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of Organic Compounds

Working with Hazardous Chemicals

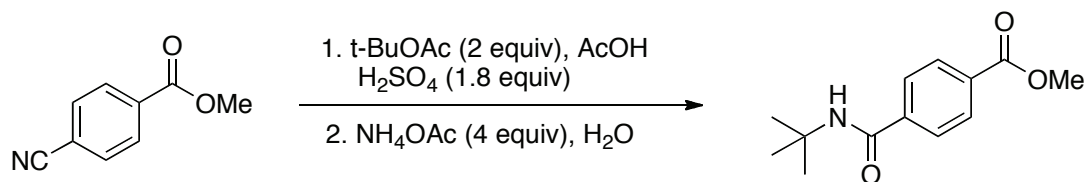
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

An Efficient and Scalable Ritter Reaction for the Synthesis of *t*-Butyl Amides



Submitted by Jacqueline E. Milne and Jean C. Baum.¹

Checked by Travis C. McMahon and John L. Wood.²

*Caution: Flammable isobutylene gas is generated during the reaction. The use of acetic acid as solvent minimizes the amount of isobutylene gas generated by creating an equilibrium with isobutylene to regenerate *tert*-butyl acetate.*

1. Procedure

Methyl 4-(tert-butylcarbamoyl)benzoate. A 500-mL three-necked round-bottomed flask with 24/40 joints (Note 1) is equipped with an overhead mechanical stirrer (Teflon blade, 19 x 75 x 3 mm), a nitrogen inlet, and a temperature probe (Note 2). The nitrogen inlet is removed from the 500-mL flask. Methyl 4-cyanobenzoate (50.0 g, 310 mmol, 1 equiv) (Note 3), acetic acid (50.0 mL) (Note 4), and *tert*-butyl acetate (83.2 mL, 72.0 g, 621 mmol, 2 equiv) (Note 5) are charged to the 500-mL flask, and the nitrogen inlet is reinserted to the open neck. Stirring is initiated at a rate of 300 to 350 rpm. A temperature decrease is observed on mixing, and the slurry is allowed to warm to ≥ 19 °C (Note 6). Meanwhile, a 250-mL three-necked round-bottomed flask with 19/22 joints is immersed in an ambient temperature water bath (Dewar flask, 15–25 °C), 25 mm egg-shaped magnetic stir bar, temperature probe and N₂ inlet. To the 250 mL flask, acetic acid (50 mL) is charged and a rubber septum is added to the third neck. Concentrated sulfuric acid (29.8 mL, 558 mmol, 1.8 equiv) (Note 7) is charged to the 250-mL flask in 3 mL portions by syringe, maintaining the internal temperature ≤ 40 °C (Note 8). The solution is allowed to cool and once the internal temperature reaches ≤ 25 °C, it is transferred from the 250-mL flask to a 120-mL addition funnel. The N₂ line is removed from the

joint of the 500-mL flask, the addition funnel is attached to the joint, and the N₂ inlet adapter is placed on top of the addition funnel. An ambient temperature water bath (Dewar flask, 15–25 °C) is fitted around the 500-mL flask. The solution is charged over 1 h, maintaining an internal temperature ≤ 30 °C (Note 9). The reaction is analyzed for completion after 2 h (Note 10). A 1000-mL three-necked round-bottomed flask with 24/40 joints is immersed in an ambient temperature water bath (Dewar flask, 15–25 °C), is equipped with an overhead mechanical stirrer (Teflon blade, 19 x 75 x 3 mm) and a thermocouple probe, and is charged with ammonium acetate (96.0 g, 124 mmol, 4 equiv) (Note 11) and water (250 mL) (Note 12). The ammonium acetate dissolves completely (Note 13). The reaction solution (slightly yellow, homogeneous, and viscous) is transferred from the 500-mL flask to a 250-mL addition funnel (Note 14). The addition funnel is attached to the 1000-mL flask and a N₂ line is attached to the top joint *via* an inlet adapter (24/40 joint). After the contents of the 1000-mL flask reaches ≥ 19 °C, the solution in the addition funnel is added over 1 h, maintaining the internal temperature ≤ 35 °C at a stir speed of 400 to 500 rpm (Note 15). White solids begin to form immediately and the turbidity increases as the addition proceeds. The slurry is stirred for 17–24 h at room temperature (Notes 15 and 16) and then filtered on a glass Büchner funnel (650 mL) (Note 17). The product is washed with water (2 × 100 mL) (Note 18) and dried on the filter for 2 h. The product is then dried under high vacuum (0.5 mmHg) in a 40 °C oil bath over two nights (Note 19) to yield 69.0 g (95%) of the amide at a purity of > 99.0 % (Note 20). No impurities were observable in the product > 0.5 % (observed at 254 nm, see Note 10).

2. Notes

1. It is not necessary to oven-dry the glassware.
2. The internal temperature was monitored using a IKA ETS-D5 thermocouple (240 mm length, 2 mm diameter, temperature range –50 to 450 °C). The probe is attached through a rubber septum. The submitters monitored the internal temperature using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range –200 to +250 °C). The probe is attached via a Teflon probe adapter (24/40 joint).
3. Methyl 4-cyanobenzoate (99%) is purchased from Alfa Aesar and is used as received.

4. Acetic acid (99.7%), purchased from JT Baker, is used as received.
 5. *tert*-Butyl acetate (>99%) is purchased from Alfa Aesar and was used as received. Excess *tert*-butyl acetate is used to ensure complete reaction. Decomposition of *tert*-butyl acetate occurs from reaction with sulfuric acid to generate isobutylene gas.
 6. Solids are observed that dissolve upon warming to room temperature. During a period of 1 h, the temperature rose from 12 °C to 19 °C. At 19 °C, few solids remain in a colorless solution.
 7. Concentrated sulfuric acid (95%) was purchased from JT Baker and was used without further purification. Excess sulfuric acid is used to ensure reaction completion.
 8. A total of 10 portions of sulfuric acid (3 mL each) were charged in 15 min. The internal temperature was 39 °C at the end of the addition. After stirring 30 min., the temperature reached 25 °C. Ice cubes may be added to the water bath to increase the efficiency of this step.
 9. Temperature was maintained near 24 °C during the addition. The submitters observed the temperature to be near 30 °C during the addition. A total volume of 75 mL sulfuric acid/acetic acid solution was added.
 10. The submitters monitored the reaction by HPLC under the following conditions: Luna 3 μm C18 100 Å column (100 x 3.0 mm) using 0.1% TFA in acetonitrile (A)/0.1% TFA in water (B), 90:10 A:B ramp to 10:90 A:B over 15 min with 5 min post time. Flow rate is 1 mL/min at 254 nm detection wavelength. The nitrile starting material elutes at 6.6 min and the amide product elutes at 7.7 min.
- The checkers monitored the reaction by TLC (30% EtOAc, 70% hexanes, UV detection at 254 nm). R_f (methyl 4-cyanobenzoate) = 0.60; R_f (methyl 4-(*tert*-butylcarbamoyl) benzoate) = 0.46.
- The submitters noted the reaction went to completion after 2 h, and the checkers also observed this on 25 g scale. However, the checkers observed that the addition of *tert*-butyl acetate (41.6 mL, 36.0 g, 310 mmol, 1 equiv) in two portions (first after 2 h, second after 3 h) was required on 50 g scale. The reaction was observed to be complete after a total of 3.5 h had elapsed from time the sulfuric acid/acetic acid addition was complete.
11. Ammonium acetate (>99%) was purchased from Mallinckrodt and used as received.
 12. DI water is used.
 13. No exotherm is observed.
 14. The total volume is 235 mL.

15. The quench is exothermic. The temperature is maintained close to 25 °C during the addition. The submitters observed the temperature to be near 30 °C during the addition. Some off-gassing is observed initially during the quench. A fast stir speed is recommended because the slurry becomes viscous as the quench proceeds.

16. The solubility was determined by measuring the concentration of the mother liquor by HPLC. Immediately after the quench, the solubility was 5.8 mg/mL. After stirring overnight, the solubility was 3.8 mg/mL. The submitters recommend holding overnight to maximize yield. The internal temperature was 21 °C prior to filtration.

17. The glass Büchner funnel was equipped with filter paper (Whatman, Qualitative, 90 mm). The submitters used a medium-grade fritted glass funnel (650 mL) for the filtration.

18. The checkers found that the water wash is needed to wash any remaining salts from the product.

19. The submitters dried the product in a vacuum oven under house-vacuum (20–40 mmHg) at 40 °C overnight.

20. Methyl 4-(*tert*-butylcarbonyl)benzoate has the following physical and spectroscopic data: white solid; mp: 117–120 °C (Gallenkamp melting point apparatus, uncorrected); the submitters reported 125 °C (measured by DSC); ¹H NMR (400 MHz, CDCl₃) δ: 1.48 (s, 9 H), 3.93 (s, 3 H), 5.98 (br. s., 1 H), 7.76 (d, *J*=8.23 Hz, 2 H), 8.06 (d, *J*=8.46 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ: 29.0, 52.1, 52.5, 126.9, 129.9, 132.5, 140.0, 166.1, 166.5; IR (Bruker Tensor 27) $\nu_{\max}/\text{cm}^{-1}$: 3300, 2981, 1721, 1638, 1548, 1450, 1288, 1221, 1116, 1016, 870, 825, 794, 692, 668; HRMS Calcd for C₁₃H₁₈NO₃ [M + H]⁺ 236.1287 found 236.1271; Anal Calcd for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.16; N, 6.12.

Safety and Waste Disposal Information

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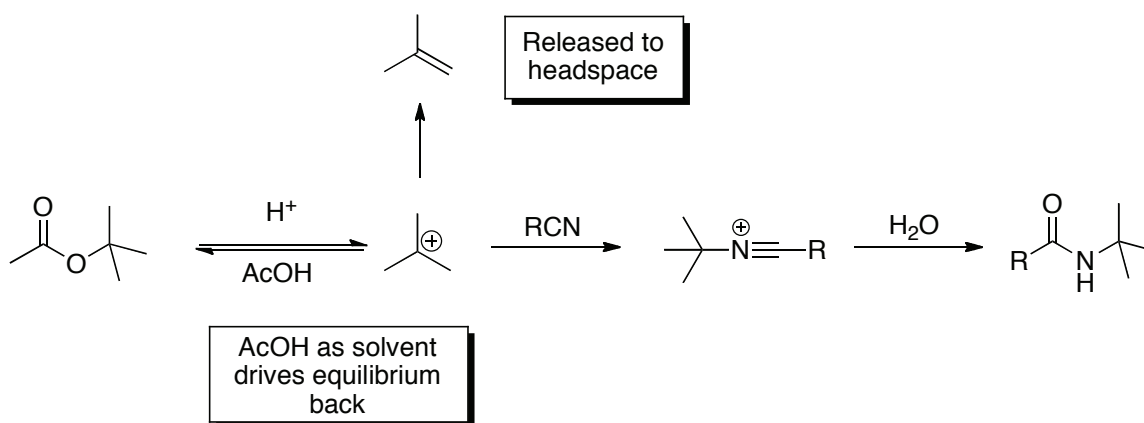
3. Discussion

The Ritter reaction involves the conversion of a nitrile to a *N-tert*-butyl amide through reaction with a *tert*-butyl cation.³ Typically, the *tert*-butyl

cation is generated from either isobutylene gas or *tert*-butanol in the presence of an acid. However, the most commonly used reaction conditions have some inherent problems that limit their use on larger scale. For example, isobutylene is a class 4 (highly flammable) gas and there have been reports of exothermic events when used in this reaction. In addition, the use of *tert*-butanol can be problematical since it exists as a semisolid at room temperature (melting point: 26 °C). An alternative *tert*-butyl cation precursor is *tert*-butyl acetate, which is attractive due to its ease of handling (boiling point: 97–98 °C), availability as a common solvent, and low cost. Unfortunately, it was observed that when *tert*-butyl acetate is employed as both the reaction solvent and the reagent, rapid and uncontrolled gas evolution results, due to the fast decomposition to isobutylene gas.⁴

The procedure described here involves the slow addition of sulfuric acid (1.8 equiv) in acetic acid to a mixture of the nitrile substrate and *tert*-butyl acetate (2 equiv) in acetic acid at 30 °C.⁵ The advantage of this reagent combination is a result of the equilibrium that exists between *tert*-butyl acetate and isobutylene in acetic acid (Figure 1). The generated carbocation either reacts along the desired reaction pathway to give *tert*-butyl amide, or is scavenged by acetic acid to regenerate the reagent. Consequently, a controlled and slow release of isobutylene occurs during the course of the reaction and the possibility of uncontrolled gas evolution is eliminated.

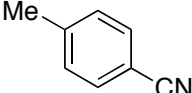
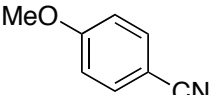
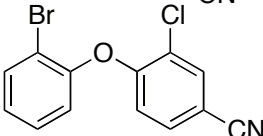
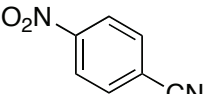
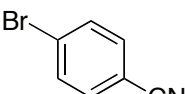
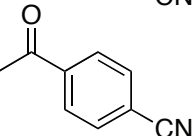
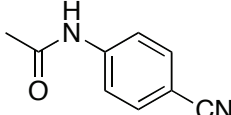
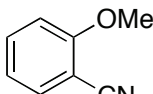
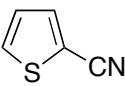

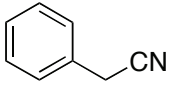
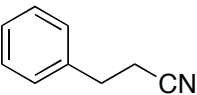
Figure 1. The Ritter Reaction Employing *tert*-Butyl Acetate



This efficient procedure has a broad substrate scope for the high yielding synthesis of both electron-donating and electron-withdrawing aromatic, alkyl, and α,β -unsaturated *tert*-butyl amides (Table 1). It is

Table 1. Substrate Scope

$$\text{R-CN} \xrightarrow[\text{(b) H}_2\text{SO}_4 \text{ (1.8 equiv), AcOH, room temperature}]{\text{(a) } t\text{-BuOAc (2 equiv), AcOH}} \text{R-C(=O)-NH-C(CH}_3)_3$$

Entry	Substrate	Time	Yield ^d
1		3	91%
2		2	90%
3		20	85% ^b
4		2	81%
5		1	85% ^a
6		2	82%
7		5	95%
8		17	80% ^c
9		1	93%
10		2	85%
11		1	94%
12		1	88%

(a) The reaction required 2.5 equiv *t*-butyl acetate and 2 equiv sulfuric acid;
 (b) Charged additional sulfuric acid (0.5 equiv) and *t*-butyl acetate (0.5 equiv) after 17 h; (c) Corrected for purity by ¹H NMR; (d) Isolated product

noteworthy that in addition to the main example, methyl 4-cyanobenzoate, the reaction conditions are compatible with other acid-sensitive functional groups (Table 1, entries 6-7).

In summary, employing *tert*-butyl acetate in the presence of sulfuric acid and acetic acid provides a safe, scalable, and robust method for the conversion of nitriles to *tert*-butyl amides.

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2. Department of Chemistry, Colorado State University, Fort Collins, CO 80523. E-mail: john.l.wood@colostate.edu
3. For a review see: Krimen, L. I.; Cota, D. L. *Org. React.* **1969**, *17*, 213–325.
4. *tert*-Butyl acetate as *tert*-butyl cation source: (a) Fernholz, H.; Schmidt, H. J. *Angew. Chem., Int. Ed.* **1969**, *8*, 521. (b) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453–1455.
5. Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207–2209.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Methyl 4-cyanobenzoate: Benzoic acid, 4-cyano-, methyl ester; (1129-35-7)

Acetic acid; (64-19-7)

tert-Butyl acetate: Acetic acid, 1,1-dimethylethyl ester; (540-88-5)

Sulfuric acid; (7664-93-9)

Ammonium acetate; (631-61-8)

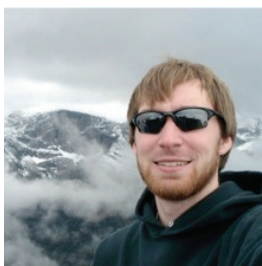
Methyl 4-(*tert*-butylcarbamoyl)benzoate: Benzoic acid, 4-[[1,1-dimethylethyl)amino]carbonyl]-, methyl ester; (67852-98-6)



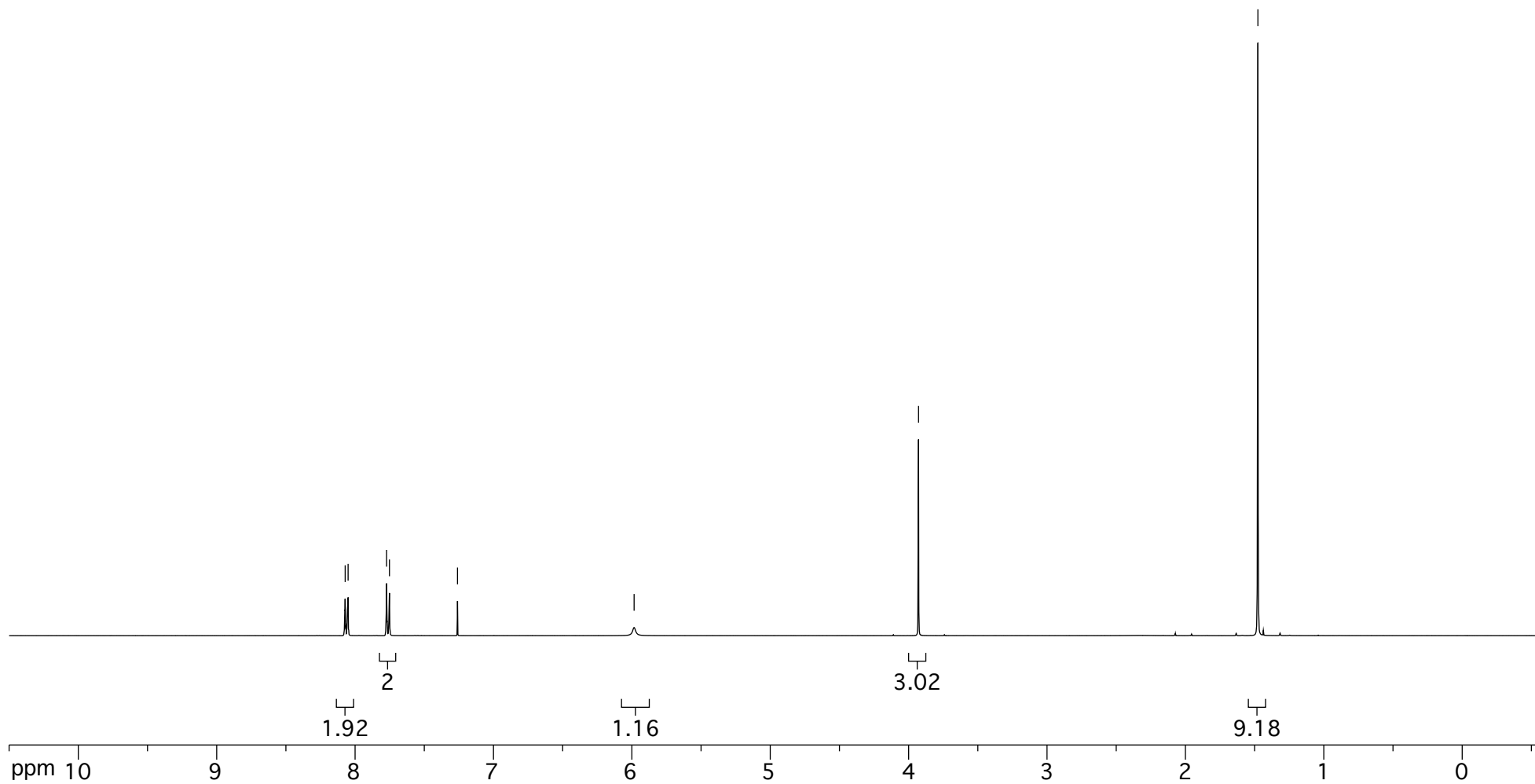
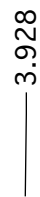
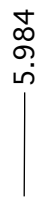
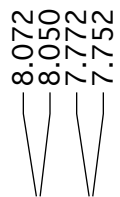
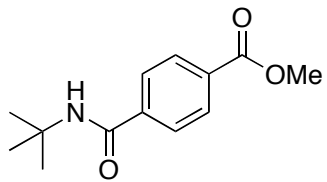
Jacqueline E. Milne received a MSci (Hons) in chemistry at the University of Glasgow in 1999 and a Ph.D. from the University of Leeds with Professor Philip Kocienski in 2003. Her graduate research explored new syntheses of α -metallated cyclic enol ethers and their application to the synthesis of D-erthro-sphingosine. In 2003 she joined Professor Stephen Buchwald's group as a postdoctoral fellow at MIT. Here she developed a new catalyst system for Negishi cross-coupling reactions. In addition, she developed an asymmetric copper-catalyzed conjugate reduction for the dynamic kinetic resolution of α,β -unsaturated lactones and applied to the synthesis of eupomatilone-3. In 2005 Jacqueline joined the Chemical Process R&D at Amgen in Thousand Oaks.

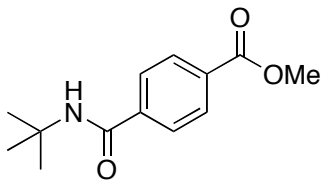


Jean Baum completed her undergraduate studies at University California, San Diego. After a six-year employment at Fluorochem, Inc. she attended the University of California, Los Angeles and obtained an M.S. degree in chemistry under the supervision of Professor Robin L. Garrell. She has been employed at Amgen since 2001 where she was recently promoted to Senior Associate Scientist within Chemical Process R&D.



Travis McMahon received his B.S. in chemistry from Western Washington University in 2008 where he did undergraduate research for Professor James R. Vyvyan. He is currently working towards his Ph.D. at Colorado State University under the supervision of Professor John L. Wood, where he is working towards the total synthesis of the tetrapetalone natural products and has also worked on the synthesis of gliotoxin, dehydrogliotoxin and analogs.





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