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CAN-mediated oxidative cleavage of 4-aryl-3,4-dihydroxypiperidines

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Abstract—A CAN-mediated oxidative cleavage of 4-aryl-3,4-dihydroxypiperidines **2Aa**–**Be** to β-amino carbonyl compounds **3Aa**–**Be** and **4Aa**–**Be** in different ratios is described. This facile strategy was also used to synthesize racemic fluoxetine (**5**).

1. Introduction

CAN (cerium ammonium nitrate) was invented by Smith et al. in 1936 and explored extensively in organic reactions in the industry and academia fields.[1] Representative examples include oxidative addition,[2] oxidation,[3] photooxidation,[4] nitration,[5] and deprotection,[6] etc. Many research groups successfully developed various useful transformations by application of this reagent. Very recently, we developed an easy and straightforward strategy toward 4-aryl-1,2,5,6-tetrahydropyridines and explored the related applications for synthesizing racemic coerulescine, horsfiline, and baclofen as shown in Figure 1.[7]

The letter presents CAN-mediated transformation of 4-aryl-3,4-dihydroxypiperidines, which provides a new and convenient method for the preparation of 2-aminoethyl (β-amino) arylketones. The β-amino carbonyl framework is structurally similar to that of known β-amino acid derivatives. The multiple potential biological activities of these similar structures have attracted many efforts from synthetic chemists. Development of a general and novel procedure for β-amino carbonyl

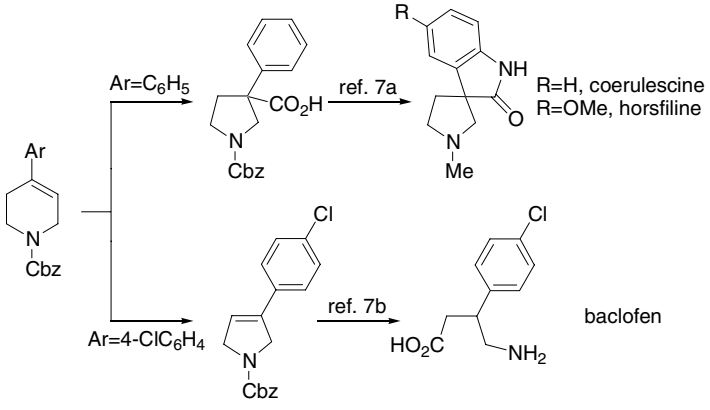

Figure 1.

Keywords: 4-Hydroxypiperidine; 4-Aryl-3,4-dihydroxypiperidines; β-Amino carbonyl compounds; Cerium ammonium nitrate; Fluoxetine.
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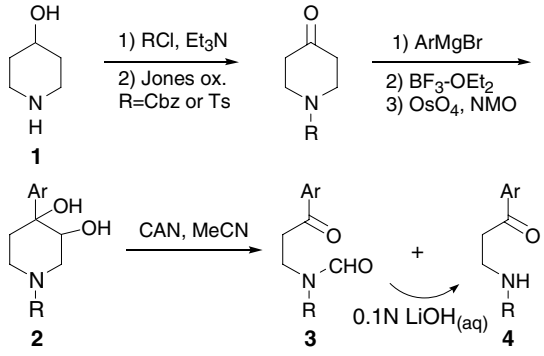
compounds provides an expedient entry point due to the importance of this structural motif in organic chemistry.[8,9]

2. Results and discussion

4-Aryl-3,4-dihydroxypiperidines **2** (a, Ar = C_6H_5; b, Ar = 4-FC_6H_4; c, Ar = 4-ClC_6H_4; d, Ar = 4-$MeOC_6H_4$; e, Ar = 3-$MeOC_6H_4$) were prepared by the concise five-step protocol from 4-hydroxypiperidine (**1**) (N-benzyloxycarbonylation or tosylation, Jones oxidation, Grignard addition, Lewis acid-mediated dehydration, and dihydroxylation).[7] Thus diols **2** were yielded by the recrystallizations in modest yields. Then, CAN-mediated oxidative cleavage of diols **2** was investigated in the next step. Two β-amino arylketones **3** and **4** were provided in different ratios (2:1–3:1) at refluxed temperature for 30 min as shown in Scheme 1.[10]

But, the oxidative cleavage of model substrate **2Aa** was unsuccessful on the other commercial available reagents (e.g., lead tetraacetate and sodium periodate) at refluxed temperature for 30 min. The difference between CAN and other reagents was not clear. These results represented the interesting reaction types for different 4-aryl groups of 3,4-dihydroxypiperidines. The experimental results also gave similar data and are summarized in Table 1.

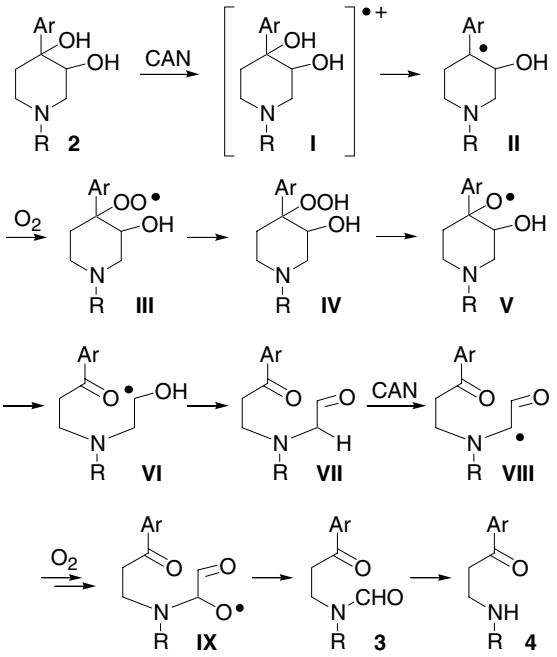


Scheme 1.

Table 1. CAN-mediated oxidative cleavage of diols **2Aa**–**Be**

Entry	**2**, (R, Ar), yield[a] (%)	**3**, yield[b,c] (%)	**4**, yield[b,c] (%)
1	**2Aa**, (Cbz, C_6H_5), 64	**3Aa**, 54	**4Aa**, 18
2	**2Ab**, (Cbz, 4-FC_6H_4), 64	**3Ab**, 58	**4Ab**, 28
3	**2Ba**, (Ts, C_6H_5), 58	**3Ba**, 52	**4Ba**, 18
4	**2Bb**, (Ts, 4-FC_6H_4), 52	**3Bb**, 55	**4Bb**, 27
5	**2Bc**, (Ts, 4-ClC_6H_4), 56	**3Bc**, 52	**4Bc**, 20
6	**2Bd**, (Ts, 4-$MeOC_6H_4$), 58	**3Bd**, 49	**4Bd**, 24
7	**2Be**, (Ts, 3-$MeOC_6H_4$), 61	**3Be**, 50	**4Be**, 25

[a] All yields were based on compound **1** confirmed.
[b] The product ratio was adjusted based on isolated products.
[c] All yields were based on compound **2** confirmed.

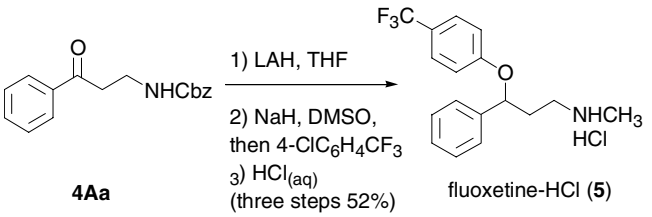


Scheme 2.

How is the oxidative cleavage of compounds **2** initiated by CAN in acetonitrile? Mechanically it is not clear if the reaction follows the same pathway as shown in Scheme 2.[2a] However, the initial event may be considered to be the formation of the cation radical **I** from **2**. Benzylic radical **II** can trap molecular oxygen leading the peroxyradical **III** and the latter can abstract hydrogen from the solvent and eliminate hydroxide radical to form the hydroperoxide **IV** and oxyradical **V**. Intermediate **VIII** can be generated via bond cleavage of **V**, hydrogen abstraction of **VI**, and oxidative addition of **VII** in the presence of excess CAN. Next, compounds **3** are provided by the repeated treatment of **VIII** with molecular oxygen and CAN-mediated bond cleavage of **IX**. In situ hydrolysis of compounds **3** is further provided to form compounds **4** in different ratios.

Furthermore, treatment of diols **2** with CAN did not cause oxidative cleavage reaction at room temperature. The reaction must be heated to increase reaction rate. If the reaction was refluxed over 2 h, the desired products **3** and **4** slowly disappeared and a complex mixture resulted. The overall reaction progress was monitored by TLC. Therefore, the best condition for this CAN-mediated reaction is refluxed temperature within 30 min in acetonitrile.

We had also tried to study the CAN-mediated oxidative cleavage of 4-alkyl (methyl and ethyl functional group) 3,4-dihydroxypiperidine, but the complex products were provided in similar condition. Although the synthetic application is decreased, the present work is complementary to existing the methodology. We believe the 4-aryl functional group of diols **2** is an important substituent, which provides a stable benzylic radical in the initial process of oxidative cleavage.



Scheme 3.

With the results in hand, the next focus was to examine the conversion from compounds **3** into **4**. Treatment of compounds **3** with aqueous lithium hydroxide solution was successfully yielded compounds **4** in nearly quantitative yields.[11] The present work can increase the overall yields for the preparation of compounds **4**. Based on the experimental simplicity, the preparation of compound **4Aa** was also conducted in a multigram scale (10 mmol) with 46% overall yield. Thus enough amounts of compound **4Aa** were provided for synthesizing racemic fluoxetine by the simple two-step procedure with CAN-mediated reaction of model substrate **2Aa** and basic hydrolysis of compound **3Aa**.

Racemic fluoxetine, marketed under the trade name Prozac®, has recently surpassed the $3 billions mark in annual scales. Fluoxetine offers the potential for treatment of additional indications such as anxiety, alcoholism, chronic pain, headache, obsessive disorders, sleep disorders, and bulimia. Due to its biological and pharmacological importance, there have been several reports on the total synthesis of fluoxetine.[12]

As shown in Scheme 3, racemic fluoxetine hydrochloride (**5**) was successfully accomplished by reduction of compound **4Aa** with lithium aluminum hydride in tetrahydrofuran, etherification with 4-chlorobenzotrifluoride and sodium hydride in dimethylsulfoxide, and subsequent hydrolysis with aqueous hydrochloric acid solution in 52% yield.[12a,13] Finally, an easy and novel approach for total synthesis of racemic fluoxetine (**5**) from 4-hydroxypiperidine (**1**) has been explored.

3. Conclusion

In conclusion, we explore a CAN-mediated transformation of diols **2** to two 2-aminoethyl arylketone derivatives **3** and **4** with different ratios and utilize the method to achieve the synthesis of racemic fluoxetine (**5**). We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various potential biological activities of compounds using 4-hydroxypiperidine (**1**) as the starting material.

Acknowledgment

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Supplementary data

Experimental procedures and photocopies of ^{1}H and ^{13}C NMR ($CDCl_3$) spectral data for compounds **3Aa**–**Be**, **4Aa**–**Be**, and **5** were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.039.

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10. CAN-mediated conversion of diols **2** into β-amino arylketones **3** and **4** is as follows: CAN (220 mg, 0.4 mmol) was added to a solution of diols **2** (0.1 mmol) in acetonitrile (10 mL) at rt. The reaction mixture was stirred at refluxed temperature for 30 min. Water (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×10 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 β-amino arylketones **3** and **4** in different ratios (see Table 1). Representative data for **3Aa**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.92–7.90 (m, 2H), 7.59–7.55 (m, 1H), 7.47–7.44 (m, 2H), 7.40–7.36 (m, 5H), 5.32 (s, 2H), 4.11 (t, $J = 7.5$ Hz, 2H), 3.24 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.52, 162.64, 153.71, 136.34, 134.49, 133.37, 128.92, 128.80 (2×), 128.65 (2×), 128.54 (2×), 127.99 (2×), 69.05, 36.84, 36.82; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_4$ (M^++1) 312.1236, found 312.1235. For **4Aa**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 7.5$ Hz, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.37–7.30 (m, 5H), 5.41 (br s, 1H), 5.09 (s, 2H), 3.63 (dd, $J = 6.0$, 12.0 Hz, 2H), 3.24 (t, $J = 5.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.15, 156.40, 136.48 (2×), 133.47, 128.68 (2×), 128.48, 128.06, 128.02 (2×), 128.00 (3×), 69.63, 38.49, 35.89; HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_3$ (M^++1) 284.1287, found 284.1288.
11. Conversion of compounds **3** to **4** is as follows: Aqueous lithium hydroxide (0.1 N, 1 mL) solution was added to a solution of compounds **3** (0.05 mmol) in tetrahydrofuran (3 mL). The reaction mixture was heated at refluxed temperature for 1 h. It was then cooled to rt, acidified with aqueous hydrochloric acid solution (2 N, 5 mL) and extracted with ether (3×10 mL). The combined organic layers were evaporated under reduced pressure to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 4/1–2/1) afforded compounds **4** in nearly quantitative yields.
12. Synthesis of fluoxetine (**5**), see: (a) Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S. *Tetrahedron* **2001**, *57*, 992; (b) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, *32*, 1901; (c) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339; (d) Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435; (e) Xu, C.; Yuan, C. *Tetrahedron* **2005**, *61*, 2169; (f) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425; (g) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412; (h) Chenevert, R.; Fortier, G. *Chem. Lett.* **1991**, 1603; (i) Mitchell, D.; Koenig, T. M. *Synth. Commun.* **1995**, *25*, 1231; (j) Liu, H.-L.; Hoff, B. H.; Anthonsen, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, *11*, 1767; (k) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059; (l) Kumar, P.; Upadhyay, R. K.; Pandey, R. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3955; (m) Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039; (n) Brown, A.; Carlyle, I.; Clark, J.; Hamilton, W.; Gibson, S.; McGarry, G.; McEachen, S.; Rae, D.; Thorn, S.; Walker, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2007.
13. Synthesis of fluoxetine hydrochloride (**5**) is as follows: Lithium aluminum hydride (38 mg, 1.0 mmol) was added to a solution of compound **4Aa** (70 mg, 0.25 mmol) in tetrahydrofuran (10 mL) at rt. The reaction mixture was heated at refluxed temperature for 3 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to rt and ethyl acetate (5 mL) was slowly added. The mixture was filtered through a short plug of Celite. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Without further purification, sodium hydride (20 mg, 60%, 0.5 mmol) was added to a solution of the resulting amino alcohol in dimethyl sulfoxide (2 mL) at rt. The reaction mixture was heated at 60 °C for 1 h. A solution of 4-chlorobenzotrifluoride (90 mg, 0.5 mmol) in dimethylsulfoxide (0.5 mL) was added to the reaction mixture at 60 °C and the resultant mixture was heated for 1 h at 100 °C. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to rt. Water (10 mL) was added to the reaction mixture and extracted with ether (3×10 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Aqueous hydrochloric acid solution (2 N, 0.5 mL) was added to the crude product in ether (5 mL) at rt. The resulting white solid was filtered and washed with ether (3×10 mL) to give compound **5** (52%, 45 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (br s, 2H), 7.41 (d, $J = 9.0$ Hz, 2H), 7.35–7.25 (m, 5H), 6.89 (d, $J = 8.7$ Hz, 2H), 5.46 (dd, $J = 4.5$, 8.1 Hz, 1H), 3.12 (br s, 2H), 2.62 (t, $J = 5.4$ Hz, 3H), 2.53–2.44 (m, 2H). The NMR spectral data of compound **5** were in accordance with those reported in the literature.[12a]