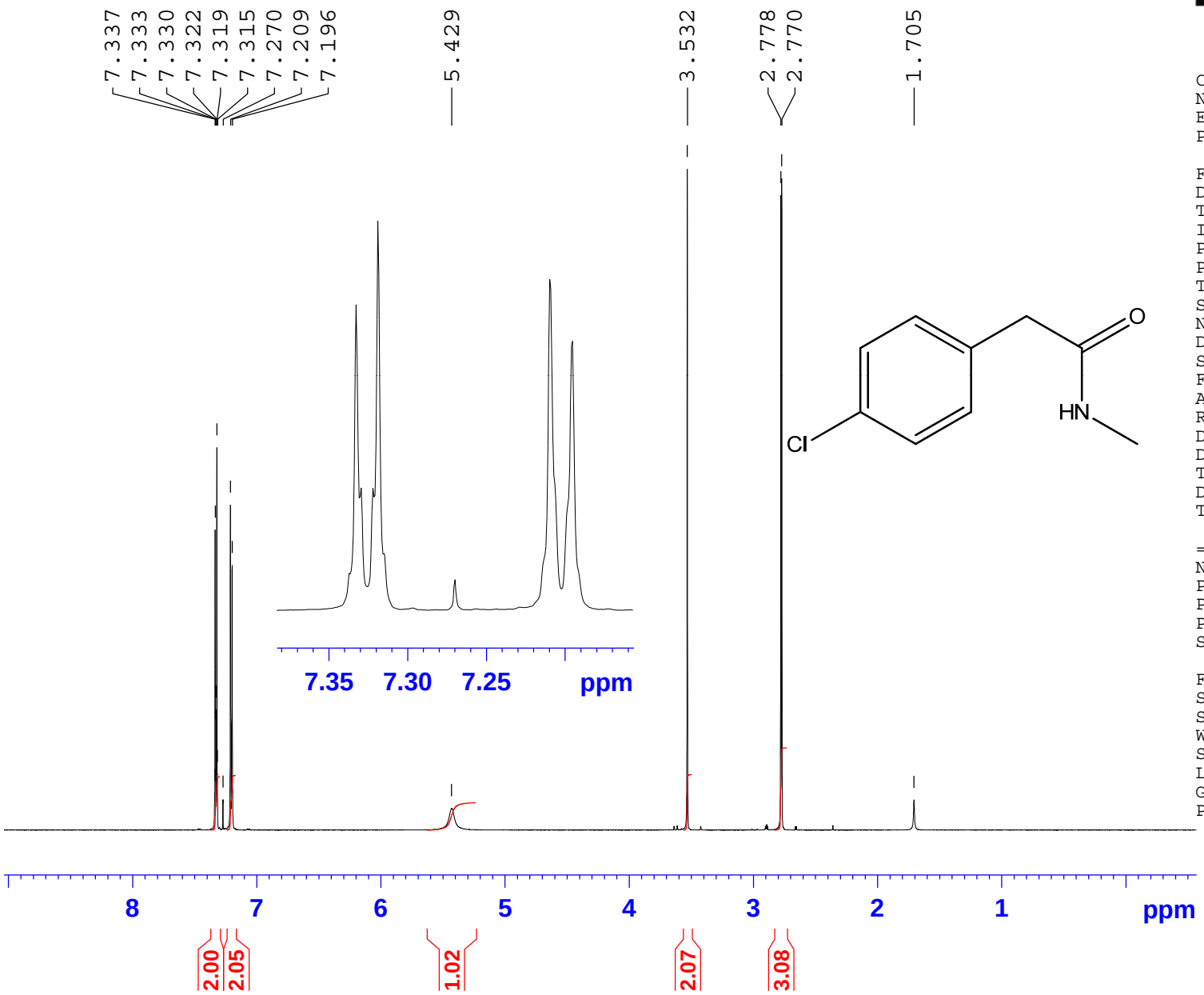
Daniel K. Keefe earned his B.S. in Chemistry from Rensselaer Polytechnic Institute and joined AMRI in 2001. He has worked in the areas of Chemical Development and Development Manufacturing, gaining experience in both non-cGMP and cGMP environments. Dan has successfully transferred numerous large-scale projects to the AMRI Rensselaer Pilot Plant and High Potency Suites.

Peter Guzzo obtained his Ph.D. in Organic Chemistry at the University of Notre Dame under Professor Marvin Miller and conducted post-doctoral studies with Professor Arthur Schultz at Rensselaer Polytechnic Institute. Currently, Pete is the Director of Discovery R&D, Chemistry at AMRI where he leads efforts on internal drug discovery programs with a particular focus on central nervous system and metabolic diseases.

Brian P. Haney was born in 1972 in Syracuse, NY. He received his B.S. in Chemistry from Allegheny College (PA.) in 1996 where he worked with Prof. Edward Walsh studying organosulfur compounds. He completed his Ph.D. at the University of Pittsburgh in 2000. His thesis work was performed under the direction of Prof. Dennis P. Curran and focused on tandem radical cyclizations and their application to the synthesis of Natural Products. He joined the Chemical Development group at AMRI in 2000, where he focused on route scouting, process development, technology transfer and Highly Potent Active Pharmaceutical Ingredient (HPAPI) development. Brian moved into AMRI's Rensselaer Large Scale Manufacturing team in 2009 and is currently the Section Head for Commercial Manufacturing.

Andrew Cosbie earned his B.S. in Chemical Engineering from the University of California, Santa Barbara in 2009. He joined Amgen later that year and has been working as a process engineer in the Chemical Process Research and Development group. Andrew has been gaining experience in process characterization, modeling of unit operations, and scale-up of chemical processes in a GMP setting.

2-(4-chlorophenyl)-N-methylacetamide



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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 12335.526 Hz
FIDRES 0.188225 Hz
AQ 2.6564426 sec
RG 25.4
DW 40.533 usec
DE 19.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.20 dB
PL1W 6.23610163 W
SFO1 600.2336014 MHz

F2 - Processing parameters
SI 32768
SF 600.2300067 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00

2-(4-chlorophenyl)-N-methylacetamide

Current Data Parameters

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EXPNO	6
PROCNO	1

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DS	64
SWH	36231.883 Hz
FIDRES	0.552855 Hz
AQ	0.9044468 sec
RG	362
DW	13.800 usec
DE	20.00 usec
TE	300.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	12.00 usec
PL1	0.75 dB
PL1W	81.79202271 W
SFO1	150.9430468 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	4.00 dB
PL12	22.84 dB
PL13	27.00 dB
PL2W	6.53000021 W
PL12W	0.08529296 W
PL13W	0.03272752 W
SFO2	600.2324009 MHz

F2 - Processing parameters

SI	32768
SF	150.9279572 MHz
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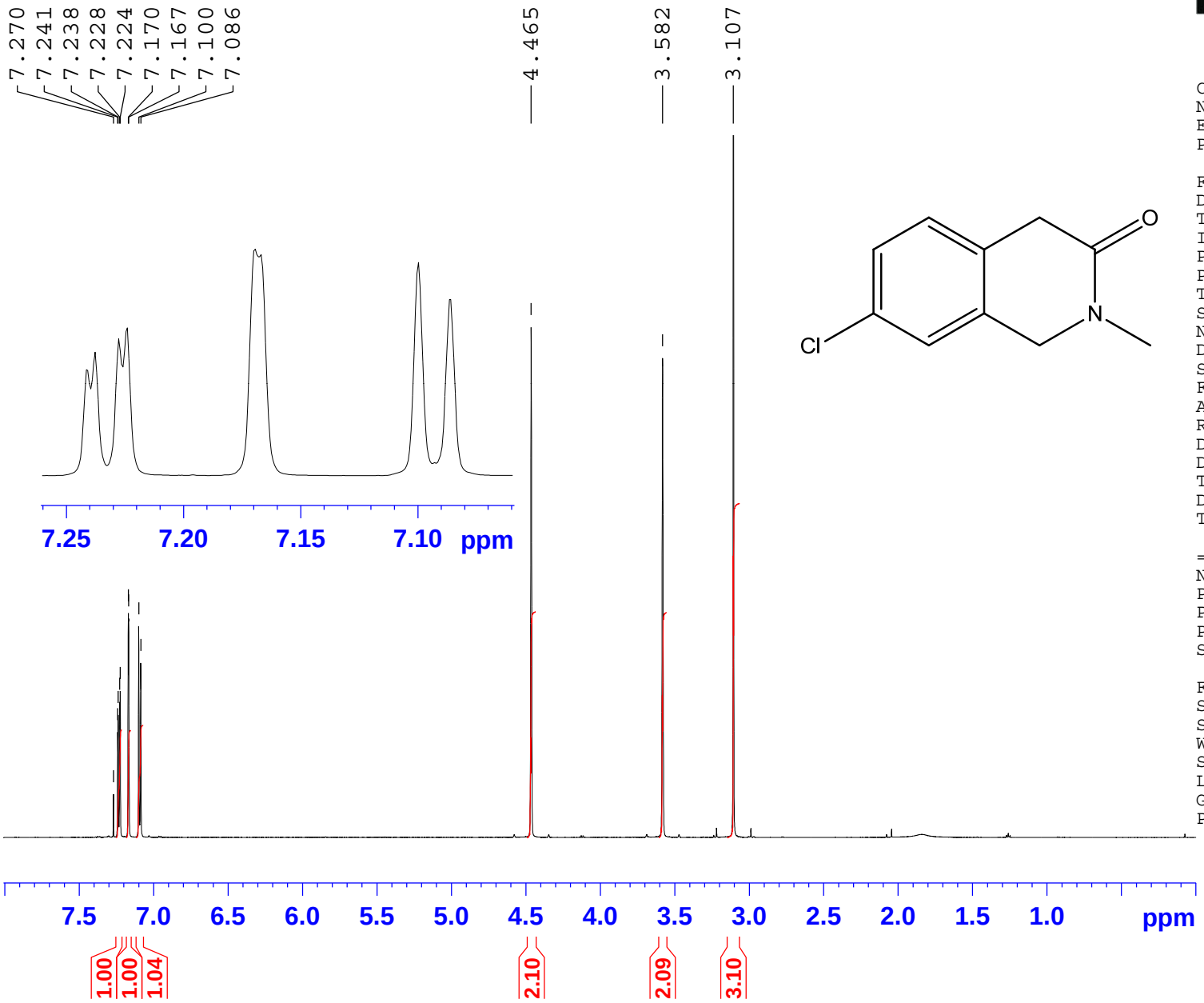
7-chloro-2-methyl-1,2-dihydroisoquinolin-3(4H)-one



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SOLVENT CDCl3
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DS 4
SWH 12335.526 Hz
FIDRES 0.188225 Hz
AQ 2.6564426 sec
RG 25.4
DW 40.533 usec
DE 19.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 4.20 dB
PL1W 6.23610163 W
SFO1 600.2336014 MHz

F2 - Processing parameters
SI 32768
SF 600.2300068 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00

7-chloro-2-methyl-1,2-dihydroisoquinolin-3(4H)-one

Current Data Parameters
NAME 162745
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110607
Time 23.10
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PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 8192
DS 64
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044468 sec
RG 362
DW 13.800 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 12.00 usec
PL1 0.75 dB
PL1W 81.79202271 W
SFO1 150.9430468 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 4.00 dB
PL12 22.84 dB
PL13 27.00 dB
PL2W 6.53000021 W
PL12W 0.08529296 W
PL13W 0.03272752 W
SFO2 600.2324009 MHz

F2 - Processing parameters
SI 32768
SF 150.9279579 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40