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CAN-mediated rearrangement of 4-benzhydrylidenepiperidines

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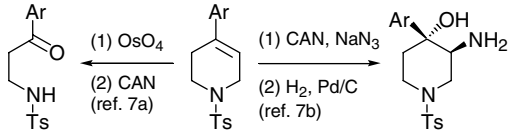
Abstract—Several 1-substituted phenyl-(4-phenylpiperidin-4-yl)methanones are synthesized in modest overall yields starting from the reaction of different 1-substituted 4-benzhydrylidenepiperidines via CAN-mediated rearrangement. This facile strategy was also used to synthesize meperidine analog.

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 the organic reactions of industries and academia fields.[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] Representative examples include oxidative addition, photooxidation, nitration, and deprotection etc.[2–6] Due to the numerous advantages associated with this eco-friendly compound, CAN has been explored as a powerful reagent for different reactions. Many research groups successfully developed various useful transformations by the application of this reagent.

Recently, we developed two straightforward strategies toward CAN-mediated oxidative cleavage of *cis*-4-aryl-3,4-dihydroxypiperidines and CAN-mediated oxidative addition of 4-aryl-1,2,5,6-tetrahydropyridines with sodium azide and followed by hydrogenation (Scheme 1).[7a,b] In order to address this issue, the CAN-mediated rearrangement of 4-benzhydrylidenepiperidines was explored.



Scheme 1.

For investigating the CAN-mediated rearrangement, several 1-substituted 4-benzhydrylidenepiperidines **2a**–**f** (a, R = $MeSO_2$; b, R = $PhSO_2$; c, R = *p*-$TolSO_2$; d, R = EtCO; e, R = PhCO; f, R = BnOCO) were chosen as the starting materials and prepared via *N*-acylation of phenyl-piperidin-4-yl-methanone (**1**)[8] with different acid chlorides in CH_2Cl_2 at 0 °C, Grignard addition with phenylmagnesium bromide reagent in THF at −78 °C, and subsequent dehydration with BF_3–OEt_2 in CH_2Cl_2 at rt.

With several compounds **2a**–**f** in hand, CAN-mediated rearrangement in CH_3CN at rt without nitrogen system was examined.[9] To explore the generality of this reaction, the results of investigations were presented in Scheme 2. The total synthetic procedure could be monitored by TLC until the reaction was complete at rt for ca. 3 h. The structure of compound **3c** was determined by single-crystal X-ray analysis as shown in Diagram 1.

The transformation is an efficient rearrangement with a facile operation procedure, which is governed by the stability of tertiary radical, and the introduction of molecular oxygen takes place. How is the oxidative rearrangement of compounds **2a**–**f** initiated by CAN? Mechanically it is not clear if the reaction follow the

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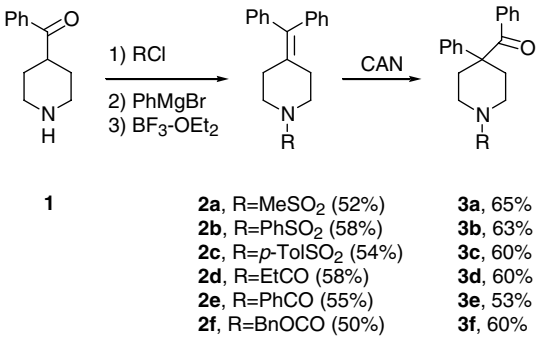


Scheme 2.

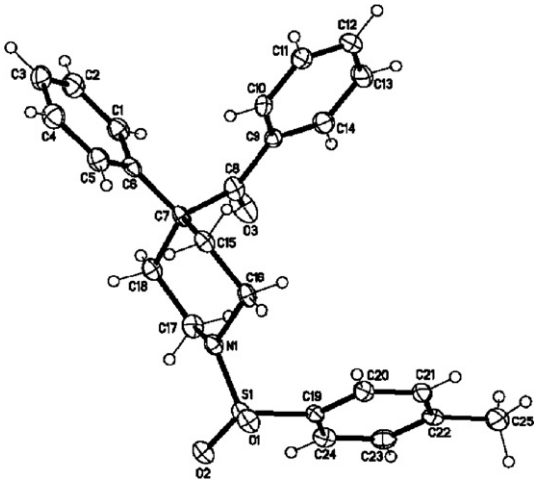
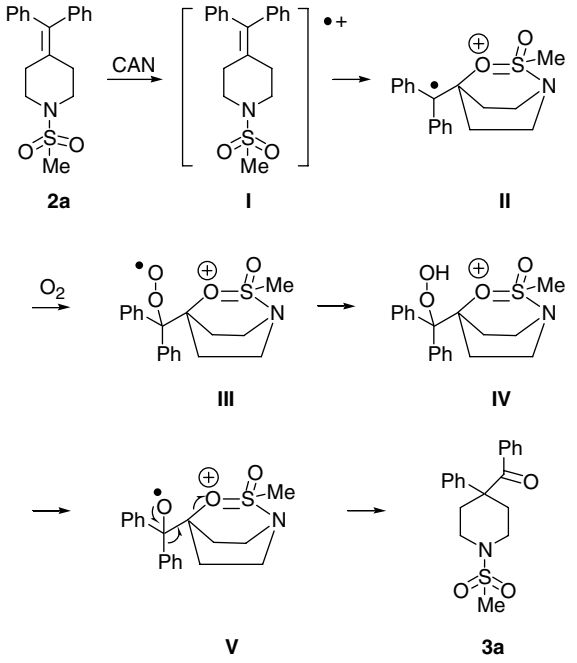


Diagram 1. X-ray crystallography of compound **3c**.

same pathway as shown in Scheme 3. However, the initial event may be considered to be the formation of the cation radical **I** from model substrate **2a**. Benzylic radical **II** can trap molecular oxygen leading peroxyradical **III** and the latter can abstract hydrogen from the solvent and eliminate hydroxide radical to form hydroperoxide **IV** and oxyradical **V**. Next, compounds **3a**–**f** were provided by the bond migration of intermediate **V**.

According to the recent literature reports,[2d,f] Nair and his coworkers had developed a series of CAN-mediated reaction with molecular oxygen. The possible reaction mechanism involving different supporting experimental data was proposed well. With the literature reports and our results, we have to envision that molecular oxygen plays an important role to promote the occurrence of rearrangement reactions by CAN.

For enhancing the reaction diversity, reaction solvents (methanol or *t*-butanol), reaction additives (sodium azide and lithium thiomethoxide) and other conditions (with or without nitrogen system) were tested under the CAN-mediated reaction. But unsatisfied results (lower yields or complex products) were yielded. In this letter, the present methodology was an optimum reaction condition among the tested conditions by us. Briefly, the best condition for this facile operation reaction is room temperature within 3 h in dry MeCN without nitrogen or argon system.

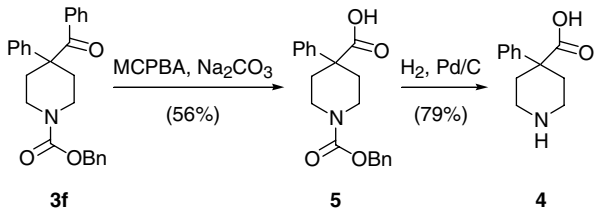


Scheme 3.

Although a great number of 4-aroyl-4-arylpiperidines and their derivatives with this specific substitution pattern are of particular interest, more significant efforts toward the development of new methods are needed.[10] The exhibited methodology could provide a new route for the preparation of various 4-aroyl-4-arylpiperidines in search of useful compounds with potential biological activities.[10c]

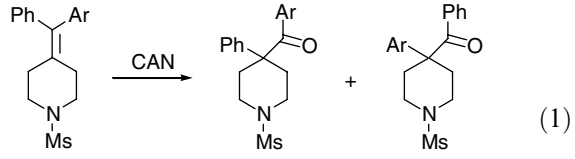
To reinvestigate the applicability of the facile reaction, we had tried to study compound **4**.[11] Compound **4** is a key precursor for preparing meperidine. Meperidine can serve as an atypical μ-opioid agonist at monoamine transporters and was initially found to be selective for the serotonin transporter over the dopamine.[12] As shown in Scheme 4, the treatment of ketone **3f** with *m*-chloroperoxybenzoic acid and sodium carbonate and followed by hydrogenolysis yielded aminoacid **4**.

Upon the treatment of three unsymmetrical compounds **6a** (Ar = 2-MePh), **6b** (Ar = 3-MeOPh) and **6c** (Ar = 4-FPh) with CAN, the inseparated mixture was obtained in 62%, 60%, and 56% yields with nearly 2:1–3:1 ratios by ^{1}H NMR spectral analysis. Based on the results, the poor regioselectivity was provided between phenyl group and aryl group with donating and withdrawing



Scheme 4.

group during the rearrangement process. In our technology, we cannot separate the three pairs of regioisomers such that the correct structures of 4-aroyl-4-phenylpiperidines and 4-benzoyl-4-arylpiperidines cannot be determined. We had also tried to study a number of reaction conditions (e.g., prolonged reaction time and elevated temperature) for increasing the regiochemical selectivity, which provided unsatisfactory results. Although the synthetic application is decreased, the present work is complementary to existing methodology.



(1)

6a, Ar=2-MePh
6b, Ar=3-MeOPh
6c, Ar=4-FPh

In conclusion, we have developed a straightforward method for synthesizing 1-substituted phenyl-(4-phenylpiperidin-4-yl)methanones via the CAN-mediated rearrangement of different 1-substituted 4-benzhydrylidenepiperidines. A key precursor of meperidine was also prepared by the simple operation. Currently studies are in progress in this direction.

Acknowledgments

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9. CAN-mediated rearrangement of olefins **2a**–**f** into compounds **3a**–**f** is as follows: A solution of ceric ammonium nitrate (CAN, 2.2 g, 2.0 mmol) in CH_3CN (10 mL) was added dropwise to a solution of olefins **2a**–**f** (1.0 mmol) in dry CH_3CN (5 mL) at rt under open system condition. The reaction mixture was stirred at rt for 1 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 4/1–2/1) afforded compounds **3a**–**f**. For compound **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 8H), 7.27–7.24 (m, 2H), 3.69 (d, $J = 12.5$ Hz, 2H), 2.84 (dt, $J = 1.5$,

12.0 Hz, 2H), 2.75 (s, 3H), 2.67 (d, $J = 12.5$ Hz, 2H), 2.19 (dt, $J = 4.5$, 12.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.01, 141.96, 136.81, 132.04, 129.44 (2×), 129.98 (2×), 128.25 (2×), 127.72, 125.82 (2×), 53.21, 43.41 (2×), 34.56 (2×), 34.41; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_3S$ 344.1320, found 344.1323. For compound **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, $J = 7.5$ Hz, 2H), 7.63–7.60 (m, 1H), 7.53 (t, $J = 7.5$ Hz, 2H), 7.40–7.30 (m, 6H), 7.19–7.17 (m, 4H), 3.69 (d, $J = 12.5$ Hz, 2H), 2.61 (d, $J = 12.0$ Hz, 2H), 2.47 (dt, $J = 2.0$, 12.0 Hz, 2H), 2.17 (dt, $J = 4.0$, 12.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.95, 141.91, 136.95, 136.02, 132.73, 131.81, 129.35 (2×), 129.99 (2×), 128.69 (2×), 128.12 (2×), 127.64, 127.51 (2×), 125.76 (2×), 53.07, 43.59 (2×), 34.31 (2×); HRMS (ESI, M^++1) calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1481. For **3c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.0$ Hz, 2H), 7.41–7.31 (m, 8H), 7.20–7.18 (m, 4H), 3.68 (dt, $J = 3.0$, 13.5 Hz, 2H), 2.60 (d, $J = 13.5$ Hz, 2H), 2.46 (s, 3H), 2.45 (td, $J = 1.5$, 13.5 Hz, 2H), 2.17 (td, $J = 4.0$, 13.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.08, 143.51, 142.05, 137.06, 133.15, 131.84, 129.66 (2×), 129.40 (2×), 128.78 (2×), 128.16 (2×), 127.67, 127.62 (2×), 125.83 (2×), 53.18, 43.63 (2×), 34.39 (2×), 21.57; HRMS (ESI, M^++1) calcd for $C_{25}H_{26}NO_3S$ 420.1633, found 420.1632. Single-crystal X-ray diagram: the crystal of compound **3c** was grown by slow diffusion of AcOEt into a solution of compound **3c** in CH_2Cl_2 to yield, colorless prism. The compound crystallizes in the monoclinic crystal system. space group P2(1), $a = 12.430(3)$ Å, $b = 6.1974(13)$ Å, $c = 14.688(3)$ Å, $V = 1042.1(4)$ Å^3, $Z = 4$, $d_{calcd} = 2.674$ mg/m^3, absorption coefficient 0.365 mm^{-1}, $F(000) = 888$, 2θ range (1.51–28.36°); R indices (all data): $R_1 = 0.0658$, $wR_2 = 0.1007$. For compound **3d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.21 (m, 10H), 4.44 (br d, $J =$ 13.5 Hz, 1H), 3.70 (br d, $J = 13.5$ Hz, 1H), 3.31 (t, $J = 12.5$ Hz, 1H), 2.73 (t, $J = 12.5$ Hz, 1H), 2.62 (br d, $J = 13.5$ Hz, 1H), 2.53 (br d, $J = 13.5$ Hz, 1H), 2.32 (q, $J = 7.5$ Hz, 2H), 2.12 (dt, $J = 3.5$, 13.5 Hz, 1H), 1.83 (dt, $J = 3.5$, 13.5 Hz, 1H), 1.12 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.23, 172.28, 142.19, 137.11, 131.79, 129.30 (2×), 128.83 (2×), 128.12 (2×), 127.52, 125.88 (2×), 53.91, 42.94, 38.83, 36.40, 33.55, 26.40, 9.45; HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_2$ (M^++1) 322.1807, found 322.1806. For compound **3e** (rotamer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.31 (m, 13H), 7.27–7.23 (m, 2H), 4.57–4.54 (m, 1H), 3.67–3.64 (m, 1H), 3.31–3.27 (m, 1H), 3.01–2.96 (m, 1H), 2.66–2.61 (m, 1H), 2.54–2.51 (m, 1H), 2.26–2.22 (m, 1H), 1.88–1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.20, 170.36, 142.13, 137.13, 133.86, 131.86, 129.58, 129.38 (2×), 128.87 (2×), 128.41 (2×), 128.18 (2×), 127.61, 126.83 (2×), 125.94 (2×), 54.08, 45.26, 39.49, 36.31, 33.96; HRMS (ESI) m/z calcd for $C_{25}H_{24}NO_2$ (M^++1) 370.1807, found 370.1810. For compound **3f**: (rotamer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.23 (m, 15H), 5.13 (br s, 2H), 4.07–3.99 (m, 2H), 3.11–2.95 (m, 2H), 2.55 (d, $J = 13.0$ Hz, 2H), 2.11–1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.35, 155.25, 142.38, 137.35, 136.71, 131.71, 129.30 (2×), 128.81 (2×), 128.42 (2×), 128.11 (2×), 127.91, 127.77 (2×), 127.48, 125.95 (2×), 67.01, 53.77, 41.26 (2×), 35.19, 34.28; HRMS (ESI) m/z calcd for $C_{26}H_{26}NO_3$ (M^++1) 400.1913, found 400.1913.

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