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An Efficient Synthesis of Both Enantiomers of Cathinone by Regioselective Reductive Ring Opening of Substituted Aziridines

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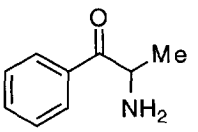
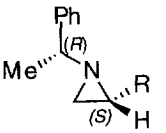
Abstract: Both enantiomers of Cathinone were prepared as HCl salts from *N*-(*R*)-α-methylbenzylaziridine-2(*S*)-carboxaldehyde **2c** and its enantiomer *N*-(*S*)-α-methylbenzylaziridine-2(*R*)-carboxaldehyde **3c** in high yield. This process makes it possible to prepare other aromatic and heteroaromatic analogs of Cathinone efficiently.

Introduction

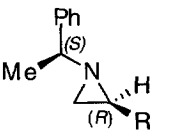
Cathinone, **1**, is the main active compound isolated from the leaves of *Catha edulis* (Khat)[1] which can be found in East African countries and the Arabian Peninsula. The compound showed analogous biological activity to that of amphetamines[2] and dopamine.[3] The above interesting activities shown by the cathinone encouraged active research on the compound[4-11] and also attracted many synthetic efforts.[12]



1 (Cathinone)



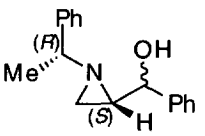
2a: R = CO_2Et
2b: R = CH_2OH
2c: R = CHO



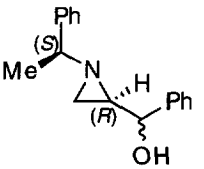
3a: R = CO_2Et
3b: R = CH_2OH
3c: R = CHO

We recently reported the synthesis and reductive ring cleavage of the enantiomerically pure aziridine-2-carboxylates (**2a**, **3a**) and aziridine-2-methanols (**2b**, **3b**) which were obtained from the reaction of optically active α-methylbenzylamine and ethyl 2,3-dibromopropionate in high yield. We found that the C(3)-*N* bond of the *N*-(-)-α-methylbenzylaziridine-2-methanol could be regioselectively reduced by catalytic hydrogenation in the presence of the Pearlman's catalyst.[13] It was also found that the configuration at C(2) of the α-amino aldehyde **2c** was stable and various organometallic reagents were stereoselectively added to

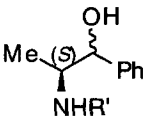
the aldehyde.[13b] Based on the previous results we envisaged a new efficient synthetic pathway to Cathinone using highly regioselective reductive ring cleavage of the aziridines, **4** and **5**. The aziridine secondary alcohols **4** and **5** were prepared as a diastereomeric mixture by PhMgBr addition to the enantiomerically pure and configurationally stable aziridine-2-carboxaldehyde **2c** and **3c** which were prepared from the corresponding alcohols **2b** and **3b** by Swern oxidation in 91% yield.[13b,14,15] The absolute configuration at C-2 of the aziridine **2** was established after reductive ring cleavage of the corresponding alcohol **2b** followed by debenzylation to provide alaninol.[13a]



4a
4b



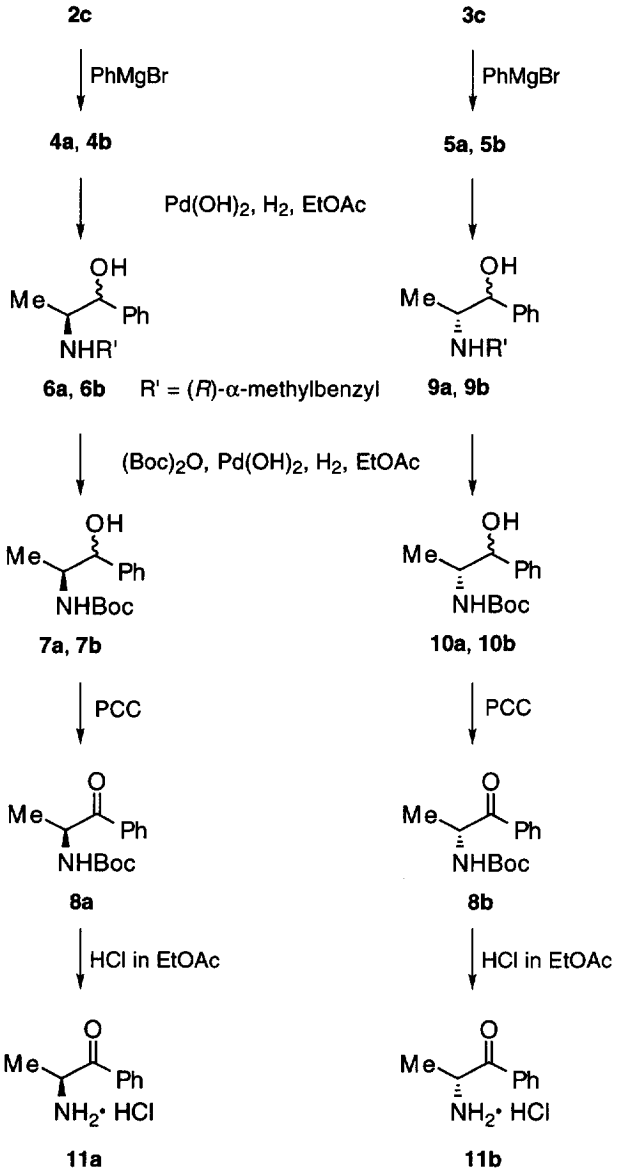
5a
5b



6a, 6b R' = (*R*)-α-methylbenzyl
7a, 7b R' = *tert*-butoxycarbonyl

Results and Discussion

The addition of phenyl Grignard reagent to the aziridine-2(*S*)-carboxaldehyde **2c** proceeded smoothly at 0 °C to provide both diastereomeric alcohols **4a** and **4b** as a (4:1) mixture in 96% yield after flash chromatography. Those two diastereomeric alcohols were separated by chromatography for the purpose of analysis. However, both alcohols were dissolved in EtOAc with 10 wt% of the Pearlman's catalyst and the mixture was stirred at room temperature under a balloon pressure of hydrogen for 14 hr to provide C(3)-*N* bond reduced products. The catalyst was filtered and the solvent was removed. A quick chromatography on silica gel provided a mixture of both (1*R*, 2*S*) and (1*S*, 2*S*) diastereomeric alcohols **6a** and **6b** in 85% yield. The ring reduction products were purified at this stage because a small amount of C(2)-*N* bond reduction product was formed during the reductive cleavage step and the N-Boc derivatives of C(2)-*N* and C(3)-*N* bond reduced products were not separable at later stage. The α-methylbenzyl group was removed by successive catalytic hydrogenation in the presence of 1 equiv. of $(Boc)_2O$ and 20 wt % of the Pearlman's catalyst to provide *N*-Boc derivatives **7a** and **7b** in 93% yield.[16] The mixture of the benzylic alcohols **7a** and **7b** was readily oxidized to the corresponding ketone **8a** by PCC in 76% yield after purification on silica gel. The other isomeric ketone **8b** was also prepared from the mixture of **5a** and **5b** by the same procedure. The *N*-Boc protecting group was cleaved by 3N HCl in EtOAc at room temperature to provide Cathinone as a HCl salt. The overall yield from **2c** to **11a** is 52% and from **3c** to **11b** is 51% (Scheme 1).



Scheme 1

This new process uses enantiomeric pair of optically pure aziridine-2-carboxaldehydes, **2c** and **3c**, which can be prepared from the readily available starting materials in high yields. This new method avoids using microorganism and the resolution of norephedrine which was used by Berrang *et al.*.[1] This procedure also makes it possible to prepare variously substituted phenyl and other aromatic analogs of Cathinone by reacting the corresponding organometallic reagents with **2c** or **3c**.

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Experimental

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and all melting points were not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz) or a Varian Gemini 300 (300 MHz) spectrometer. NMR spectra were recorded in ppm (δ) related to tetramethylsilane (δ= 0.00) as an internal standard unless stated otherwise and are reported as follows; chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

All reactions involving organometallic reagents were carried out in an inert atmosphere of nitrogen or argon. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl, and methylene chloride and DMSO from calcium hydride prior to use. Solvents and liquid reagents were transferred using hypodermic syringes. PhMgBr solution (purchased from Aldrich) was assayed for active alkyl by titration in THF using 1,10-phenanthroline as an indicator. All other reagents and solvents used were reagent grade. Small and medium scale purifications were performed by flash chromatography.

Preparation of **2c**, **4(a, b)**, **6a**, and **7a** was previously reported.[13b]

***(1R,2S)*-2-*N*-[*(R)*-(-)-α-methylbenzyl]amino-1-phenyl-1-propanol (6b).** mp 67-68 °C; $[\alpha]^{24}_D$ = +50.8° (*c* 0.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.21 (m, 10H), 4.44 (d, *J*=4.3 Hz, 1H), 3.91 (q, *J*=6.6 Hz, 1H), 2.81 (m, 1H), 2.44 (br, 1H), 1.36 (d, *J*=6.6 Hz, 3H), 0.87 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 145.3, 141.7, 128.7, 128.1, 127.2, 126.7, 126.4, 126.1, 75.0, 56.0, 55.6, 24.8, 14.6; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.83; H, 8.50; N, 5.41.

(-)-(1*R*,2*S*)-2-*N*-Boc-Amino-1-phenyl-1-propanol (7b). mp 90-92 °C; $[\alpha]^{25}_D$ = -64.5° (*c* 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 4.86 (br, 1H), 4.64 (br, 1H), 4.02 (br, 1H), 3.27 (br, 1H), 1.47 (s, 9H), 0.99 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.5, 141.2, 128.2, 127.5, 126.4, 79.6, 76.5, 51.8, 28.2, 14.2; Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.94; H, 8.60; N, 5.59.

(-)-(2*S*)-2-*N*-Boc-Amino-1-phenyl-1-propanone 8a. To a suspension of PCC (1.19 mmol, 255 mg) in 10 mL of anhydrous methylene chloride was added the solution of a mixture of **7a** and **7b** (200 mg, 0.80 mmol) in 2.0 mL of CH_2Cl_2 and the dark-brown mixture was stirred at room temperature for 1.5 hr. Dry ether (10.0 mL) was added to the reaction mixture and the mixture was filtered, and the black deposit was washed with ether. The filtrate was concentrated under reduced pressure to give the crude amino ketone

8a as a solid. The crude product was purified by flash chromatography on silica gel to give 161 mg (76%) of **8a** as a white solid. mp 70-72 °C; $[\alpha]^{27}_D$ = -6.7° (*c* 1.00, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.5 Hz, 2H), 7.44-7.64 (m, 3H), 5.58 (d, *J*=7.0 Hz, 1H), 5.31 (qu, *J*=7.0 Hz, 1H), 1.46 (s, 3H), 1.40 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.9, 155.4, 134.4, 133.8, 129.0, 128.8, 79.6, 50.9, 28.1, 19.6. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.48; H, 7.63; N, 5.63.

(+)-(2*R*)-2-*N*-Boc-Amino-1-phenyl-1-propanone 8b. The compound has the same physical data as **8a** except $[\alpha]^{25}_D$ = +6.5° (c 1.00, $CHCl_3$).

(-)-(2S)-2-Amino-1-phenyl-1-propanone hydrochloride 11a. To the thoroughly dried (-)-(2*S*)-2-*N*-Boc-Amino-1-phenyl-1-propanone **8a** (100 mg, 0.40 mmol) was added 3.0 mL of 3N HCl in EtOAc and the mixture was stirred vigorously at room temperature. After 30 min. of stirring, the solution turned to a white suspension conforming the formation of the insoluble salt. The mixture was concentrated and the crude product was recrystallized from ^iPrOH-Et_2O to give 67 mg (90%) of the **11a** as a white crystalline salt. mp 180-182 °C. $[\alpha]^{27}_D$ = -47.1° [c 1.00, H_2O, lit. $[\alpha]^{21}_D$ = -46.9° (c 1.00, H_2O)]. ^1H NMR (200 MHz, D_2O) δ 8.26 (d, *J*=8.4 Hz, 2H), 7.85-7.94 (m, 1H), 7.70-7.84 (m, 2H), 5.31 (q, *J*=7.4 Hz, 1H), 1.77 (d, *J*=7.4 Hz, 3H). ^{13}C NMR (50.3 MHz, D_2O) δ 197.6, 136.1, 134.5, 130.6, 130.2, 53.1, 18.0. Anal. Calcd for $C_9H_{12}ClNO$: C, 58.23; H, 6.52; N, 7.54. Found: C, 58.07; H, 6.80; N, 7.47.

(+)-(2R)-2-Amino-1-phenyl-1-propanone hydrochloride 11b. The compound has the same physical data as **11a** except $[\alpha]^{27}_D$ = +47.3° (c 0.33, H_2O).

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