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Green Chemistry Approach to the Synthesis of N-Substituted Piperidones

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Abstract: An efficient green chemistry approach to the synthesis of N-substituted piperidones and piperidines was developed and applied to the synthesis of 1-(2-pyridinyl-methyl)-piperidin-4-one, **1**, a key starting material for the synthesis of **LY317615**, an antiangiogenic agent currently under development at Eli Lilly and Company (Chart 1).[1] The general utility of this methodology, which presents significant advantages over the classical Dieckman approach to this class of compounds, was also demonstrated by the direct synthesis of a series of substituted piperidones and piperidines, including potential dopamine D4 receptor antagonists **2** and **3**, that have been evaluated in the clinic as antipsychotic agents (Chart 2).[2]

To support clinical evaluation of **LY317615**, multikilogram quantities of 1-(2-pyridinyl-methyl)-piperidin-4-one, **1**, were required (Chart 1). A synthesis of **1** in 50% yield was reported by Hosken via a classical three-step sequence, involving a bis-Michael addition of 2-(aminomethyl)-pyridine, **4**, with ethyl acrylate, **5**, to generate **6** followed by Dieckman cyclization and base-catalyzed decarboxylation (Scheme 1).[3] This method represents the most general approach to the synthesis of N-substituted piperidones reported in the literature.[4]

Our initial scale-up of the Dieckman cyclization sequence to produce kilogram quantities of **1** resulted in significant processing problems that included (1) a need for a large excess of ethyl acrylate (7 equiv) to ensure complete formation of the bis-Michael adduct **6**; (2) long reaction times (7−10 days); (3) a need to completely remove residual ethyl acrylate from **6** prior to the Dieckman cyclization, otherwise the yield and quality of **1** were significantly reduced; and (4) significant problems in isolation of **1**, following decarboxylation, and partitioning of **1** into organic solvents proved to be a significant challenge due its high aqueous solubility. In fact, five extractions of the aqueous layer with CH_2Cl_2 were required to achieve efficient isolation of **1** in 70% yield.[5] Furthermore, a competing side reaction with CH_2Cl_2 produced a troublesome chloroiminium salt impurity.[6] Overall the Dieckman process for preparing **1** was inefficient and required multiple solvents and cumbersome aqueous workups. In addition, the dilute reaction conditions required for scale-up resulted in large generation of solvent and reagent waste streams that were environmentally undesirable.

An alternate approach to N-substituted piperidones developed by Kuehne has some advantages over the classical Dieckman conditions.[7] Mainly, the troublesome bis-Michael addition is avoided since the desired piperidone is prepared by an exchange reaction between 4-oxo-piperidinium iodide, **7**, and a primary amine (Scheme 2). However, shortcomings of this approach are (1) exchange reactions frequently do not go to completion; (2) the approach is not applicable to systems where quaternary amine salts cannot be easily formed; and (3) it lacks the

CHART 1

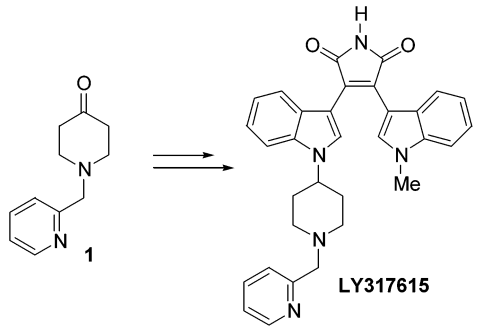
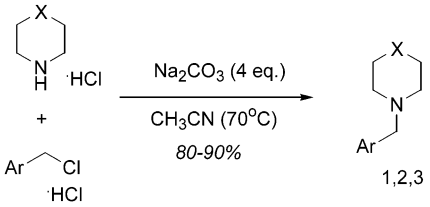
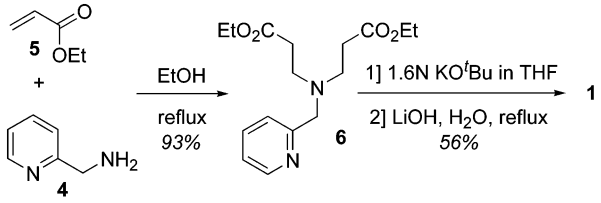


CHART 2



SCHEME 1



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(1) (a) Faul, M. M., Gillig, J. R.; Jirousek, M. R.; Ballas, L. M.; Schotten, T.; Kahl, A.; Mohr, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1857. (b) Faul, M. M.; Grutsch J. L.; Kobierski, M. E.; Kopach, M. E.; Krumrich, C. A.; Staszak, M. A.; Sullivan, K. A.; Udodong, U.; Vicenzi, J. T. *Tetrahedron*. In press.

(2) (a) Belliotti, T. R.; Blankley, C. J.; Kestemn, S. R.; Wise, L. D.; Wustrow, D. J. U.S. Patent 5,945,421, August 31, 1999. (b) Maryanoff, C. A.; Reitz, A. B.; Scott, M. K. U.S. Patent, 8 pp, Continuation-in-part of U.S. Patent 5,314,885.

(3) Hosken, G. D.; Hancock, R. D. *J. Chem. Soc., Chem. Comm.* **1994**, 1363.

(4) (a) Schaefer, J. P.; Bloomfield J. J. *Org. React.* **1967**, *15*, 1. (b) McElvain, S. M. *J. Am. Chem. Soc.* **1926**, *48*, 2179. (c) Leonard; N. J.; Barthel, E., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 3632. (d) McElvain, S. M.; Stork, G. *J. Am. Chem. Soc.* **1946**, *68*, 1049. (e) Reed; Cook. *J. Chem. Soc.* **1945**, 399. (f) Dickerman; Lindwall. *J. Org. Chem.* **1949**, *14*, 530. (g) Bolyard, N. W.; McElvain, S. M. *J. Am. Chem. Soc.* **1929**, *51*, 922. (h) Elpern, B.; Wetterau, W.; Carabateas, P.; Grumbach, L. *J. Am. Chem. Soc.* **1958**, *80*, 4916.

(5) Partition coefficients: CH_2Cl_2 $k = 8.6$, EtOAc $k = 0.9$, MTBE $k = 0.8$.

(6) Hansen, S. H.; Nordholm, L. *J. Chromatogr.* **1981**, *204*, 97.

(7) (a) Kuehne, M.E.; Muth R. S. *J. Org. Chem.* **1991**, *56*, 2701. (b) Kuehne, M.E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513. (c) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.; Frey, L.; Karady, S., Shi, Y.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324. (d) Tortolani, D.; Poss, M. *Org. Lett* **1999**, 1, 1261.

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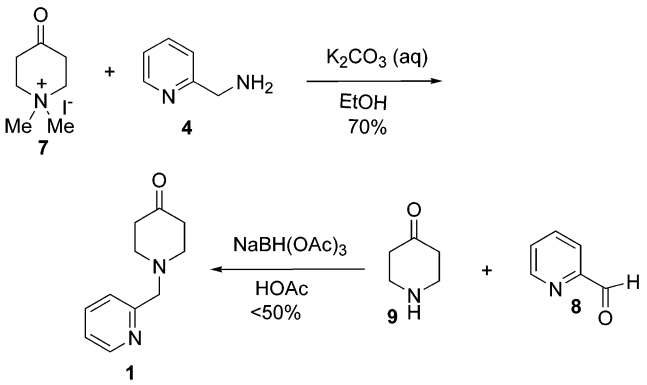
SCHEME 2

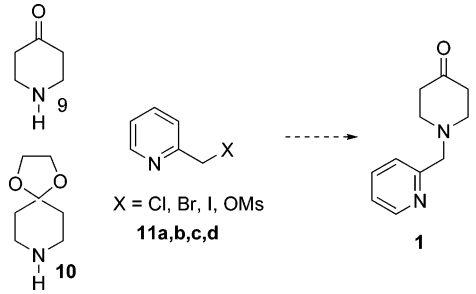


broad generality of the Dieckman condensation. In addition, hindered amines are known to produce cross-coupled side products.[8] However, utilizing Kuehne's methodology successfully afforded **1** in 70% yield via an exchange reaction between **7** and **4** (Scheme 2).[7a,b] Iodide salt **7** was prepared in 75% yield by treatment of commercially available 4-methyl-piperidone with CH_3I in diethyl ether. A mixture of **4** and **7** was then stirred in aqueous ethanol at 90 °C in the presence of excess K_2CO_3 until the exchange reaction was complete. The disadvantage to Kuehne's approach was that aqueous workup was tedious and required multiple extractions with CH_2Cl_2 to isolate **1** from the aqueous layers as per the Dieckman process. The third approach evaluated for preparation of **1** was reductive amination of 2-pyridinecarboxaldehyde, **8**, with 4-piperidone, **9**, or ketal **10**, which produced impure mixtures of **1** due to competitive reduction of **8** to 2-(hydroxymethyl)-pyridine and self-condensation of **9**.[9]

Although the above modifications have been beneficial in the specific examples for which they were developed, a direct approach to N-substituted piperidones that is applicable to a wide range of substrates has not been demonstrated. In this paper, we describe a new general green chemistry approach to the synthesis of a variety of N-substituted piperidones and piperidines. An alternate synthesis of N-substituted piperidones, e.g., **1**, that has not been previously reported in the literature, involves direct alkylation of 2-picolyl chloride with 4-piperidone or the keto-protected derivative thereof. Thus, it was anticipated that a single-step, one-pot process to produce **1** could be achieved under mildly basic conditions (Scheme 3). This new approach to **1** potentially provides improved atom economy, as well as solvent and waste stream minimization, and the potential to deliver multikilogram quantities of **1** to support clinical development of **LY317615**.

Initially, construction of **1** was attempted by alkylation of ketal **10** with 2-picolyl chloride hydrochloride, **11**, in the presence of Na_2CO_3 in refluxing acetonitrile. While these conditions quantitatively coupled the above fragments, deprotection of the intermediate ketal was sluggish.[10] This led to investigation of a more efficient approach to **1** using commercially available 4-piperidone hydrochloride monohydrate, **9**. Since in situ liberation of the free base of **11a** was successful vide infra, it was anticipated that this approach would also be effective using **9**. The transformation proceeded smoothly using 3−4 equiv of powdered Na_2CO_3 or K_2CO_3 in acetonitrile at 70 °C.[11] Under these conditions, alkylation was complete in 4−6 h and **1** was isolated in 90% yield after filtration of the salts and removal of solvent in vacuo. Powdered Na_2CO_3 or K_2CO_3 was comparable and clearly produced the best results, while reactions using granular forms of the above reagents were sluggish and produced **1** in lower yield and purity.[12] The alkylation was successful with a variety of other bases such as Hunig's base and $NaHCO_3$ but was unsuccessful with triethylamine, DBU, pyridine, and morpholine.[13] However, use of amine bases requires aqueous workup, which on the basis of our experience would be difficult for **1**. In addition, the main waste byproduct via the carbonate base alkylation strategy was CO_2, which was desirable from an environmental perspective relative to amine bases and facilitates workup. The best solvents for the alkylation were polar aprotic solvents such as acetonitrile or DMF as per literature precedent.[14] Ultimately, acetonitrile was chosen as the solvent for scale-up because waste streams were minimized and an aqueous workup was not required.[15]

SCHEME 3



Alternate leaving groups (X = Br, I, OMs) were evaluated in the alkylation but afforded **1** in reduced yield and with increased levels of impurities due mainly to quaternization. Reduction of the reaction temperature

(8) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(9) Aqueous workup was problematic due to the large neutralization volumes required and the difficulty in separating **1** from residual 2-(hydroxymethyl)-alcohol and related polar impurities. The best results were achieved with ketal **10**, but competitive reduction of **8** (15−30%) was not suppressed. See ref 10 for deprotection conditions.

(10) **Method A.** To a solution of **11** (2 mmol) in 2:1 acetic acid/water (7.5 mL) was added 0.1 mL of concentrated HCl, and the solution was heated to 60 °C for 18 h. The solution was poured into ethyl acetate and treated with saturated sodium carbonate solution until the aqueous layer was basic. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The organic layer was washed with water followed by saturated NaCl solution and then concentrated to an oil. NMR showed an 8:1 ratio of product to starting material. **Method B.** To a solution of **11** (4 mmol) in acetone were added pyridinium *p*-toluenesulfonate (1.3 mmol) and a few drops of water. The resulting solution was heated to reflux for 3 h. NMR of a reaction aliquot showed complete disappearance of starting material but also no desired product and a complex mixture of other products.

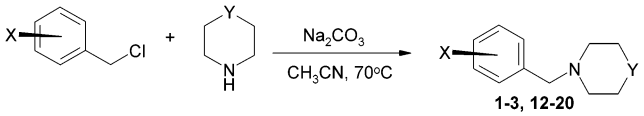
(11) Na_2CO_3 (2 equiv) is required to free base 2-picolyl chloride hydrochloride and 4-piperidone monohydrate hydrochloride in situ.

(12) Typically, **1** is produced in >99% purity by HPLC A.N. analysis when powdered carbonate base is used. Granular carbonate bases require longer alkylation reaction times at 70 °C, and up to 10% quaternization is observed. 2-(hydroxymethyl)pyridine is typically observed at <0.5% for this reaction.

(13) Main byproducts observed are the amine base/2-picolyl chloride direct addition product.

(14) Bellouard, F.; Chuburu, F.; Kervarec, N.; Toupet, L.; Triki, S..; LemMest, Y.; Handel, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3499.

TABLE 1. Examples of Alkylation Scope[a]



compound	alkylating agent	amine	yield (%)
1	2-picolyl chloride	4-piperidone	90
2	2-chloromethyl quinoline	1-phenyl piperazine	80
3	2-chloromethylquinoline	4-phenyl-1,2,3,6-THP	80
12	2-picolyl chloride	4-piperazino aceto-phenone	92
13	2-picolyl chloride	4-piperidino piperidine	84
14	2-picolyl chloride	isonipecotamide	35
15	3-picolyl chloride	4-piperidone	81
16	4-picolyl chloride	4-piperidone	84
17	2-chloromethyl-quinoline	4-piperidone	86
18	2-methoxy-benzyl chloride	4-piperidone	88
19	2-chloromethyl-benzimidazole	4-piperidone	86
20	2-nitrobenzyl chloride	4-piperidone	90

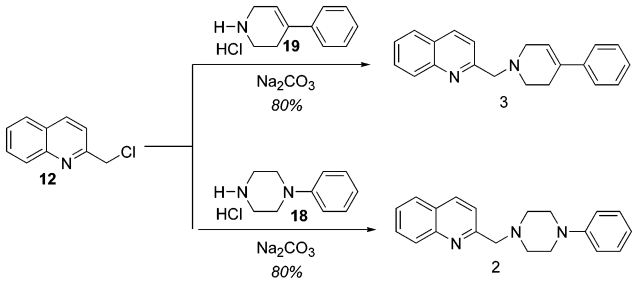
[a] All amines and alkylating reagents were used as their hydrochloride salts unless otherwise specified.

to 23 °C produced higher impurity levels than the picolyl chloride system at 70 °C, which is consistent with a carbocation mechanism. Thus, in the systems with stronger activation, the carbocation is generated faster and has a propensity to undergo side reactions such as quaternization or reaction with water to produce 2-(hydroxymethyl)pyridine. In fact, control experiments of the title reaction revealed that 2-picolyl chloride free base is formed at 23 °C with powdered Na_2CO_3, while the 4-piperidone free base is slowly formed once the reaction temperature reaches >50 °C. Thus, when picolyl chloride is used, slow generation of a transient carbocation occurs, which is an important feature in obtaining a productive alkylation reaction, but equally important appears to be rate-limiting formation of the 4-piperidone free base.

Overall, the chemical transformation to produce **1** via picolyl chloride was excellent (90% yield, single-solvent system). However, the physical properties of **1** were quite challenging in that it existed as a low-melting oily solid in pure form (mp 23−25 °C). In addition, **1** was sensitive to hydration under ambient conditions and the solid was converted to an oil as it hydrated. For these reasons, **1** was converted to its CSA salt, which is a stable under ambient conditions.

Utilizing the standard conditions developed for the preparation of **1** allowed the preparation of a series of N-substituted piperidones and piperidines to demonstrate the general utility of this approach (80−92%, **2**, **3**, **12**−**20**; Table 1).[16] As one might expect, the structural isomers to **1** (**15** and **16**) were prepared from the reaction of 3- and 4-picolyl chloride, respectively, with 4-piperidone monohydrate hydrochloride. Predictably, electron-rich chloromethylarene alkylating reagents such as 2-methoxybenzyl chloride and 2-(chloromethyl)benzimidazole reacted rapidly with 4-piperidone at room temperature to produce piperidines **18** and **19**. In contrast, electron-deficient chloromethyl-arenes such as 2-(chloromethyl)quinone and 2-nitrobenzyl chloride required overnight reaction at 70 °C for complete reactions to occur. With these data in hand, we envisioned that this methodology could be extended to the synthesis of potential dopamine D4 receptor antagonists **2** and **3** (Scheme 4).[2] In this manner, commercially available 2-(chloromethyl)-quinoline and 1-phenyl piperazine were treated with powdered Na_2CO_3 in acetonitrile to produce **2** in 80% yield.[17] In addition, **3** was also prepared in 80% yield via the direct alkylation of 2-(chloromethyl)quinoline with 4-phenyl-1,2,3,6-tetrahydropyridinehydrochloride.[18]

SCHEME 4



In summary, we have demonstrated that N-substituted piperidones can be prepared via a simple one-pot process using carbonate bases. A straightforward green chemical process was utilized that appears to have widespread utility for synthesis of 4-piperidones and piperidines, including those containing both electron-donating and -withdrawing groups. For the synthesis of **1**, this new practical approach provides the best yield, atom economy, and waste stream minimization.

Experimental Section

Representative Procedure for Preparation of N-Substituted Piperidones (1−3) and Piperidines (12−20). To a suspension of 1.0 equiv of alkylating agent and 1.05 equiv of amine in 10 volumes of acetonitrile (based upon alkylating agent) was added 3.0 or 4.0 equiv of powdered Na_2CO_3 (depending upon the amount of acid equivalents to be neutralized). The mixture was stirred for 45 min at ambient temperature, 45 min at 40 °C, 45 min at 50 °C, and 45 min at 60 °C and then heated to 70 °C (unless otherwise noted) with vigorous stirring until complete disappearance of the alkylating agent was noted by TLC or HPLC. The reaction mixture was allowed to cool to room temperature and filtered to remove the insoluble solids and then the filter cake was washed with acetonitrile. The crude products were purified by flash chromatography and/or crystallization.

Acknowledgment. The authors would like to thank Mr. Curtis Miller and Mr. David Anderson for their contributions to this project.

Supporting Information Available: ^1H and ^{13}C NMR and HRMS data for compounds **1**−**3** and **12**−**20** are summarized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Throughput for the scale-up process was excellent; 10 volumes (L/kg of 2-picolyl chloride hydrochloride) were used for the alkylation.
(16) Yield for **14** was 35% due to competitive alkylation of the amide functionality.
(17) Powdered Na_2CO_3 (1 equiv) was employed.
(18) Powdered Na_2CO_3 (2 equiv) was employed.