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Aminohydroxylation and dihydroxylation of 4-aryl-1,2,5,6-tetrahydropyridines

Meng-Yang Chang,[a,*] Chun-Yu Lin[b] and Tsun-Cheng Wu[a]

[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan*
[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan*

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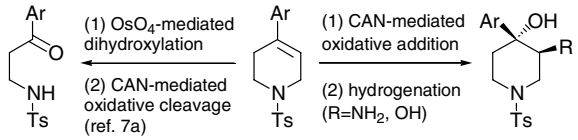
Abstract—Substituted 3-amino-4-aryl-4-hydroxypiperidines and 4-aryl-3,4-dihydroxypiperidines are synthesized in the modest overall yields starting from the regio- and stereoselective *trans*-aminohydroxylation and dihydroxylation of 4-aryl-1,2,5,6-tetrahydropyridines via CAN-mediated oxidative addition and hydrogenation.

1. Introduction

Among various cerium(IV) complexes, cerium ammonium nitrate (CAN) is one of the most important oxidants in organic synthesis, as it is sufficiently stable in different solvents and is commercially available.[1] It was invented by Smith et al. in 1936 and explored extensively in organic reactions of industry and academia field.[1a] This reagent has been reviewed for reactions involving carbon–carbon, carbon–nitrogen, carbon–sulfur, carbon–selenium, carbon–halogen, and other carbon–heteroatom bond formations.[1,2] Representative examples include oxidative addition,[2,3] photooxidation,[4] nitration,[5] and deprotection.[6] Many research groups successfully developed various useful transformations by application of this reagent.

Very recently, we developed an easy and straightforward strategy toward CAN-mediated oxidative cleavage of *cis*-4-aryl-3,4-dihydroxypiperidines and explored the related applications in the synthesis of fluoxetine.[7a] Continuing our investigation on the application of this methodology,[7] CAN-mediated oxidative addition reaction of 4-aryl-1,2,5,6-tetrahydropyridines, followed by hydrogenation, was further investigated as shown in Scheme 1.



Scheme 1.

The regio- and stereoselective *trans*-aminohydroxylation and dihydroxylation could provide the resultant structural frameworks of 3-amino-4-aryl-4-hydroxypiperidines and 4-aryl-3,4-dihydroxypiperidines via the simple two-step route. According to the related literature reports, 3- or 4-substituted 4-arylpiperidines and their derivatives are currently receiving considerable attention because of their useful pharmacological properties,[8] utility in natural product synthesis,[9] possible application as an amino acid surrogate for enzyme inhibitors, and important motif of anti-depressant agents like paroxetine and femoxetine.[10] Development of a general and novel procedure for these derivatives provides an expedient entry point due to the importance of this structural motif in organic chemistry.

Since Sharpless' unique discovery of aminohydroxylation reaction and dihydroxylation,[11,12] a major challenge for chemists has been to find ways of controlling the regio- and stereochemical outcome of this important reaction. The specifically asymmetric

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* Corresponding author. Tel.: +886 7 5919464; fax: +886 7 5919348; e-mail: mychang@nuk.edu.tw

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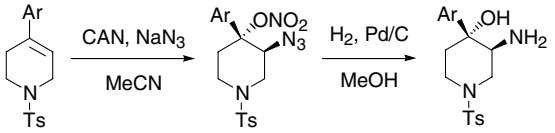
controlled functionalization of α,β-unsaturated olefins has been established as a reliable method, whereas difficulties are often encountered in this process due to lack of cheaper reagents, harshness of reaction conditions and availability of starting materials.[5] In order to address this issue, herein a two-step *trans*-aminohydroxylation and dihydroxylation of 4-aryl-3,4-dihydroxypiperidines employing CAN-mediated oxidative addition and hydrogenation were explored.

2. Results and discussion

For investigating the CAN-mediated oxidative addition, different substituted 4-aryl-1,2,5,6-tetrahydropyridines **1a**–**f** (a, Ar = C_6H_5; b, Ar = 4-FC_6H_4; c, Ar = 4-ClC_6H_4; d, Ar = 4-BrC_6H_4; e, Ar = 2-MeC_6H_4; f, Ar = 3-CF_3-C_6H_4) were chosen as the starting materials and prepared via Grignard addition of 1-tosylpiperidin-4-one and subsequent dehydration.[7] With enough amounts of compounds **1a**–**f** in hand, CAN-mediated oxidative addition was examined. In the presence of azide ion, oxidative addition leading to the corresponding *trans*-3-azido-4-aryl-4-nitratopiperidines **2a**–**f** was observed (Scheme 2).[13]

The transformation is an efficient oxidative addition with regio- and stereospecific selectivity, which is governed by the stability of tertiary carbocation, and introduction of azido group takes place. The total synthetic procedure could be monitored by TLC until the reaction was complete at room temperature for ca. 3 h. The related stereochemical structure of compound **2b** with *trans*-configuration was determined by single-crystal X-ray analysis (Fig. 1).[14] Furthermore, treatment of compounds **2a**–**f** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon furnished aminoalcohols **3a**,**b** and **3e**,**f**.[15] Not surprisingly, the 4-chloro and 4-bromo atoms of compounds **2c** and **d** were easily hydrogenated to give product **3a**.[16]



1a, Ar=C_6H_5	**2a**, 65%	**3a**, 83%
1b, Ar=4-FC_6H_4	**2b**, 63%	**3b**, 85%
1c, Ar=4-ClC_6H_4	**2c**, 60%	**3a**, 75%
1d, Ar=4-BrC_6H_4	**2d**, 60%	**3a**, 70%
1e, Ar=2-MeC_6H_4	**2e**, 53%	**3e**, 80%
1f, Ar=3-$CF_3C_6H_4$	**2f**, 60%	**3f**, 85%

Scheme 2.

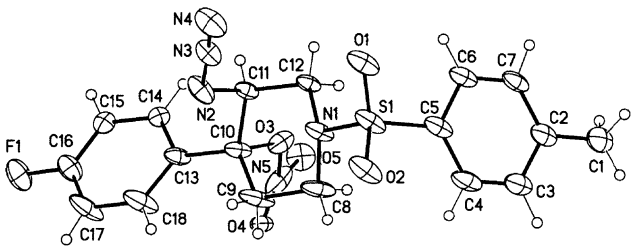
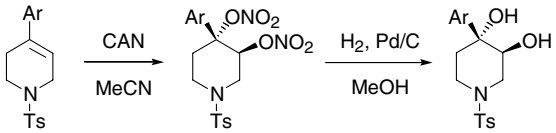


Figure 1. X-ray crystallography of compound **2b**.

When the 4-aryl functional group was changed as 4-methyl or 4-methoxyphenyl group, the expected products could not be provided. For the 4-methyl group, the starting material was recycled as the major product. Based on these results, we envisioned that aryl group is an important substituent, which provides a stable benzylic radical in the initial process. The electron donating aryl group (e.g., 4-methoxyphenyl) could diminish the stability of the benzylic radical to cause the complex products during the oxidative addition procedure. Although the synthetic application is decreased, the present work is complementary to the existing methodology.

When CAN-mediated oxidative addition of compounds **1a**–**d** was carried out in the absence of sodium azide, *trans*-4-aryl-3,4-dinitratopiperidines **4a**–**d** were isolated, as illustrated in Scheme 3.[13] Furthermore, treatment of compounds **4a**–**d** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon furnished *trans*-diols **5a** and **b**. Here we explored the *trans*-dihydroxylation of compounds **1a**–**d** via CAN-mediated oxidative addition and hydrogenation under mild condition. Besides the feasible combination of CAN and sodium azide, CAN-mediated oxidative addition of model substrate **1a** with other sodium salts (e.g., alkoxide, thioalkoxide, alkylsulfonate, and halide) was unsuccessful. Compound **4a** was isolated as the major product.

While poring over the related literature of CAN-mediated oxidative reaction, we found that Nair and coworkers had developed the CAN-mediated oxidative fragmentation of 1-aryl-1-cycloalkenes in methanol to afford different products under deoxygenated conditions.[17] In comparison with the reaction in acetonitrile by us, the generated results were exhibited as unexpected to the literature reports.[17] For changing reaction solvent as the methanol, CAN-mediated treatment of compound **1a** in methanol did not cause reaction at room temperature within 3 h. The reaction must be heated to increase the reaction rate. If the reaction was refluxed over 6 h in methanol, the desired product **4a** slowly disappeared and a complex mixture resulted. Therefore, the best condition for this reaction is room temperature within 3 h in acetonitrile. Although the synthetic originality is decreased,[2d,17] the present work is complementary to the existing methodology. With the results, we envisioned that the nitrogen atom in the six-membered



1a, Ar=C_6H_5	**4a**, 58%	**5a**, 84%
1b, Ar=4-FC_6H_4	**4b**, 65%	**5b**, 81%
1c, Ar=4-ClC_6H_4	**4c**, 65%	**5a**, 72%
1d, Ar=4-BrC_6H_4	**4d**, 57%	**5a**, 74%

Scheme 3.

ring skeleton plays an important role for the reaction. The difference between arylcyclohexene and 4-aryl-1,2,5,6-tetrahedropyridine framework was not further investigated.

To reinvestigate the applicability of the reaction to five-membered heterocyclic ring, we have tried to study the model substrate 3-phenylpyrroline.[7b,c] The structure of 3-phenylpyrrole was isolated in nearly 20% yield during the CAN-mediated reaction. It is worthy of note that products **3** could be applied in the preparation of 3-aminopiperidine skeleton[16] and the related analogs of balanol core with potent inhibitor of human protein kinase C (PKC).[18]

3. Conclusion

In conclusion, we provided a quite facile and cheaper preparation in the specific regio- and stereoselective synthesis of 3-amino-4-aryl-4-hydroxypiperidines and 4-aryl-3,4-dihydroxypiperidines, via the aminohydroxylation and dihydroxylation of 4-aryl-1,2,5,6-tetrahydropyridine employing CAN-mediated oxidative addition reaction and hydrogenation. The CAN-mediated asymmetric chemistry with chiral auxiliary will be studied.

Acknowledgments

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Supplementary data

Photocopies of ^{1}H and ^{13}C NMR ($CDCl_3$) spectral data for compounds **2a**–**f**, **3a**,**b**, **3e**,**f**, **4a**–**d** and **5a**,**b** were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.174.

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13. *CAN-mediated oxidative addition of olefins* **1a**–**f** *into compounds* **2a**–**f** *is as follows*: A deoxygenated solution of ceric ammonium nitrate (0.27 g, 0.5 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of olefins **2a**–**f** (0.3 mmol) and sodium azide (26 mg, 0.4 mmol) in dry acetonitrile (5 mL) at rt. The reaction mixture was stirred at rt for 1 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 4/1–2/1) afforded compounds **2a**–**f**. Representative data for **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.45–7.42 (m, 5H), 7.37 (d, $J = 8.0$ Hz, 2H), 3.96–3.89 (m, 2H), 3.84 (d, $J = 1.5$ Hz, 1H), 3.02 (dd, $J = 2.5$, 12.5 Hz, 1H), 2.88–2.80 (m, 2H), 2.71 (td, $J = 3.5$, 11.5 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.08, 137.67, 133.23, 129.93 (2×), 129.56, 129.24 (2×), 127.47 (2×), 125.21 (2×), 87.53, 62.17, 45.69, 40.98, 25.84, 21.52; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{20}N_5O_5S$ (M^++1) 418.1185, found 418.1186. For **2b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.41 (dd, $J = 4.5$, 8.5 Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.14 (t, $J = 8.5$ Hz, 2H), 3.94 (dd, $J = 2.0$, 13.0 Hz, 1H), 3.91–3.88 (m, 1H), 3.82 (br s, 1H), 3.01 (dd, $J = 2.0$, 13.0 Hz, 1H), 2.81–2.79 (m, 2H), 2.73–2.67 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.07, 162.07, 144.16, 133.64, 133.22, 129.97 (2×), 127.48 (2×), 127.36, 116.44, 116.26, 87.09, 62.08, 45.57, 40.97, 26.07, 21.54; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}FN_5O_5S$ (M^++1) 436.1091, found 436.1093. For **2c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.5$ Hz, 2H), 7.43 (dt, $J = 2.0$, 8.5 Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.35 (dt, $J = 2.0$, 8.5 Hz, 2H), 3.96 (dt, $J = 2.0$, 13.0 Hz, 1H), 3.90 (ddd, $J = 3.0$, 5.0, 12.0 Hz, 1H), 3.81 (br s, 1H), 3.02 (dd, $J = 2.0$, 13.0 Hz, 1H), 2.80–2.77 (m, 2H), 2.70 (td, $J = 4.5$, 12.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.20, 136.37, 135.70, 133.25, 130.00 (2×), 129.52 (2×), 127.51 (2×), 126.72(2×), 86.94, 61.94, 45.53, 40.95, 26.00, 21.58; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}ClN_5O_5S$ (M^++1) 452.0796, found 452.0792. For **2d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 3.96 (dt, $J = 2.0$, 13.0 Hz, 1H), 3.91–3.88 (m, 1H), 3.80 (br s, 1H), 3.02 (dd, $J = 2.0$, 13.0 Hz, 1H), 2.80–2.75 (m, 2H), 2.73–2.67 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.21, 136.92, 133.27, 132.49 (2×), 130.01 (2×), 127.52 (2×), 126.97 (2×), 123.92, 86.97, 61.89, 45.51, 40.94, 25.96, 21.59; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}BrN_5O_5S$ (M^++1) 496.0290, found 496.0294. For **2e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.35–7.20 (m, 4H), 4.23 (d, $J = 2.0$ Hz, 1H), 3.95–3.87 (m, 2H), 3.03 (dd, $J = 2.5$, 13.0 Hz, 1H), 2.96 (ddd, $J = 4.0$, 4.5, 13.0 Hz, 1H), 2.85–2.80 (m, 1H), 2.73 (td, $J = 2.0$, 12.5 Hz, 1H), 2.53 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.12, 135.05, 134.37, 133.44, 133.29, 129.97 (2×), 129.55, 128.13, 127.56 (2×), 126.80, 88.84, 58.95, 45.58, 41.16, 27.49, 21.59, 21.22; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}N_5O_5S$ (M^++1) 432.1342, found 432.1346. For **2f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.65 (s, 1H), 7.63–7.59 (m, 3H), 7.38 (d, $J = 8.0$ Hz, 2H), 3.98 (dt, $J = 1.5$, 13.0 Hz, 1H), 3.93–3.91 (m, 1H), 3.84 (d, $J = 1.5$ Hz, 1H), 3.06 (dd, $J = 2.0$, 13.0 Hz, 1H), 2.89–2.79 (m, 2H), 2.74 (td, $J = 2.5$, 12.0 Hz, 1H), 2.47 (s, 3H); HRMS (ESI, M^++1) calcd for $C_{19}H_{19}F_3N_5O_5S$ 486.1059, found 486.1061.
14. *Single-crystal X-ray diagram*: Crystal of compound **2b** was grown by slow diffusion of ethyl acetate into a solution of compound **2b** in dichloromethane to yield a colorless prism. The compound crystallizes in the monoclinic crystal system. Space group P2(1)/c, $a = 14.200(3)$ Å, $b = 8.0088(19)$ Å, $c = 18.171(4)$ Å, $V = 1949.5(8)$ Å^3, $Z = 4$, $d_{calcd} = 1.484$ mg/m^3, absorption coefficient 0.218 mm^{-1}, $F(000) = 904$, 2θ range (1.52–28.38°).
15. *A representative procedure for hydrogenation of compounds* **3a**–**b** *and* **3e**–**f** *is as follows*: 10% palladium on activated carbon (10 mg) was added to a stirring solution of compounds **2a**–**f** (0.2 mmol) in methanol (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir at rt for 10 h. The catalyst was filtered through a short plug of Celite and washed with methanol (2×10 mL). The combined organic layers were evaporated under reduced pressure to yield the crude compound. Purification on silica gel (hexane/ethyl acetate = 1/1–1/4) afforded compounds **3a**,**b** and **3e**,**f**. For **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.45–7.30 (m, 7H), 3.79–3.76 (m, 1H), 3.62 (dt, $J = 2.5$, 11.5 Hz, 1H), 3.04–3.01 (m, 2H), 2.79–2.68 (m, 2H), 2.45 (s, 3H), 1.73 (d, $J = 2.0$, 12.5 Hz, 1H), 1.45 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.75, 143.56, 133.24, 129.70 (2×), 128.74 (2×), 128.13, 127.66 (2×), 125.58 (2×), 73.13, 54.52, 48.43, 42.12, 30.30, 21.23; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}N_2O_3S$ (M^++1) 347.1429, found 347.1427. For **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.45–7.41 (m, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.09–7.04 (m, 2H), 3.80–3.77 (m, 1H), 3.63 (dt, $J = 2.0$, 11.0 Hz, 1H), 3.04 (dd, $J = 2.5$, 11.5 Hz, 1H), 3.03–3.01 (m, 1H), 2.77 (td, $J = 2.5$, 12.5 Hz, 1H), 2.70 (td, $J = 4.5$, 13.0 Hz, 1H), 2.45 (s, 3H), 1.71 (d, $J = 13.0$ Hz, 1H), 1.46 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.34, 161.37, 143.63, 133.25, 129.74 (2×), 127.65 (2×), 127.54, 127.48, 115.59, 115.42, 72.94, 54.49, 48.56, 42.06, 30.61, 21.55; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{22}FN_2O_3S$ (M^++1) 365.1335, found 365.1339. For **3e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.26–7.17 (m, 4H), 3.79–3.76 (m, 1H), 3.63 (d, $J = 11.5$ Hz, 1H), 3.50 (br s, 1H), 3.01 (dd, $J = 2.5$, 11.5 Hz, 1H), 2.87 (td, $J = 4.5$, 12.5 Hz, 1H), 2.81 (td, $J = 2.0$, 12.5 Hz, 1H), 2.58 (s, 3H), 2.45 (s, 3H), 1.71 (d, $J = 12.5$ Hz, 1H), 1.53 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.57, 141.09, 137.04, 133.51, 133.09, 129.71 (2×), 128.18, 127.72 (2×), 127.22, 125.76, 75.23, 51.02,

48.03, 42.26, 32.23, 21.92, 21.55; HRMS (ESI) m/z calcd for $C_{19}H_{25}N_2O_3S$ (M^++1)361.1586, found 361.1588. For **3f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.67 (d, $J = 8.5$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 3.80–3.77 (m, 1H), 3.61 (dt, $J = 2.0$, 11.0 Hz, 1H), 3.07 (dd, $J = 2.0$, 11.0 Hz, 1H), 3.01 (br s, 1H), 2.81–2.72 (m, 2H), 2.46 (s, 3H), 1.75–1.68 (m, 1H), 1.40 (br s, 3H); HRMS (ESI) m/z calcd for $C_{19}H_{22}F_3N_2O_3S$ (M^++1) 415.1303, found 415.1310.

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