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A new route to heterocyclic compounds by the mercuric acetate oxidation of *N*-alkyl substituted 4-piperidones

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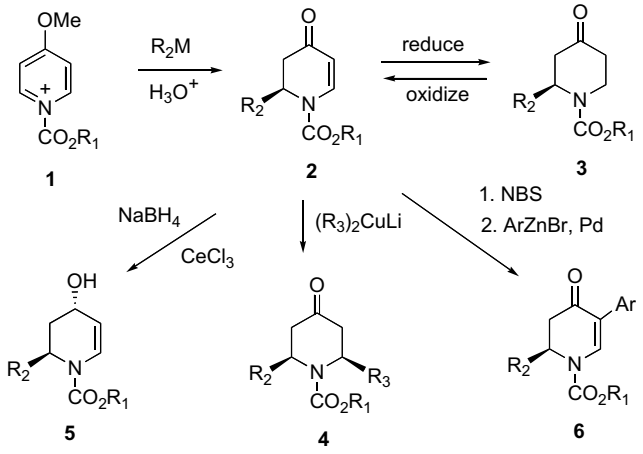
ABSTRACT

N-Alkyl substituted 4-piperidones readily undergo oxidation in high yield upon reaction with mercuric acetate. Application of the oxidation to the synthesis of the skeletal framework of several alkaloids is described.

2,3-Dihydro-4-pyridones (**2**) are important synthetic intermediates, particularly for the preparation of alkaloids and medicinal agents.[1] The presence of the vinylogous amide found in six-membered azaheterocycles facilitates the introduction of other substituents onto the piperidine ring in a regio- and stereocontrolled manner.[2] Due to A[1,3] strain,[3] the C_2 group of the dihydropyridone **2** is forced into a pseudoaxial position providing a conformational bias in the molecule. This effect allows for control of the stereoselectivity of 1,2- and 1,4-addition to the enone moiety, C_3 enolate alkylation, Luche reduction of the C_4 carbonyl and intramolecular radical cyclization.[4,5] The C_5 position can also be halogenated using NBS and a subsequent palladium-mediated coupling provides various 5-substituted derivatives (Scheme 1).[6] A widely used method for the synthesis of the dihydropyridone system involves the reaction of carbon nucleophiles with various 1-acylpyridinium salts (**1**).[1,7] Because of the abundance of piperidine-containing natural products,[8] this method has been extensively utilized by Comins et al. for the asymmetric synthesis of many quinolizidine, indolizidine and perhydroquinoline alkaloids.[4] Another approach that has been occasionally employed for the preparation of 2,3-dihydro-4-pyridones consists of an oxidation of the related 4-piperidone system (i.e., **3**→**2**).[9] 4-Piperidones are readily available from the Dieckmann cyclization of aminodicarboxylate esters or by the condensation of carbonyl compounds with ammonia via a Mannich reaction.[10,11] One general problem associated with this method is that the oxidation only works well when an electron-withdrawing group is attached to the nitrogen atom. In addition, the reaction frequently leads to a mixture of 2,3-dihydro-4-pyridone isomers. Oxidation of these N-acylated 4-piperidones is typically effected by using $PhSeCl/H_2O_2$, Saegusa or IBX methods (carbonyl directed dehydrative protocols).[9] In contrast, the few reported examples of oxidation of *N*-alkyl substituted 4-piperidones almost always involve the use of a peracid induced Polonovski reaction[12] and generally results in meager yields of the corresponding vinylogous amide. Thus, a high yielding oxidation method for the preparation of substituted 2,3-dihydro-4-pyridones from *N*-alkyl substituted 4-piperidones would be an advance in the area of heterocyclic synthesis.



Scheme 1.

As part of an ongoing synthetic program aimed at the development of new approaches to functionalized piperidine ring systems, we have explored the use of the tandem conjugate addition–dipolar cycloaddition cascade of keto oximes **8** with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**7**) as a route to various marine alkaloids.[13] This reaction cascade is easy to perform and affords azaoxabicyclic cycloadducts **9** in good to excellent yields with essentially complete stereocontrol (Scheme 2).[14] Raney-Ni reduction of cycloadduct **9** triggers a sequential nitrogen–oxygen bond cleavage followed by desulfonylation to furnish a 2,2-disubstituted 4-piperidone of type **10**. With an easy entry into 4-piperidones such

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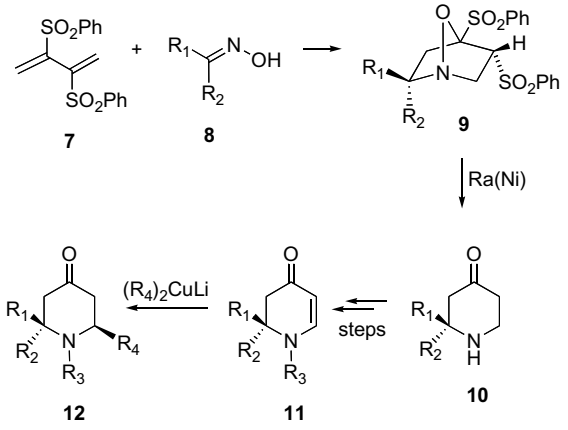
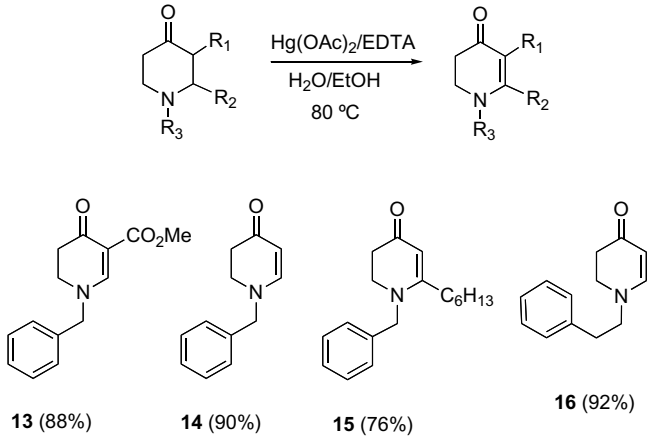


Scheme 2.

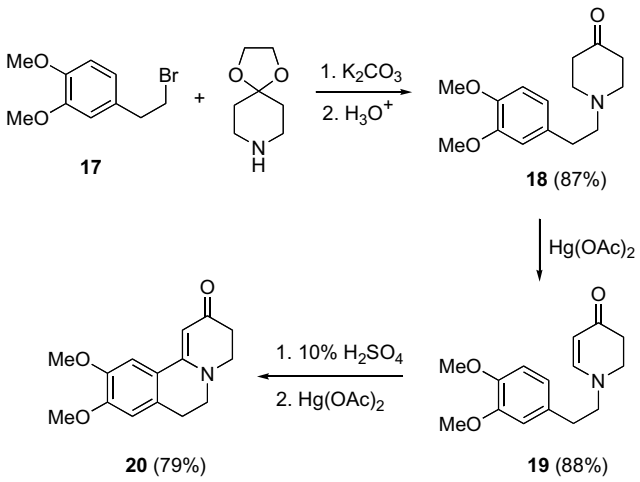
as **10**, our intention was to further oxidize the system in order to produce the corresponding 2,3-dihydro-4-pyridone **11**. This would be followed by reaction with several cuprate reagents to afford 2,2,6-trisubstituted 4-piperidones **12** which are useful intermediates for alkaloid synthesis.[13]

The ubiquity and utility of the dihydropyridone system coupled with the difficulties that are associated with the oxidation of *N*-alkyl substituted 4-piperidones suggested a more detailed investigation. The earlier success of the mercuric acetate oxidation of piperidines by Leonard et al.[15] led us to test the utility of this oxidizing agent with various 4-piperidones. Scheme 3 outlines several 2,3-dihydro-4-pyridones that were prepared in good yield from the corresponding *N*-alkyl 4-piperidone precursor using mercuric acetate conditions.[16] It should be noted that only the more substituted dihydropyridone (i.e., **13** and **15**) was obtained from the oxidation, thereby indicating a distinct preference for the formation of the thermodynamically most stable product.

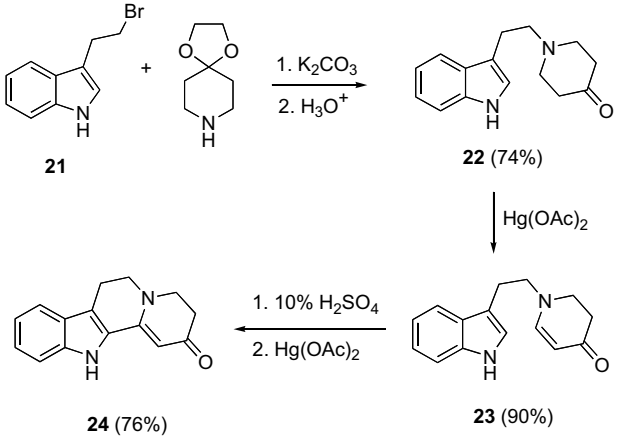
We then conducted a brief exploration of the synthetic utility of the reaction to create the skeletal framework of various alkaloids. Reaction of the commercially available bromide **17** with 1,4-dioxa-8-azaspiro[4.5]decane in the presence of K_2CO_3 followed by a subsequent hydrolysis of the ketal provided 4-piperidone **18** in 87% yield. Mercuric acetate oxidation of **18** gave **19** in 88% yield. Treatment of **19** with 10% H_2SO_4 at 90 °C induced initial enamide protonation and this was followed by a Pictet–Spengler cyclization. A subsequent mercuric acetate oxidation of the cyclized 4-piperidone intermediate afforded dihydropyridone **20** in 79% yield for the two-step sequence (Scheme 4). Consistent with previous



Scheme 3.



Scheme 4.



Scheme 5.

observations (i.e., **13** and **15**), only the more heavily substituted enamide **20** was formed in the final oxidation step.

We also investigated a similar approach to the core skeleton of the yohimbenone framework. Reaction of 3-(2-bromoethyl)-1*H*-indole (**21**) with 1,4-dioxa-8-azaspiro[4.5]decane followed by ketal hydrolysis furnished 4-piperidone **22** in 74% yield. Treatment of **22** with mercuric acetate provided a 90% yield of the corresponding dihydropyridone **23**. This heterocycle represents a useful intermediate for alkaloid synthesis, as is shown by its sequential acid cyclization/mercuric acetate oxidation to give tetrahydroindolo[2,3-*a*]quinolizinone **24** in 76% yield for the two-step sequence (Scheme 5).

In summary, we have demonstrated that *N*-alkyl substituted 4-piperidones readily undergo oxidation in high yield upon reaction with mercuric acetate. The resulting 2,3-dihydro-4-pyridones represent useful synthetic intermediates for a host of reactions. Studies concerning the application of the mercuric acetate oxidation to various 4-piperidones prepared by a conjugate addition/dipolar cycloaddition cascade of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene are in progress and will be reported in due course.

Acknowledgment

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References and notes

1. (a) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199; (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719; (c) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807. and references cited therein.
2. (a) Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141; (b) Comins, D. L.; Joseph, S. P.; Peters, D. D. *Tetrahedron Lett.* **1995**, *36*, 9449; (c) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248; (d) Comins, D. L.; Chen, X.; Joseph, S. P. *Tetrahedron Lett.* **1996**, *37*, 9275.
3. Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.
4. (a) Comins, D. L.; Joseph, S. P.; Hong, H.; Alawar, R. S.; Foti, C. J.; Zhang, Y.; Chen, X.; La Munyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477; (b) Comins, D. L.; Joseph, S. P. In *Ad vances Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 251–294.
5. Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.
6. Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435.
7. Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651.
8. Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985.
9. (a) For some representative examples, see: Dodd, D. S.; Oehlschlager, A. C. *J. Org. Chem.* **1992**, *57*, 2794; (b) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett.* **1997**, *38*, 7565; (c) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263; (d) Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611; (e) Leeming, P.; Ray, C. A.; Simpson, S. J.; Wallace, T. W.; Ward, R. A. *Tetrahedron* **2003**, *59*, 341; (f) Clive, D. L. J.; Huang, X. *Chem. Commun.* **2003**, 2062; (g) Clive, D. L. J.; Huang, X. *J. Org. Chem.* **2004**, *69*, 1872.
10. Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine, Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.
11. (a) Bosch, J.; Domingo, A.; Lopez, F.; Rubiralta, M. *J. Heterocycl. Chem.* **1980**, *17*, 241; (b) Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595.
12. (a) Zhao, Z.; Dalvie, D.; Naiman, N.; Castagnoli, K.; Castagnoli, N., Jr. *J. Med. Chem.* **1992**, *35*, 4473; (b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 4865; (c) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701; (d) Stutz, P.; Stadler, P. A. *Tetrahedron Lett.* **1973**, *14*, 5095; (e) Tubery, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 6457; (f) Guarna, A.; Occhiato, E. G.; Machetti, F.; Scarpi, D. *J. Org. Chem.* **1998**, *63*, 4111; (g) Mohrle, H.; Claas, M. *Pharmazie* **1988**, *43*, 749; (h) Ali, M. A.; Bhogal, N.; Fishwick, C. W. G.; Findlay, J. B. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 819; (i) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993.
13. Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett.* **2008**, *10*, 1871.
14. (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 2417; (b) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154; (c) Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B. H. *J. Org. Chem.* **1991**, *56*, 2713.
15. (a) Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439; (b)Leonard, N. J.; Hauck, F. P. *J. Am. Chem. Soc.* **1957**, *79*, 5279; (c) Leonard, N. J.; Cook, A. G. *J. Am. Chem. Soc.* **1959**, *81*, 5627; (d) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1959**, *81*, 5631.
16. *A typical mercuric acetate oxidation*: To a round-bottomed flask charged with 0.25 g (0.88 mmol) of 1-benzyl-4-oxo-3-piperidinecarboxylate were sequentially added 30 mL of a solution of H_2O/EtOH (2:1), 0.3 g (0.92 mmol) of $Hg(OAc)_2$, and 0.34 g (0.92 mmol) of EDTA. The mixture was heated to 80 °C for 2 h, cooled to rt and filtered through a pad of Celite. The filtrate was partitioned between CH_2Cl_2 and aqueous NH_4Cl. The organic layer was extracted with CH_2Cl_2, washed with water, brine, then dried over anhydrous Na_2SO_4. The ether layer was concentrated under reduced pressure to give 0.19 g (88%) of dihydropyridone **13** as a colorless oil which required no further purification: IR (CH_2Cl_2): 1719, 1658, 1601, 1436, 1337, 1155, and 1054 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.56 (t, 2H, J = 7.2 Hz), 3.52 (t, 2H, J = 7.2 Hz), 3.84 (s, 3H), 4.62 (s, 2H), 7.34 (t, 2H, J = 6.6 Hz), 7.43–7.48 (m, 3H), 8.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 46.3, 51.7, 61.3, 100.5, 128.0, 129.2, 129.5, 134.2, 160.0, 166.4, and 186.6; HRMS calcd for $[C_{14}H_{15}NO_3+H^+]$: 246.1052, found: 246.1125.