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Heteropoly acid-catalyzed aza-Prins-cyclization: an expeditious synthesis of 4-hydroxypiperidines

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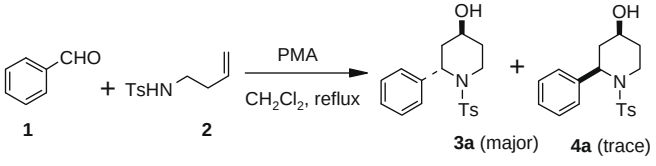
ABSTRACT

4-Hydroxypiperidines are prepared in good yields and with high selectivity by means of aza-Prins-cyclization using 10 mol % phosphomolybdic acid under mild reaction conditions. This is the first report on the preparation of 4-hydroxypiperidines via aza-Prins-cyclization.

Piperidines are among the most promising therapeutic agents for a wide variety of diseases, including Alzheimer's disease and Parkinson's disease.[1] The development of new and efficient methods for the preparation of structurally diverse piperidine derivatives has been encouraged for the drug-discovery process.[2] They are useful drug candidates for the treatment of respiratory illnesses such as asthma, bronchitis and pneumonia.[3] As a result, various methods have been developed for the synthesis of substituted piperidines in a stereo- and enantioselective manner.[4,2b,c] Of these, aza-Prins-cyclization is a simple and direct method for the preparation of *trans*-2,4-disubstituted piperidines.[5] In addition, the aza-silyl-Prins reaction is a method for the preparation of *trans*-2,6-disubstituted tetrahydropyridine derivatives.[6] In spite of its potential utility in natural product synthesis, only a few reports exist on aza-Prins-cyclizations.[5,6] Furthermore, there have been no reports on the synthesis of hydroxypiperidines via aza-Prins-cyclization.

Recently, heteropoly acids (HPAs) have received considerable attention in organic synthesis as powerful solid acid catalysts.[7] They are most attractive, because of their unique properties such as well-defined structure, Brønsted acidity, ability to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons and high proton mobility.[8] Among various heteropoly acids, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is a simple and commercially available solid acid catalyst.[9]

In continuation of our research programme on Prins-cyclization,[10] we herein report a novel method for the synthesis of hydroxy piperidines from *N*-tosyl homoallylic amines and aldehydes by means of aza-Prins-cyclization using phosphomolybdic acid under mild conditions. Initially, we attempted the coupling of benzaldehyde with *N*-tosyl homoallylic amine in the presence of 10 mol % phosphomolybdic acid in refluxing dichloromethane. The reaction went to completion in 6.5 h and the corresponding 4-hydroxy-2-



Scheme 1. Preparation of **3a**.

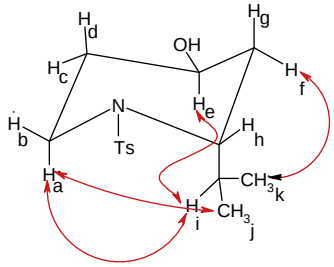


Figure 1. Characteristic NOE's of **3l**.

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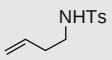
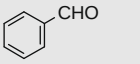
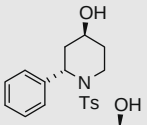
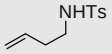
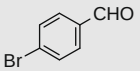
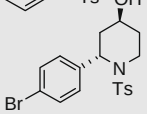
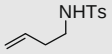
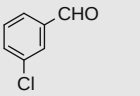
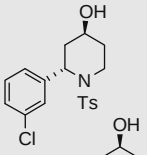
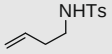
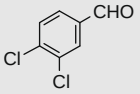
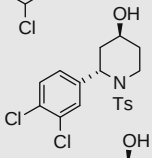
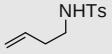
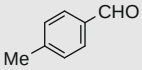
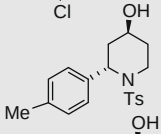
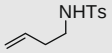
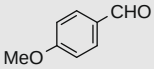
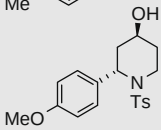
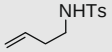
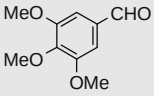
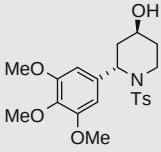
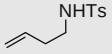
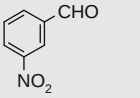
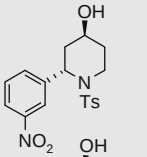
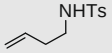
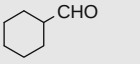
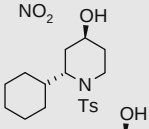
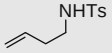
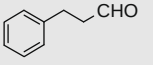
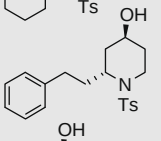
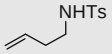
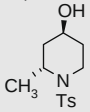
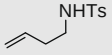
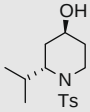
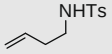
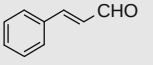
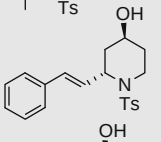
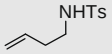
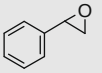
Table 1
PMA promoted aza-Prins-cyclization

Entry	Homoallyl amine	Aldehyde	Hydroxypyridine[a]	Time (h)	Yield[b] (%)	Trans/cis[c]
a				6.5	90	97:3
b				8.0	87	94:6
c				9.0	91	95:5
d				8.5	85	93:7
e				6.5	89	95:5
f				9.5	86	96:4
g				14.0	82	94:6
h				13.0	80	94:6
i				6.5	87	98:2
j				7.5	91	94:6
k		CH_3CHO		5.5	79	97:3
l				7.0	81	96:4
m				6.0	85	97:3
n				9.0	80	98:2

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] The stereoisomers were determined by HPLC.

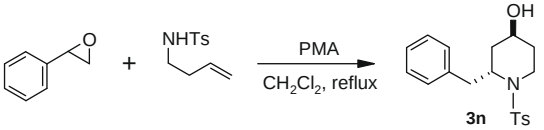
phenylpiperidine **3a** was obtained in 90% yield with trans-selectivity (Scheme 1).

The structures of products were established by various NMR experiments. The structure of **3l** shown in Figure 1 was deduced from the NMR data, where the two substituents, hydroxy and isopropyl, are trans to each other. The coupling constants observed for $J(H_a–H_d)$, $J(H_d–H_e)$ and $J(H_e–H_g)$ were all greater than 10.0 Hz indicating clearly the *anti*-conformation of these protons. The presence of strong NOEs between H_i and H_a, H_i and H_e indicates that these are in the same plane, which is supported by NOEs between isopropyl CH3 s to H_a and H_f. We could not observe the NOE between H_d and H_g because of resonance overlaps. By observing these characteristic NOEs, the *trans*-conformation of H_h and H_e was confirmed.

This result provided an incentive for the further study of reactions with various aromatic aldehydes such as *p*-bromobenzaldehyde, *m*-chlorobenzaldehyde, 3,4-dichlorobenzaldehyde *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde and *m*-nitrobenzaldehyde. In all cases, the respective *trans*-2-aryl-4-hydroxypiperidines were obtained in high yields (Table 1, entries b–h). This method is equally effective for both electron-rich and electron-deficient aldehydes. Aliphatic aldehydes such as cyclohexanecarboxaldehyde, hydrocinnamaldehyde, acetaldehyde and isobutaraldehyde also underwent smooth coupling with *N*-tosylhomoallylic amine to furnish the corresponding *trans*-2-alkyl-4-hydroxypiperidines (Table 1, entries i–l). Acid-sensitive *trans*-cinnamaldehyde also gave the corresponding *trans*-4-hydroxy-2-styrylpiperidine in 87% yield (Table 1, entry m).

Next, we studied the reaction of styrene oxide with *N*-tosylhomoallylic amine in the presence of 10 mol % of PMA. Interestingly, styrene oxide underwent a rearrangement on the surface of PMA to give phenyl acetaldehyde, which was subsequently reacted with *N*-tosylhomoallylic amine to furnish *trans*-2-benzyl-4-hydroxypiperidine (Table 1, entry n**,** Scheme 2).

It is important to mention that no *N*-tosyl deprotection was observed during the aza-Prins-cyclization. In the absence of PMA, no aza-Prins-cyclization was observed even in refluxing 1,2-dichloroethane. The effects of various Brønsted acids such as Montmorillonite K10 clay, SBA-15 and ion-exchange resins were screened. Of these acid catalysts, PMA was found to be superior in terms of conversion. For example, the reaction between benzaldehyde and *N*-tosylhomoallylic amine in the presence of 10 mol % of PMA and 10% w/w SBA-15 or K10 clay or Amberlyst-15 gave the desired product **3a**, in 90%, 40%, 62% and 70% yields, respectively. As solvent, dichloromethane gave the best results. In all cases, the reactions proceeded readily in refluxing dichloromethane to give the products in good yields and with high diastereoselectivity. The formation of the products may be explained by initial aminal formation and subsequent Prins-type cyclization (Scheme 3). The scope and generality of this process is illustrated in Table 1.[11]



Scheme 2. Preparation of **3n**.

In summary, we have developed an efficient protocol for the preparation of 4-hydroxy-2-aryl- or 2-alkyl piperidines via aza-Prins-cyclization using phosphomolybdic acid as a novel catalyst. The use of heteropoly acid makes this method simple, convenient and economically viable for large-scale synthesis.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.148.

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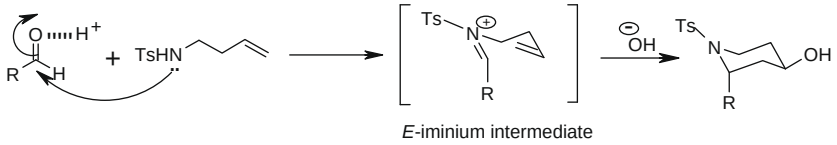
11. *General procedure*: A mixture of *N*-tosylhomoallylic amine (1 mmol), aldehyde (1 mmol) and phosphomolybdic acid (10 mol %) in dichloromethane (5 mL) was stirred at reflux temperature for a specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 0.5:9.5) gave the pure 4-hydroxy tetrahydropyridine. The products thus obtained were characterized by IR, NMR and mass spectroscopy. The spectral data were found to be consistent with authentic samples.*Compound* **3i**: *2-cyclohexyl-1-[(4-methylphenyl)sulfonyl]-4-piperidinol*: Solid, mp 94–96 °C. IR (KBr): ν 3448, 2927, 2852, 1598, 1493, 1450, 1332, 1200, 1155, 1082, 1023, 930, 812, 734, 668, 555 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, J = 8.2 Hz), 7.28 (d, 2H,



Scheme 3. A plausible reaction mechanism.

J = 8.2 Hz), 3.95 (ddd, 1H, *J* = 15.2, 4.7, 1.7 Hz), 3.76 (dddd, 1H, *J* = 11.3, 11.3, 4.5, 2.0 Hz), 3.69 (dd, 1H, *J* = 11.0, 5.5 Hz), 2.98 (ddd, 1H, *J* = 15.2, 12.0, 2.8 Hz), 2.45 (s, 3H), 2.05 (ddd, 1H, *J* = 13.0, 3.8, 1.9 Hz), 1.84–1.98 (m, 5H), 1.32–1.77 (m, 8H), 1.00 (dddd, 1H, *J* = 12.0, 11.9, 4.7, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 25.9, 26.1, 30.0, 30.3, 36.6, 39.4, 39.8, 58.9, 64.4, 126.9, 129.7, 138.7, 143.0. LC–MS: *m/z*: (M^++H) 338.*Compound* **3j**: *1-[(4-methylphenyl)sulfonyl]-2-phenethyl-4-piperidinol*: Solid, mp 151–154 °C. IR (KBr): *v* 3534, 2928, 2858, 1734, 1647, 1600, 1454, 1334, 1238, 1155, 1076, 1026, 971, 913, 870, 812, 707, 668, 549 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 8.1 Hz), 7.27 (m, 7H), 4.17 (ddd, 1H, *J* = 15.0, 4.0, 1.2 Hz), 3.85 (dddd, 1H, *J* = 11.4, 11.4 , 4.3, 2.0 Hz), 3.80 (dd, 1H, *J* = 11.0, 5.4 Hz), 3.04 (ddd, 1H, *J* = 15.0, 12.0, 2.8 Hz), 2.62 (m, 2H), 2.43 (s, 3H), 1.87 (ddd, 1H, *J* = 13.0 , 3.0, 1.9 Hz), 1.70 (dddd, 1H, *J* = 11.9, 2.5, 3.6, 3.9 Hz), 1.60 (ddd, 1H, *J* = 12.0,11.5, 4.3, 3.7 Hz), 1.55 (dddd, 1H, *J* = 12.0, 11.9, 4.7, 3.7 Hz), 1.06–1.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 32.9, 33.1, 33.8, 36.9, 39.5, 53.5, 64.5, 126.0, 126.9, 128.4, 129.8, 138.3, 141.4, 143.2. LC–MS: *m/z*: (M^++H) 360.*Compound* **3l**: *2-isopropyl-1-[(4-methylphenyl)sulfonyl]-4-piperidinol*: Solid, mp 158–160 °C. IR (KBr): *v* 3519, 2957, 2926, 2872, 1598, 1456, 1336, 1235, 1156, 1075, 1029, 967, 928, 812, 737, 673, 565, 533 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, 2H , *J* = 8.2 Hz), 7.28 (d, 2H, *J* = 8.2 Hz), 3.90 (ddd, 1H, *J* = 15.2, 4.7, 1.7 Hz), 3.78 (dddd, 1H, *J* = 11.3, 11.3, 4.5, 2.0 Hz), 3.69 (dd, 1H, *J* = 11.0, 5.5 Hz), 2.98 (ddd, 1H, *J* = 15.2, 12.0, 2.8 Hz), 2.42 (s, 3H), 2.01 (ddd, 1H, *J* = 13.0, 3.8, 1.9 Hz), 1.87 (m, 1H), 1.70 (dddd, 1H, *J* = 11.9, 2.8, 3.7, 3.9 Hz), 1.10 (ddd, 1H, *J* = 12.9, 11.3, 5.5 Hz), 1.02 (dddd, 1H, *J* = 12.0, 11.9, 4.7, 3.7 Hz), 0.96 (d, 3H, *J* = 6.5 Hz), 0.96 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 20.5, 21.7, 27.8, 33.7, 34.6, 40.1, 60.5, 64.7, 127.2, 130.0, 139.0, 143.3. LC–MS: *m/z*: (M^++H) 298.*Compound* **3m**: *1-[(4-methylphenyl)sulfonyl]-2-[(E)-2-phenyl-1-ethenyl]-4- piperidinol*: Solid, mp 170–173 °C. IR (KBr): *v* 3430, 2924, 2854, 1703, 1634, 1599, 1453, 1336, 1157, 1081, 1022, 931, 813, 758, 671, 555 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, 2H, *J* = 8.2 Hz), 7.00–7.20 (m, 7H), 6.32 (m, 1H), 5.82 (m, 1H), 4.80 (ddd, 1H, *J* = 15.0, 4.6, 1.5 Hz), 3.83 (dddd, 1H, *J* = 11.2, 11.2, 4.2, 2.0 Hz), 3.70 (dd, 1H, *J* = 11.0, 5.5 Hz), 2.99 (ddd, 1H, *J* = 15.0, 12.0, 2.5 Hz), 2.35 (s, 3H), 1.99 (ddd, 1H, *J* = 13.0, 3.8, 1.8 Hz), 1.80 (dddd, 1H, *J* = 11.9, 2.5, 3.7, 3.9 Hz), 1.59 (ddd, 1H, *J* = 12.9, 11.3, 5.5 Hz), 1.35 (dddd, 1H, *J* = 12.0, 11.9, 4.5, 3.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 34.2, 39.1, 40.5, 55.1, 64.7, 126.3, 127.3, 127.8, 128.5, 129.6, 130.5, 132.2, 136.2, 137.3, 143.3. LC–MS: *m/z*: (M^++H) 358.*Compound* **3n**: *2-benzyl-1-[(4-methylphenyl)sulfonyl]-4-piperidinol*: Solid, mp 145–149 °C. IR (KBr): *v* 3487, 2927, 2858, 1723, 1597, 1495, 1453, 1333, 1153, 1044, 937, 813, 752, 701, 666, 550 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, 2H, *J* = 8.2 Hz), 7.24 (m, 7H), 4.37 (ddd, 1H, *J* = 15.2, 12.0, 2.8 Hz), 3.98 (dddd, 1H, *J* = 11.3, 11.3, 4.5, 2.0 Hz), 3.83(dd, 1H, *J* = 11.0, 5.5 Hz), 3.08 (ddd, 1H, *J* = 15.2, 12.0, 2.8 Hz), 2.73 (m, 2H), 2.39 (s, 3H), 1.89 (ddd, 1H, *J* = 13.0, 3.8, 1.9 Hz), 1.76 (dddd, 1H, *J* = 11.9, 2.8, 3.7, 3.9 Hz), 1.29 (ddd, 1H, *J* = 12.9, 11.3, 5.5 Hz), 1.19 (dddd,1H, *J* = 12.0, 11.9, 4.7, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 29.8, 34.3, 37.3, 39.8, 55.1, 63.5, 126.7, 127.2, 128.7, 129.2, 129.8, 135.6, 139.2, 143.2. LC–MS: *m/z*: (M^++H) 346.