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High-Yielding Syntheses of 1-Piperidin-4-yl Butyro- and Valerolactams through a Tandem Reductive Amination−Lactamization (Reductive Lactamization)

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Abstract:

We report a procedure for the concise and high-yielding syntheses of 1-piperidin-4-yl-substituted butyro- and valerolactams. Beginning with 1-benzyl-4-piperidone and γ- or δ-amino esters or acids, we have effected a tandem reductive amination−lactamization using sodium triacetoxyborohydride. This procedure represents an inexpensive and scaleable alternative to previous multistep syntheses of these important pharmaceutical building blocks.

1-Piperidin-4-yl-substituted butyro- and valerolactam moieties have been used in a variety of biologically active molecules, including tachykinin antagonists,[1] dual NK1/NK2 inhibitors,[2] and blood coagulation factor X (FXa) inhibitors.[3] Recently, these subunits have been used within our internal medicinal chemistry programs.[4] As the demand for these piperidinyl lactams increased, we sought an improved and scaleable synthesis for **1**, **2**, and **3** (Figure 1).

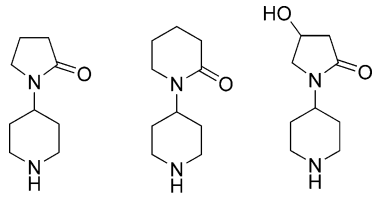

Figure 1. **1-Piperidin-4-yl lactam targets.**

A previously reported synthesis of compound **1** (Scheme 1) employed a functionalized acid chloride in conjunction with *N*-Cbz-4-aminopiperidine (**5**).[5] *N*-Cbz-4-aminopiperidine is derived from the 4-(*N*-Boc-amino)piperidine (**4**) in modest yields by a protection/deprotection sequence.[6] Following the two-step installation of the lactam, the Cbz protecting group is removed by hydrogenation in the presence of catalytic $Pd(OH)_2$.

This methodology was used in the initial synthesis of compounds **1** and **2** by our medicinal chemistry teams. However, this sequence was lengthy, and it suffered from use of expensive starting materials and reagents that were not amenable to use on large scale.[7] A sequence toward related compounds, which suffers from similar shortcomings, has also been reported in the patent literature.[8]

A second synthesis reported in the literature[2] involved a reductive amination between a lactam and 1-benzyl-4-piperidone using $NaCNBH_3$ (Scheme 2). However, in our hands, this reaction failed to yield the desired product.

Our retrosynthetic analysis of **1** revealed a protected 4-piperidone and a linear amino acid as potential starting materials (Scheme 3).

An analogous method for the synthesis of tertiary lactams has been published by Abdel-Magid et al.[9] In this case, a lactam ring was installed onto aliphatic and carbocyclic ketones using ethyl-4-aminobutyrate. The discovery of this tandem reductive amination/lactamization, which the authors coined "reductive lactamization", was made while building on their exploration into the uses of sodium triacetoxyborohydride.[10] We were attracted to this method of synthesis by both its operational simplicity and the potential for utilization of inexpensive, commercially available starting materials.[7]

Results and Discussion

Initially we chose 1-Boc-4-piperidone and ethyl 4-aminobutyrate as the starting materials for our synthesis of compound **1** (Scheme 4). The Boc protecting group was

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(1) For examples, see: (a) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. PCT Int. Publ. No. WO2003/080619, 2003. (b) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. PCT Int. Publ. No. WO2003/062245, 2003. (c) Middleton, D. S.; Stobie, A. PCT Int. Publ. No. WO2003/051868, 2003. (d) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. PCT Int. Publ. No. WO2003/050123, 2003.

(2) Ting, P. C.; Lee, J. F.; Anthes, J. C.; Shih, N. Y.; Piwinski, J. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 491.

(3) Kubo, K.; Imaeda, Y. PCT Int. Publ. No. WO2005/058823, 2005.

(4) Axe, F. U.; Bembenek, S. D.; Butler, C. R.; Edwards, J. P.; Fourie, A. M.; Grice, C. A.; Savall, B. M.; Tays, K. L.; Wei, J. PCT Int. Publ. No. WO2005/012297, 2005. (b) Axe, F. U.; Bembenek, S. D.; Butler, C. R.; Edwards, J. P.; Fourie, A. M.; Grice, C. A.; Savall, B. M.; Tays, K. L.; Wei, J. PCT Int. Publ. No. WO2005/012296, 2005.

(5) Miller, S. C. PCT Int. Publ. No. WO94/10146, 1994.

(6) Recent literature details the direct and selective substitution of secondary amines in the presence of primary amines: Laduron, F.; Tamborowski, V.; Moens, L.; Horvath, A.; De Smaele, D.; Leurs, S. *Org. Process Res. Dev.* **2005**, *9*, 102.

(7) A search using the Scifinder database was able to locate 4-(Boc-amino)-piperidine priced at $6.6/g (250 g) and 1-benzyl-4-piperidone priced at $0.31/g (5 kg).

(8) Reichard, G. A.; Aslanian, R. G.; Alaimo, C. A.; Kirkup, M. P.; Lupo, A., Jr.; Mangiaracina, P.; McCormick, K. D.; Piwinski, J. J.; Shankar, B. B.; Shih, Neng-Yang; Spitler, J. M.; Ting, P. C.; Ganguly, A.; Carruthers, N. I. (Cont.-in-part of U.S. Ser. No. 460,819, abandoned) U.S. Patent 5,696,267, 1997.

(9) Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.

(10) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. (b) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537. (c) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (d) Abdel-Magid, A. F.; Maryanoff, C. A. Use of Sodium Triacetoxyborohydride in Reductive Amination of Ketones and Aldehydes. In *Reductions In Organic Synthesis: Recent Advances and Practical Applications*; Abdel-Magid, A. F., Ed.; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; pp 201−216.

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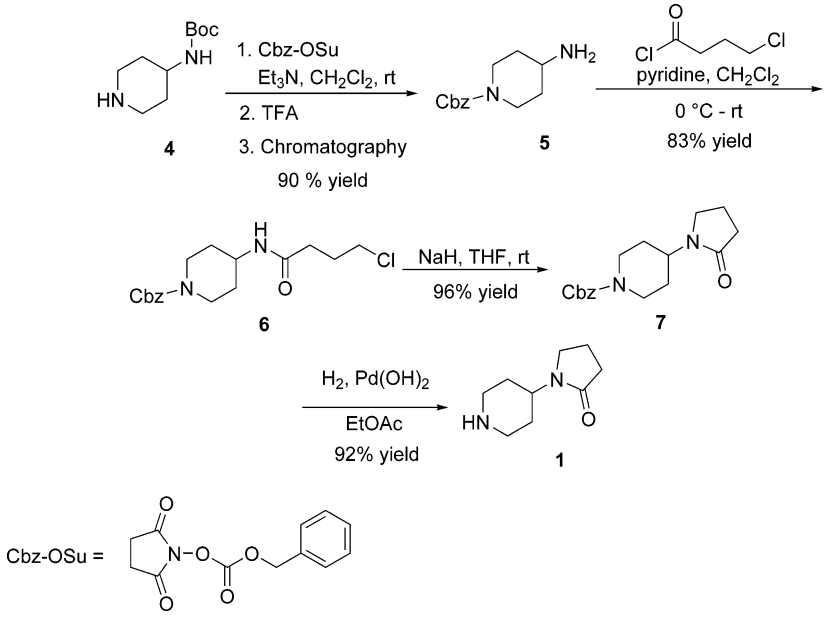
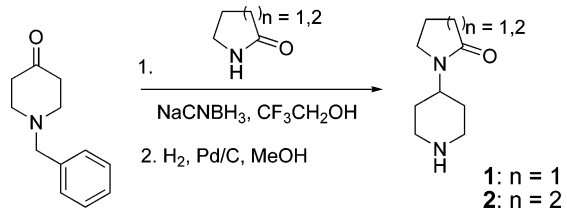
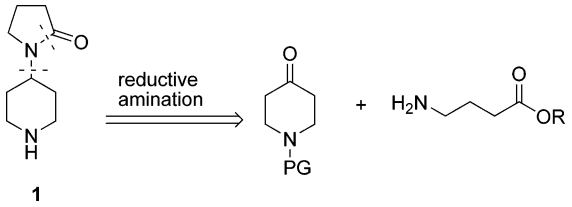
Scheme 1. **Literature synthesis of lactam 1**



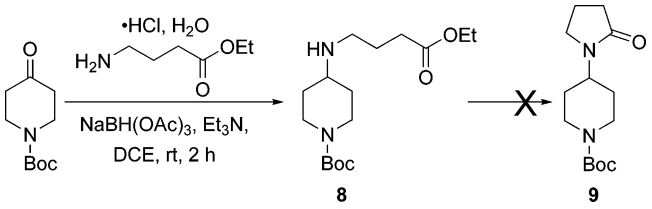
Scheme 2. **Literature synthesis of compounds 1 and 2**



Scheme 3. **Retrosynthetic deconstruction of lactam 1**



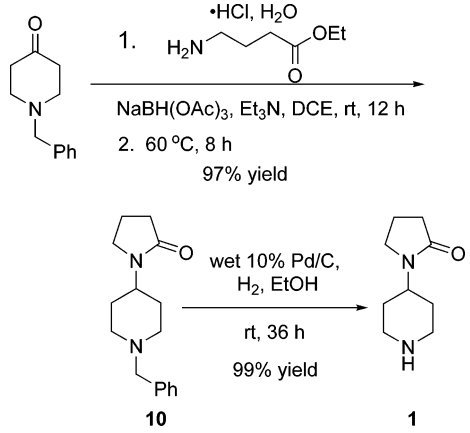
Scheme 4. **Initial unsuccessful synthesis of lactam 10**



chosen for its expected relative ease of removal in the final steps of the synthesis. The reductive amination is complete after 2 h at room temperature. Unexpectedly, compound **8** did not cyclize to form the desired lactam system **9** due to in situ Boc deprotection and subsequent degradation of the resultant species.

The use of elevated temperatures and/or the addition of NaOH or TsOH did not effect a cyclization of compound **8** to form lactam **9**. The addition of TFA did result in complete removal of the Boc protecting group; however, compound **1** was not observed. These findings led us to explore other protected piperidones.

Scheme 5. **First successful synthesis of lactam 1 through reductive lactamization**



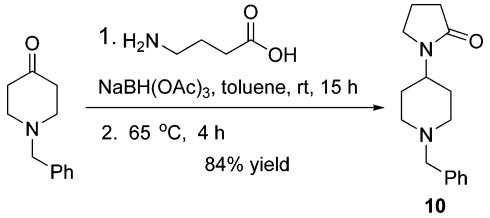
Screening the commercially available *N*-acetyl, *N*-Cbz, *N*-carbethoxy, and *N*-benzyl-4-piperidone we were able, in each case, to produce the fully cyclized 1-piperdin-4-yl lactam system in good yield. Ultimately, 1-benzyl-4-piperidone was chosen as our preferred starting material due to its low cost, commercial availability, and ease of handling.

Using 1-benzyl-4-piperidone as the starting material, the synthesis of 1-piperidin-4-yl-pyrrolidin-2-one (**1**) was completed in a two-step sequence (Scheme 5).

In the first step of the sequence, ethyl 4-aminobutyrate and sodium triacetoxyborohydride[11] were employed to install the lactam ring onto the 1-benzyl-4-piperidone. The butyrate is commercially available as the hydrated HCl salt, and thus, triethylamine was employed to buffer the reaction. We have found that the preferred process for the installation of the lactam ring involves aging the reaction at ambient temperature until the reductive amination is complete. Heating is subsequently applied to produce complete cyclization to the

(11) The reductive lactamization, when using sodium borohydride in methanol, required 60 h at 45 °C to yield 70% product. The mass balance was the trans-esterified, uncyclized, reductive amination product.

Scheme 6. **Second-generation synthesis of compound 10 through reductive lactamization**



lactam.[12] The obtained product is generally of sufficient purity for further use; however, it may be purified by recrystallization from hot EtOAc/heptane. We have found that 1,2-dichloroethane, THF, 2-methyl-THF, MTBE, toluene, and (trifluoromethyl)benzene are all good solvent choices for this reaction. Our initial experiments utilized 1,2-dichloroethane in keeping with the previous literature precedent.[9] Currently, our preferred solvent for this transformation is toluene. In the second step of the sequence, the benzyl group was cleaved by hydrogenation, using ethanol and 10% Pd/C, to yield **1**.

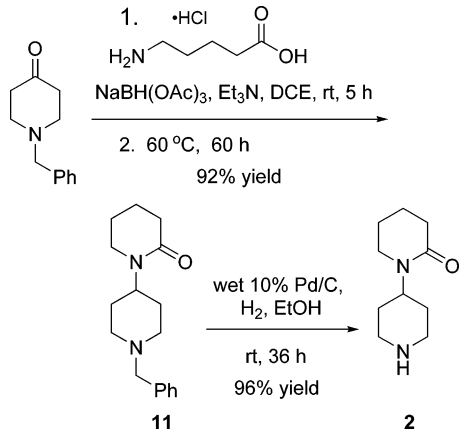
The initial method for the production of these lactams required the portionwise addition of the reducing agent into the reaction mixture (Method A). This method became problematic when investigated on a 0.375 mol scale due to an increase in solution viscosity, a potentially hazardous exotherm, and the mechanical difficulties involved with adding solid sodium triacetoxyborohydride. Due to these potential process hazards, an alternate procedure, where the reaction flask was charged with the butyrate, borohydride, and triethylamine followed by controlled addition of the piperidone, has also been developed (Method B). This procedure alleviates the difficulties observed with Method A and has emerged as our method of choice. This method has been successfully demonstrated on a 0.75 mol scale.

Subsequently, it was found on a 5.0-g scale that we could accomplish the same transformation in comparable yields and ease by replacing the ethyl 4-aminobutyrate with 4-aminobutyric acid (GABA) (Method C). This variation of the transformation obviates the use of triethylamine in the reaction (Scheme 6). The direct application of free amino acids should provide access to a wider range of analogues while concomitantly lowering material costs.

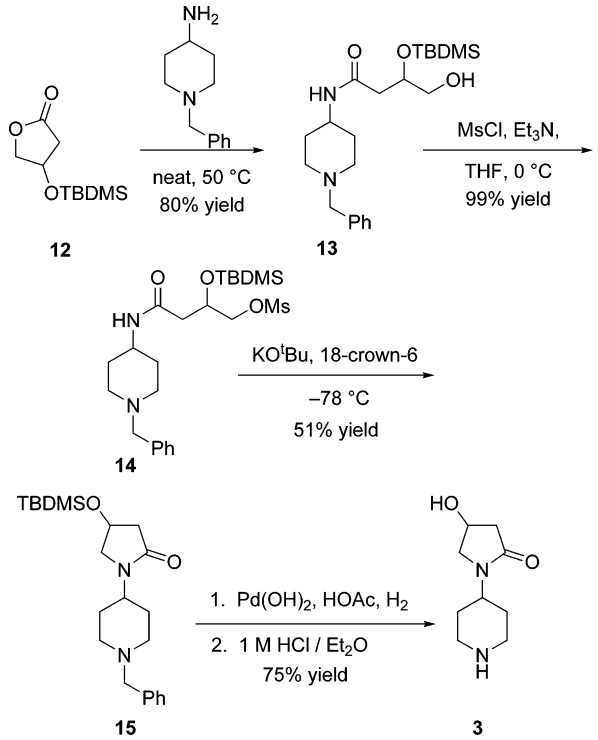
Direct application of this process using 1-benzyl-4-piperidone and 5-aminovaleric acid as the feedstocks provided valerolactam **2** in good yield (Scheme 7). It is interesting to note that an extended reaction time was required to complete the lactamization of the acyclic intermediate to form compound **11**. The benzyl group was removed by hydrogenation, as in the synthesis of **1**.

In addition to syntheses of lactams **1** and **2**, we also sought a process for the synthesis of the 4-hydroxy-1-piperidin-4-yl-pyrrolidin-2-one (**3**). The medicinal chemistry route (Scheme 8) was based on the work of Osamu Kanno et al.[13]

Scheme 7. **Synthesis of lactam 2 through reductive lactamization**



Scheme 8. **Medicinal chemistry synthesis of hydroxy lactam 3**

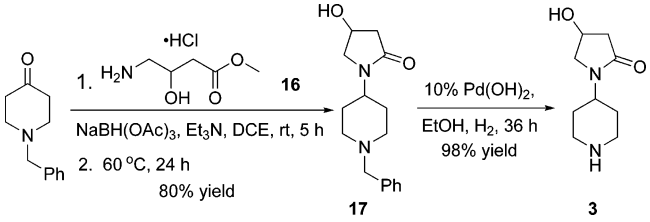


We reasoned that our reductive lactamization process could also be employed for the synthesis of 4-hydroxylactam **3**. Our initial attempts utilized commercially available, racemic 4-amino-3-hydroxylbutyric acid. However, use of the acid directly for the reductive lactamization failed to yield hydroxylactam **17** in any appreciable yield. When methyl 4-amino-3-hydroxylbutyrate (**16**) was used, hydroxylactam **17** was produced in good yield and high purity (Scheme 9). Deprotection of the benzyl group with Pd/C was found to be ineffective. Employing $Pd(OH)_2/C$, the hydrogenolysis proceeded cleanly and in excellent yield. The addition of 10% acetic acid to the reaction media was found to increase the rate of the deprotection; however, the isolated acetate salt of compound **3** proved very hygroscopic and quickly deliquesced into a dark-red oil.

(12) This protocol was developed after an initial iteration presented a process hazard on 10.0-g scale. When a vessel was charged with all of the reagents and heated to 60 °C directly, a severe exotherm coupled with violent off gassing was observed.

(13) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173.

Scheme 9. **Synthesis of hydroxylactam 3 through reductive lactamization**



Conclusion

By employing a reductive lactamization process, scaleable syntheses of compounds **1** and **2** were developed by our laboratories. As proof of the method's generality, we have also successfully applied this process to a concise, high-yielding synthesis of racemic **3**. The benefits of this process are the use of widely available and inexpensive commercial feedstocks as well as mild reaction conditions. A further strength of our optimized process is that it does not require any chromatography. The crude reaction products are obtained in good purity and can be further purified by recrystallization if necessary. The ability to use both amino esters and, in some cases, the amino acids to construct the lactam greatly widens the utility of this process. Furthermore, this process is an example of a direct reductive amination using an open-chain amino acid, a reaction that is rarely seen in organic synthesis.[14] This modular approach to the lactam formation should enable the assemblage of a wide range of substitution patterns.

Experimental Section

General Experimental Chemical Procedures. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a Bruker DPX 400 or Bruker DPX 500 spectrometer. Melting points were taken using a TA Instruments DSCQ 100 apparatus. High-resolution mass spectra were taken on a Bruker microTOF apparatus. Infrared spectroscopy was performed on a Nicolet Avatar 360 FT-IR as a neat pellet. Flash column chromatography was performed using Merck silica gel 60. HPLC analysis was performed on a Hewlett-Packard 1100 (Agilent ZORBAX Eclipse XDB-C8, 5 μm, 4.6 mm $\times$ 150 mm, flow rate 1 mL/min, gradient (acetonitrile/water with 0.05% trifluoroacetic acid): 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water). Combustion analyses were preformed by Numega Resonance Labs, San Diego, California. All reagents were purchased from Aldrich and used as received with the exception of ethyl-4-aminobutyrate hydrochloride, which was purchased from Alfa Aesar. All solvents utilized were purchased in anhydrous form from E.M. Scientific and passed through two columns of neutral alumina (DCE, THF, MTBE, MeOH) or one column of neutral alumina and one column of Q5 oxygen scavenger (toluene) with the exception of 2-methyl THF and (trifluoromethyl)benzene which were purchased in anhydrous form from Aldrich in "Sure Seal" glass bottles and used directly. "Brine" refers to a saturated aqueous solution of NaCl.

1-(1-Benzyl-piperidin-4-yl)-pyrrolidin-2-one (10). *Method B.* To a 5-L jacketed reactor equipped with an overhead mechanical stirrer, thermocouple probe, J-Kem dose controller, and dynamic nitrogen inlet were added ethyl-4-aminobutyrate hydrochloride (150.9 g, 0.90 mol), $NaBH(OAc)_3$ (206.6 g, 0.97 mol), and anhydrous toluene (2.25 L). Stirring was commenced, and triethylamine (379.5 g, 3.75 mol) was added over a 5-min period. Once addition was complete, the reactor was aged at 20 °C for 10 min. A solution of 1-benzyl-4-piperidone (141.9 g, 0.75 mol) in anhydrous toluene (250 mL) was then added over a 1-h period. A slight exotherm of ~6 °C was observed during addition. After completion of addition, the solution was aged at 20 °C for 1 h and then heated to 75 °C for an additional 2 h. The solution was then cooled to 20 °C and quenched by the slow addition of water (1 L). A mild exotherm of ~14 °C was observed during the addition. The layers were separated after 20 min of stirring, and the organic layer was extracted again with water (1 L). The organic layer was then extracted with 1 N aqueous HCl (3 $\times$ 500 mL). The aqueous layers were combined, adjusted to a pH of ~12 with 6 N aqueous NaOH, and extracted with *i*-PrOAc (2 $\times$ 1 L). All organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum until a thick, stirrable slurry was achieved. This slurry was diluted with heptane (1.5 L) with stirring. The resultant slurry was slowly cooled to 10 °C, and the product was collected by filtration. The cake was air-dried for 20 min and then placed in a 55 °C vacuum oven for 24 h to yield 1-(1-benzyl-piperidin-4-yl)pyrrolidin-2-one (**11**) (178.0 g, 92% yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.24 (m, 5H), 3.99 (tt, J = 11.9 Hz, J = 4.4 Hz, 1H), 3.50 (s, 2H), 3.35 (t, J = 7.0 Hz, 2H), 2.95−2.91 (m, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.09 (dt, J = 11.8 Hz, J = 2.6 Hz, 2H), 1.99 (pentet, J = 7.6 Hz, 2H), 1.72 (dq, J = 12.2 Hz, J = 8.3 Hz, 2H), 1.64−1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.52, 138.31, 129.15, 128.22, 127.05, 63.08, 52.78, 48.88, 42.93, 31.57, 29.30, 18.14. IR (neat): 1667, 1492, 1421, 1365, 1342, 1310, 1265, 1220, 1145, 1124, 1023, 989, 792, 737, 698 cm^{-1}. Anal. Calcd (found): C, 74.38 (74.47); H, 8.58 (8.44); N, 10.84 (10.90). MS (electrospray): exact mass calcd for $C_{16}H_{22}N_2O$ 258.1732; m/z found 259.1803 $[M + H]^+$; mp 81.3 °C.

1-Piperidin-4-yl-pyrrolidin-2-one (1). To a 2.25-L Parr flask were added 1-(1-benzyl-piperidin-4-yl)-pyrrolidin-2-one (**11**) (91.6 g, 0.355 mol), ethanol (200 proof, 550 mL), and 10 wt % Pd/C (9.0 g, wet catalyst). The Parr flask was then shaken under a hydrogen atmosphere (45 psi) until hydrogen consumption ceased, ~36 h. The catalyst was removed through filtration (Zapcap-CR, 0.45 μm Nylon) and washed with EtOAc. The combined filtrates were concentrated under vacuum to yield 1-piperidin-4-yl-pyrrolidin-2-one (**1**) (57.1 g, 95% yield) as a pale-yellow oil that solidified to an off-white solid upon standing. On smaller scale (5.0 grams) the use of acidic media (3:1 EtOH/HOAc) reduced the reaction time to ~18 h.

(14) Levadala, M. K.; Banerjee, S. R.; Maresca, K. P.; Babich, J. W.; Zubieta, J. *Synthesis* **2004**, 1759.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.06 (tt, J = 11.9 Hz, J = 4.2 Hz, 1H), 3.37 (t, J = 7.0 Hz, 2H), 3.13−3.11 (m, 2H), 2.71 (dt, J = 12.1 Hz, J = 2.5 Hz, 2H), 2.39 (t, J = 8.1 Hz, 2H), 1.99 (pentet, J = 7.6 Hz, 2H), 1.67−1.64 (m, 2H) 1.58 (dq, J = 12.1 Hz, J = 4.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.45, 49.05, 45.84, 42.95, 31.57, 30.42, 18.13. IR (neat): 2941, 1657, 1492, 1424, 1317, 1285, 1214, 1141, 1091, 1006, 932, 870, 810, 682, 633 cm^{-1}. Anal. Calcd (found): C, 64.25 (64.03); H, 9.59 (9.91); N, 16.65 (16.34). MS (electrospray): exact mass calcd for $C_9H_{16}N_2O$ 168.1263; m/z found 169.1338 $[M + H]^+$; mp 106.2 °C.

Acknowledgment

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Supporting Information Available

Experimental details concerning the syntheses of compounds **10** (methods A and C), **11**, **2**, **16**, **17**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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