An Oxidative Approach to a Hydroxypiperidinone Utilizing a Rh-Catalyzed C-H Activation Process

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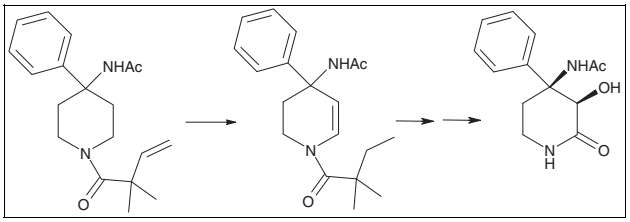

C-H activation and isomerization using a Rh-catalyst provided quick access to dehydropiperidine derivatives that could be further oxidized to hydroxypiperidinone derivatives.

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INTRODUCTION

The rapid synthesis of proposed metabolites of drug candidates often requires innovative solutions to synthetically challenging problems. Indeed, during the development of saredutant [1], hydroxypiperidinone **1** (Scheme 1) was isolated from metabolism studies, and an authentic sample was needed for confirmation of the structural assignment. Many *de novo* approaches were considered and attempted without success.

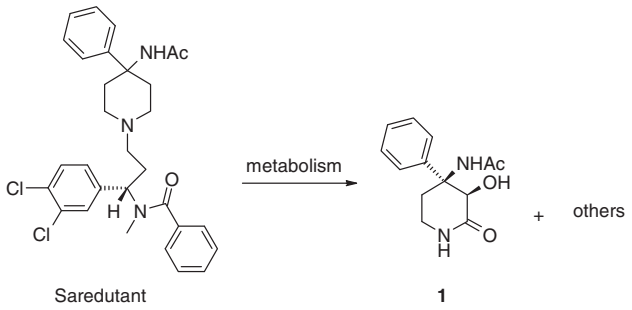
The emergence of organometallic mediated C-H activation to catalyze the cleavage of a strong C-H bond for the formation of new C-C, CO, and C-X bonds has become a key synthetic transformation [2]. However, the utility of C-H activation as an isomerization or olefin migration method has not been fully exploited. Sames [3] described a C-H activation process that resulted in the isomerization of a simple pyrrolidine amide derivative **2a** ($X = CH_2$, $n = 0$) to the corresponding enamide **3a** ($X = CH_2$, $n = 0$) in 54% isolated yield using a Rh-catalyst [4] (Scheme 2), providing the impetus for further development of C-C bond forming processes. The adaptation of this isomerization/olefin migration process to the synthesis of other nitrogen heterocycle derivatives was subsequently reported by Brookhart [5] using both Rh- and Co-catalysts (Scheme 1) using vinylsilylamines **2b**. [6] We now describe the application of the C-H activation approach using an *in situ* generated Rh-catalyst to produce a dehydropiperidine derivative [7] for an expedient synthesis of hydroxypiperidinone **1** (Scheme 2).

RESULTS AND DISCUSSION

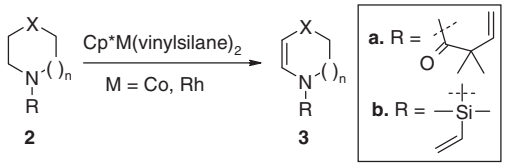
In order to pursue the C-H activation approach, the noncommercial olefinic acid **4** was required. Even though there are literature procedures [8] to synthesize acid **4**, we decided to pursue a new approach to this compound as chloride **5** was available by LDA alkylation of ethyl isobutyrate with bromochloroethane [9]. Initial direct thermal elimination attempts to olefinic ester **6** by heating chloride **5** in the presence of NaI at 60°C gave α,α-dimethyl-γ-butyrolactone as the only significant product. However, when the chloride was heated in DBU in the presence of NaI at 75°C for 12 h, olefinic ester **6** was produced as the major product and isolated in 31% yield after work-up and simple distillation. Simple saponification of the ester provided the required olefinic acid **4** in high yield for the subsequent synthesis (Scheme 3).

Initial model studies for the C-H activation process were performed on the simple 4-phenylpiperidine analog **7** that was prepared from commercially available 4-phenylpiperidine and olefinic acid **4** using EDC. Often, a limitation for organic chemists pursuing organometallic transformations is the commercial unavailability of the air sensitive catalysts necessitating an in house synthesis. Simple protocols that do not require the synthesis of a catalyst to explore the viability of these very selective organometallic processes without focusing on turnovers and yields would facilitate greater application of these transformations. Thus, instead of preparing the Brookhart catalyst [2,3], attempts to produce the active catalyst *in situ* were explored by treating $[Cp^*RhCl]_2$ with Zn powder. When cyclohexane, a noncoordinating solvent [10], was used as the solvent, <0.1% conversion of the starting material was observed even with heating for 24 h. The lack of conversion was postulated to arise from the low solubility of the Rh-complex and Zn metal. However, using NMP as the solvent with heating to 100°C, conversion to new products was observed by GC–MS that strongly indicated that the isomerization was successful as the fragmentation pattern of two of the new products had 186 fragments (cleavage alpha to keto group with loss of alkyl residue), whereas the starting material had 188 fragments. The other product

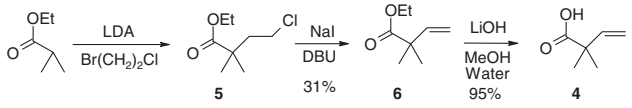
Scheme 1. Metabolite of saredutant.



Scheme 2. C-H activation/isomerization of pyrrolidine.



Scheme 3. Synthesis of olefinic acid **4**.

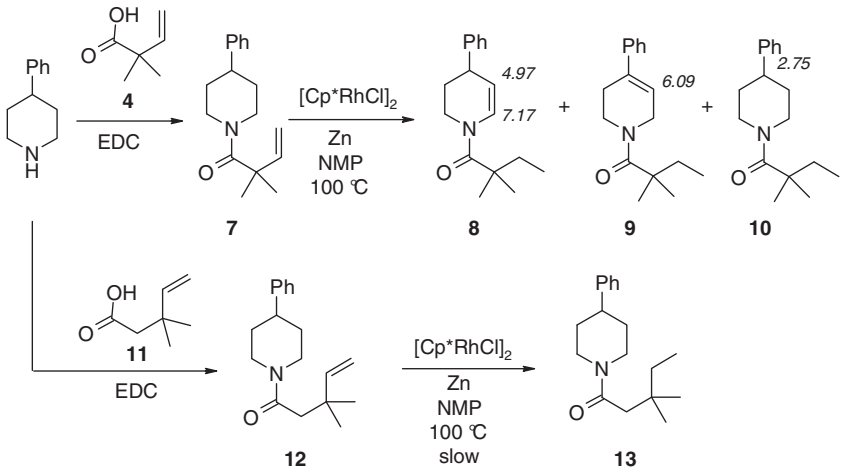


had a mass of M + 2 and was assigned as the simple reduction product. Indeed, upon isolation of the crude mixture, ^{1}H NMR confirmed the formation of isomers **8** and **9** along with reduction product **10** (Scheme 4).

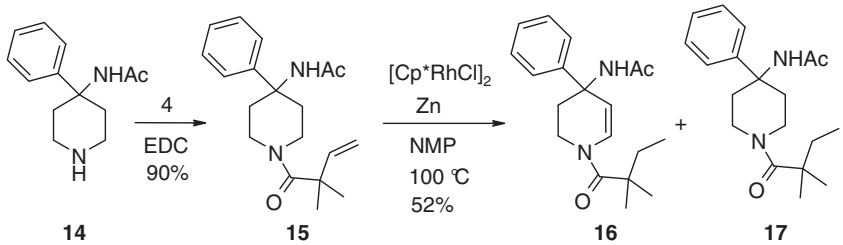
As methyl 3,3-dimethyl-4-pentanoate with one additional carbon on the tether is commercially available, simple saponification to acid **11** and coupling with 4-phenylpiperidine provided the corresponding model substrate **12** for the C-H activation chemistry (Scheme 4). Not surprisingly, upon treatment of **12** under the Rh-catalyst conditions, <0.1% of the enamide was observed with slow conversion to the reduction by-product **13** being the major product.

Having demonstrated the feasibility of the C-H activation on a model piperidine system, attention was turned to applying this approach toward the synthesis of hydroxypiperidinone **1**. Coupling of the available piperidine **14** with olefinic acid **4** using EDC provided the desired olefinic amide **15** in 90% yield (Scheme 5). Subjecting olefinic amide **15** to the C-H activation/isomerization conditions ([Cp*RhCl]$_2$, Zn powder, NMP,100°C) provided the desired dehydropiperidine **16** and reduction product **17** as an approximately 3:1 mixture from which **16** was isolated in 52% yield after chromatography. In this instance, compared with the model piperidine **7**, further isomerization of the olefin is not possible

Scheme 4. C-H activation using model systems.



Scheme 5. C-H activation for synthesis of dehydropiperidine **16**.



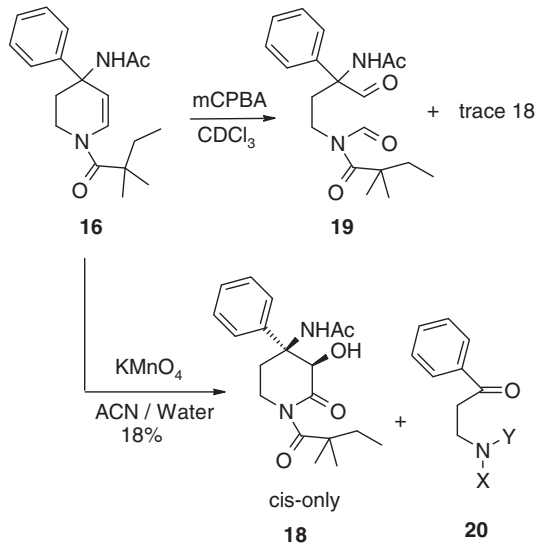
as the 4-position is quaternary. To drive the reaction to completion, additional catalyst was added. Even though further optimization of this process is clearly needed to lower the catalyst loading (up to 33% catalyst used), we achieved our objective of demonstrating the C-H activation process on a 5-g scale and prepared ample quantities of dehydropiperidine **16** for oxidation studies.

Epoxidation of dehydropiperidine **16** with further oxidation to the desired hydroxyl imide **18** using mCPBA was explored. However, oxidative cleavage to produce aldehyde formamide **19** was the major pathway with a small amount (<10%) of the desired hydroxyl imide **18** being formed (Scheme 6) [11]. Quite nicely, simple oxidation with $KMnO_4$ [12] in aqueous acetonitrile or aqueous acetone as the solvent provided the desired hydroxyl imide **18** as a single isomer with the acetamide and hydroxyl group in a *cis*-relationship. Overoxidation was also observed with cleavage to phenyl ketones **20** being significant side products. Simple slurrying of the crude product in heptane provided pure hydroxyimide **18** in 18% isolated yield.

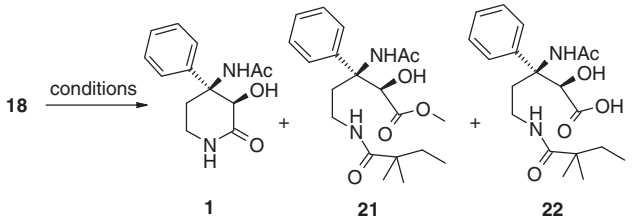
The selective hydrolysis of hydroxyl imide **18** to the desired hydroxypiperidinone **1** without ring opening to the undesired amides (Scheme 7) was anticipated to be difficult owing to the sterically hindered neopentyl tether. Thus, screening of several conditions was undertaken to find suitable conditions to provide a reasonable amount of the desired hydroxypiperidinone **1**. The use of $NaHCO_3$ in aqueous MeOH at room temperature provided a fairly clean reaction profile with 68% of desired hydroxypiperidinone **1** and 13.7% of ring-opened methyl ester **21** being formed. Interestingly, the selectivity for the desired hydrolysis to hydroxypiperidinone **1** compared with the ring-opened methyl ester **21** decreased significantly when the reaction was performed at 45°C with only 21% of the hydroxypiperidinone **1** formed. Other bases such as LiOH and K_2CO_3 provided a lower amount of the desired product plus additional side products, such as the ring-opened acid **22**. Acid hydrolysis with HCl also seems viable but, with the time constraints, was not further pursued [13]. The final selective hydrolysis of imide **18** was performed using the $NaHCO_3$ in aqueous MeOH at room temperature for 2 days (80% conversion) with warming to 45°C for completion of the reaction. Slurrying the crude mixture in CH_2Cl_2 and heptane provided 22 mg (30%) of hydroxypiperidinone **1** to complete the synthesis.

In conclusion, we have demonstrated an easy method for C-H activation/isomerization using an *in situ* generated Rh-catalyst for rapid access to dehydropiperidine derivatives. These intermediates are suitable precursors toward the preparation of functionalized piperidine derivatives such as the oxidation product hydroxypiperidinone **1**.

Scheme 6. Oxidation of dehydropiperidine **16**.



Scheme 7. Hydrolysis of imide **18** to hydroxypiperidinone **1**.



SUPPLEMENTARY MATERIAL AVAILABLE

NMR spectra and other supporting data are provided.

Acknowledgment. The author would like to acknowledge the extensive NMR experiments performed by Dirk Friedrich for structure elucidation and the samples of chloride **5** and piperidine **14** provided by Greory Kubiak and Isaac Chekroun, respectively. The author also acknowledges the extraordinarily stimulating discussions with John Herbert, Guy Rossey, and David Lythgoe.

REFERENCES AND NOTES

[1] Saredutant, a neurokinin 2(NK2) antagonist, was in development for the treatment of major depressive disorder, see Rogacki, N.; Lopez-Grancha, M.; Naimoli, V.; Potestio, L.; Stevens, R. J.; Pichat, P.; Bergis, O. E.; Cohen, C.; Varty, G. B.; Griebelb, G. Pharmacol Biochem Behav. 2011, 98, 405.

[2] For leading references for C-H activation, see (a) Seregin, I. V.; Gevorgyan, V. Chem Soc Rev 2007, 36, 1173. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. Aldrichim. Acta 2007, 40, 35. (c) Alberico, D.; Scott, M. E.; Lautens, M. Chem Rev 2007, 107, 174. (d) Satoh, T.; Miura, M. Chem. Lett. 2007, 36, 200. (e) Godula, K.; Sames, D. Science 2006, 312, 67. (f) Pastine, S.J.; Gribov, D.V.; Sames, D. J Am Chem Soc 2006, 128, 14220. (g) Wang, D-H.; Hao, X-S.; Wu, D-F.; Yu, J-Q. Org Lett 2006, 8, 3387. (h) Lyons, T. W.; Sanford, M. S. Chem Rev 2010, 110, 1147.

[3] Deboef, B.; Pastine, S.J.; Sames, D. J Am Chem Soc 2004, 126, 6556.

[4] Lenges, C. R.; White, P. S.; Brookhart, M. J Am Chem Soc 1999, 121, 4385.

[5] Bolig, A. D.; Brookhart, M. J Am Chem Soc 2007, 129, 14544.

[6] The chemistry described in this report began in October 2007 and finished several months later, so the Brookhart publication (reference 5) in November 2007 was unknown.

[7] For leading references for traditional synthesis of dehydropiperidines, see Magnus, P; Hulme, C.; Weber, W. J Am Chem Soc 1994, 116, 4501. Coldham, I.; Leonori, D. J Org Chem 2010, 75, 4069. Flick, A. C.; Padwa, A. Tetrahedron Lett 2008, 49, 5739.

[8] Gu, Z.; Zakarin, A. Org Lett 2010, 13, 1080. Aurell, M.J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. Tetrahedron 1998, 54, 4357. Kim, H. R.; Shin, S.I.; Park, H.J.; Jeon, D.J.; Ryu, E.K. Synlett 1998, 7, 789. Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; Kiso, Y. J Org Chem. 2000, 65, 8402.

[9] D'hooghe, M.; Van Driessche, B.; De Kimpe, N.; Heterocycles 2009, 77, 255. Also, chloride **5** was available in kg quantities from scale-up of an unrelated project.

[10] See references 3–5 for discussions on importance of non-coordinating solvents.

[11] Adam, W.; Reinhardt, D. Tetrahedron 1995, 45, 12257.

[12] Oxidation of 2,3-dehydropiperidines has not been reported; for oxidation of 4,5-dihydropiperidines, see Soldatenkov, A.T.; Temesgen, A. V.; Bekro, I.A. Chemistry of Heterocyclic Compounds 2001, 37, 1216.

[13] It should be noted that hydroxypiperidinone **1** has limited solubility in organic solvents such as CH_2Cl_2, so inadvertent losses may have occurred.