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EFFICIENT SYNTHESIS OF NEW BENZOCYCLOBUTENIC PHENETHYLAMINES

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Abstract: *New benzocyclobutenic phenethylamines were easily obtained from simple starting materials by arynic condensations of ketones enolates.*

Previous studied from our laboratory showed that polycyclic benzocyclobutene derivatives have interesting chemical[1] as well as biological[2] properties. Thus several benzocyclobutenols were found to be anticonvulsants,[2a] while interesting adrenergic activities were found with several aminobenzocyclobutenols.[2b]

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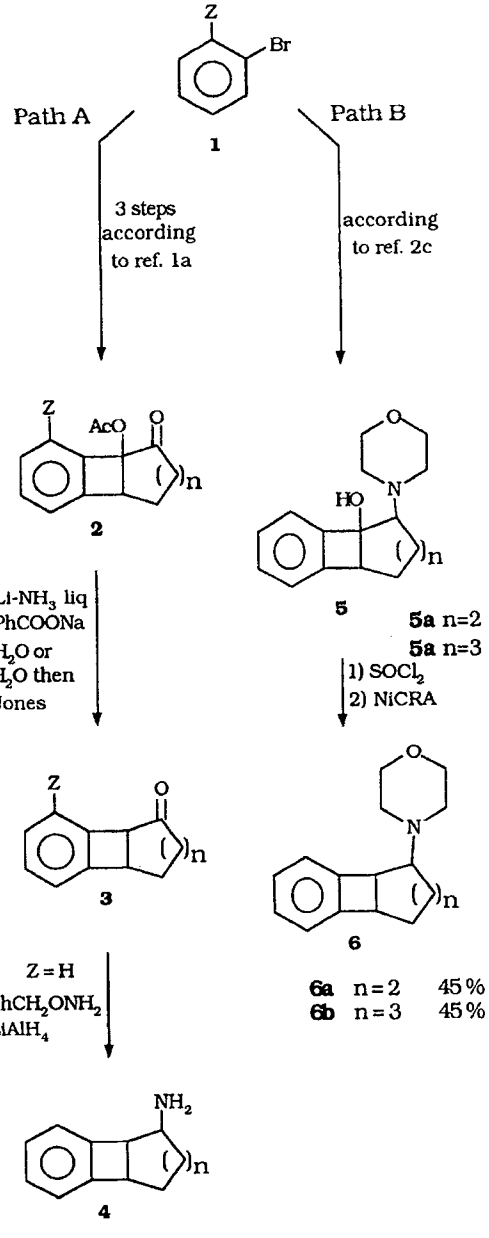
Scheme



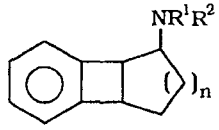
	Z	n	Yield/**1**
2b	H	3	50
2c	H	4	45
2d	H	8	25
2e	NEt2	4	31
2f	OH	2	44

	Z	n	Yield/**2**
3a	H	2	83
3b	H	3	84
3c	H	4	92
3d	H	8	96
3e	NEt2	4	88
3f	OH	2	77

	n	Yield/**3**
4a	2	79
4b	3	59
4c	4	50

On the other hand, it is well known that phenethylamines are very important in medicinal chemistry. Thus we thought that such amine derivatives constructed on the benzocyclobutene squeleton might be of interest.

We report in the present paper our first attempts to prepare new phenethylamine **A**



A

Taking into account our previous results,[1] we considered the pathways given in the Scheme.

Path A was explored in order to obtain the unsubstituted amines **4**. New ketones **2b-f** were obtained according to a previously published procedure described for the preparation of **2a** Z = H, n = 2.[1a]

Reduction of these compounds **2** with Li-liq. NH_3 followed by quenching with sodium benzoate led to the corresponding ketones **3** sometimes accompanied by the corresponding alcohols. These latters were easily oxidized into **3** with Jones reagent. Finally, **3a-f** were obtained with yields varying between 77 and 96 %.

The transformation of **3a-c** into **4a-c** was then explored. The best results were obtained by reduction with $LiAlH_4$ of the

corresponding benzyloximes. Under these conditions **4a-c** were obtained with 50 to 88% yields.

Following path B : **5a,b** were easily obtained according to a previously published procedure.[2c] In our hands, removal of the hydroxy group using radical processes[5] was unsuccessful.

On the other hand **5a,b** were easily transformed into corresponding halogenated amines. However we never succeeded in reducing the chlorine with classical reagents such as Bu_3SnH.[6] On the contrary NiCRA[7] was particularly efficient and **6a,b** were obtained from **5a,b** with 45 % yields.

In conclusion, starting from benzocyclobutene derivatives, two pathways were explored to obtain two different kinds of benzocyclobutene phenethylamines.

Typical experimental procedures

General procedure for the preparation of 2

New compounds **2b-f** were obtained following the previous described procedure using for the preparation of analogous **2a**.[1a]

2b : IR (NaCl) ν (cm^{-1}) : 1710 (C=O) ; 1750 (OCO-CH_3). ^1H NMR (CCl_4) δ (ppm) : 1.03-2.53 (m, 1 s, 2.06 (4xCH_2) (O-CO-CH_3) ; 3.71-4.02 (m, benzylic H) ; 7.02-7.58 (m, arom. H). UV (MeOH) λmax (log ε) : 274 (3.13) ; 267 (3.15) ; 259 (3.13). MS (m/e) : $C_{15}H_{16}O_3$ M = 244.

2c : IR (KBr) ν (cm^{-1}) : 1710 and 1745 (C=O). ^1H NMR (CCl_4) δ

(ppm) : 0.96-2.88 (m, 13 H, 5 x CH_2 and CH_3CO s at 2.08) ; 3.47-3.92 (m, 1 H, benzylic H) ; 6.88-7.56 (m, 4 H, arom. H). UV (MeOH) λmax (log ε) : 259.5 (3.21) ; 266 (3.35) ; 272 (3.34). Mp (EtOAc/petroleum ether) : 76-78°C. Analysis : $C_{16}H_{18}O_3$: % Calc : C 74.39 ; H 7.02. Found : C 73.92 ; H 6.78.

2d : IR (KBr) ν (cm^{-1}) : 1715 and 1745 (C=O). ^1H NMR (CCl_4) δ (ppm) : 1.03-2.50 (m, 21 H, 9 x CH_2 and CH_3CO s at 2.04) ; 3.66-4.07 (m, 1 H, benzylic H) ; 6.80-7.50 (m, 4 H, arom. H). UV (MeOH) λmax (log ε) : 260 (3.10) ; 265.5 (3.26) ; 272 (3.82). Analysis : $C_{20}H_{26}O_3$: % Calc : C 76.39 ; H 8.33. Found : C 76.30 ; H 8.82.

2e : IR (KBr) ν (cm^{-1}) : 1725 and 1755 (C=O). ^1H NMR (CCl_4) δ (ppm) : 0.08-2.50 (m, 19 H, 5 x CH_2, CH_3CO and $(C\underline{H}_3CH_2)_2N$, t at 1.05, J = 8 Hz and s at 2.08) ; 3.16 (q, J = 8 Hz, 4 H, $(CH_3C\underline{H}_2)_2N$) ; 3.76-4.05 (m, 1 H, benzylic H) ; 6.20-6.50 (m, 2 H, arom. H). 6.93-7.23 (m, 1 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 12.92, 21.46 (3 x CH_3) ; 24.98, 26.67, 29.61, 37.92 (CH_2) ; 43.58 (CH_2-CH_3) ; 56.07 (CH) ; 91.42 (C-OAc) ; 108.33, 111.20, 132.07 (arom. C) ; 122.26 (arom. C-N) ; 134.97, 148.75 (arom. C) ; 169.33 (CH_3-C=O) ; 207.99 (C=O). UV (MeOH) λmax (log ε) : 266 (4.07). Analysis : $C_{20}H_{27}NO_4$: % Calc : C 72.91 ; H 8.26 ; N 4.25. Found : C 72.99 ; H 8.13 ; N 4.12.

2f : IR (KBr) ν (cm^{-1}) : 1700-3080 (OH) ; 1760 ($OCOCH_3$) ; 1700 (C=O). ^1H NMR ($CDCl_3$) δ (ppm) : 1.25-2.62 (m, s at 2.22, $OCOCH_3$, 3 x CH_2) ; 3.93-4.14 (pseudo t at 4.03, benzylic H) ; 6.68-6.83 (m, 2 H, arom. H) ; 7.24-7.50, m (1 H, arom. H) ; 7.90 (s, Ph-OH). UV (MeOH) λmax (log ε) : 265 (3.37). Mp (petroleum ether) : 158°C. Analysis : $C_{14}H_{14}O_4$: % Calc : C 68.28 ; H 5.73. Found : C 68.00% ; H 5.67.

General procedure for the preparation of 3

To a solution of ketones **2** (2 mmol) in 80 ml of liq. NH_3-THF (1-1) was added 14 mmol of lithium. Once a blue

coloration appeared, large excess of PhCOONa was added and the mixture allowed to warm to room temperature. After usual work-up, the ketoacetates **3** were purified by flash chromatography.

3a : IR (NaCl) ν (cm^{-1}) : 1700 (CO). ^1H NMR (CCl_4) δ (ppm) : 1.10-2.40 (m, 6 H, 3 x CH_2) ; 3.78-4.11 (m, 2 H, benzylic H) ; 6.80-7.25 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 18.44, 26.24, 40.55 (aliph. C) ; 43.36, 53.50 (benzylic C) ; 121.33, 122.38, 128.10, 128.24, 141.48, 147.06 (arom. C) ; 210.13 (C=O). UV (MeOH) λmax (log ε) : 268.1 (ep.) ; 268.7 (3.20) ; 274 (3.15). Mp (ether/petroleum ether) : 54°C. Analysis : $C_{12}H_{12}O$ % Calc : C 83.68 ; H 7.02. Found : C 83.55 ; H 7.17.

3b : IR (KBr) ν (cm^{-1}) : 1705 (CO). ^1H NMR (CCl_4) δ (ppm) : 1.00-2.58 (m, 8 H, 4 x CH_2) ; 3.13-3.59 (m, 1 H, benzylic H) ; 4.20 (d, J = 5 Hz, 1 H, benzylic H α CO) ; 6.78-7.31 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 24.20, 26.36, 30.72, 48.62 (aliph. C) ; 45.62, 58.74 (benzylic C) ; 121.60, 124.14, 127.66, 127.83, 140.96, 146.34 (arom. C) ; 210.13 (C=O). UV (MeOH) λmax (log ε) : 259 (3.10) ; 265 (3.27) ; 271 (3.23). Mp (ether/petroleum ether) : 39°C. Analysis : $C_{13}H_{14}O$: % Calc : C 84.28 ; H 7.07. Found : C 83.72 ; H 7.71.

3c : IR (KBr) ν (cm^{-1}) : 1705 (CO). ^1H NMR (CCl_4) δ (ppm) : 1.00-2.70 (m, 10 H, 5 x CH_2) ; 3.40-3.91 (m, 1 H, benzylic H) ; 4.48 (d, J = 6 Hz, 1 H, benzylic H α CO) ; 6.71-7.40 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 24.15, 28.14, 30.06, 30.20, 47.19 (aliph. C) ; 51.08, 56.46 (benzylic C) ; 121.35, 124.14, 127.66, 127.83, 140.36, 146.34 (arom. C) ; 210.13 (C=O). UV (MeOH) λmax (log ε) : 261.9 (3.18) ; 266.9 (3.27) ; 272.6 (3.19). Mp (ether/ petroleum ether) : 82°C. Analysis : $C_{14}H_{16}O$: % Calc : C 84.81 ; H 7.11. Found : C 85.04 ; H 7.41.

3d : IR (NaCl) ν (cm^{-1}) : 1705 (CO). ^1H NMR (CCl_4) δ (ppm) : 0.66-2.18 (m, 16 H, 8 x CH_2) ; 2.36-2.83 (m, 2 H, $C\underline{H}_2C(O)$; 3.56-3.93 (m, 1 H, benzylic H) ; 4.08 (d, J = 3 Hz, 1 H, benzylic H α CO) ; 6.81-7.33 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) :

23.22, 24.99, 25.13, 25.85, 26.61, 26.96, 28.88, 32.41, 41.66 (aliph. C) ; 46.82, 58.95 (benzylic C) ; 121.78, 122.44, 127.44, 127.88, 142.27, 148.61 (arom. C) ; 210.80 (C=O). UV (MeOH) λmax (log ε) : 264 (3.21) ; 268 (3.32) ; 273.5 (3.26). MS (m/e) : $C_{18}H_{24}O$: 256.

3e : IR (KBr) ν (cm^{-1}) : 1695 (CO). ^1H NMR (CCl_4) δ (ppm) : 0.95-2.70 (m, 16 H, 5 x CH_2, $N(C\underline{H}_2CH_3)_2$) ; 3.40-3.75 (m, 1 H, benzylic H) ; 4.60 (d, J = 5.5 Hz, 1 H, benzylic H α CO) ; 6.12-6.41 (m, 2 H, arom. H) ; 6.79-7.07 (m, 1 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 13.36 (CH_3), 24.40, 28.07, 29.46, 30.20, 43.61 (aliph. C) ; 46.81 ($\underline{C}H_2$-CH_3) ; 49.89, 57.77 (benzylic C) ; 108.40, 110.75, 122.27, 129.64, 143.83, 148.99 (arom. C) ; 212.35 (C=O). UV (MeOH) λmax (log ε) : 266.2 (4.33). Mp (ether/ petroleum ether) : 47°C. Analysis : $C_{18}H_{23}NO$: % Calc : C 80.25 ; H 8.60 ; N 5.19. Found : C 80.91 ; H 8.32 ; N 5.14.

3f : IR (KBr) ν (cm^{-1}) : 1700 (CO). ^1H NMR (CCl_4) δ (ppm) : 1.00-2.10 (m, 6 H, 3 x CH_2) ; 3.52-4.26 (m, 2 H, benzylic H) ; 5.40 (m, 1 H, OH) ; 6.45-6.71 (m, 2 H, arom. H) ; 6.90-7.20 (m, 1 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 19.26, 26.83, 40.91 (aliph. C) ; 43.46, 51.01 (benzylic C) ; 114.34, 115.04, 124.76, 130.29, 147.87, 150.76 (arom. C) ; 212.81 (C=O). UV (MeOH) λmax (log ε) : 270.7 (3.26) ; 276.2 (3.22). Mp (ether/petroleum ether): 113°C. Analysis : $C_{12}H_{12}O_2$: % Calc : C 76.56 ; H 6.42. Found : C 76.51 ; H 6.32.

General procedure for the preparation of 4

Ketones **3** were then treated with NH_2OCH_2Ph-HCl according classical procedure[3] and the benzyloximes thus obtained were reduced with $LiAlH_4$ in anhydrous ether following an usual procedure.[4]

4a : IR (NaCl) ν (cm^{-1}) : 3600-3610 (NH_2). ^1H NMR ($CDCl_3$) δ (ppm) : 1.00-2.10 (m, 8 H, 3 x CH_2, $N\underline{H}_2$) ; 2.50-2.70 (m, 1 H, $C\underline{H}NH_2$) ; 3.20-3.60 (m, 2 H, benzylic H) ; 6.90-7.30 (m, 4 H,

arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 18.81, 25.42, 27.48 (aliph. C) ; 35.71, 47.73, 47.49 (benzylic C) ; 119.51, 121.27, 127.51, 128.88 (arom. C) ; 147.51, 147.90 (C=O). UV (MeOH) λmax (log ε) : 263 (3.30) ; 268 (3.37) ; 273.5 (3.17). Analysis : $C_{12}H_{25}N$: % Calc : C 83.87 ; H 8.72 ; N 8.08. Found : C 82.99 ; H 8.53 ; N 7.93.

4b : IR (KBr) ν (cm^{-1}) : 3500-3200 (NH_2). ^1H NMR ($CDCl_3$) δ (ppm) : 1.20-2.00 (m, 10 H, 4 x CH_2, $N\underline{H}_2$) ; 2.80-3.10 (m, 1 H, $C\underline{H}NH_2$) ; 3.20-3.70 (m, 2 H, benzylic H) ; 7.0-7.30 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 29.32, 29.67, 30.71, 31.89 (aliph. C) ; 46.66, 53.94, 55.72 (benzylic C) ; 121.70, 127.00, 127.29 (arom. C) ; 146.39, 148.16 (C=O). UV (MeOH) λmax (log ε) : 263 (3.09) ; 268 (3.18) ; 273 (3.13). Analysis : $C_{13}H_{17}N$: % Calc : C 83.36 ; H 9.15 ; N 7.47. Found : C 83.23 ; H 9.17 ; N 7.19.

4c : IR (KBr) ν (cm^{-1}) : 3500-3200 (NH_2). ^1H NMR ($CDCl_3$) δ (ppm) : 1.09-2.30 (m, 12 H, 5 x CH_2, $N\underline{H}_2$) ; 2.70-2.90 (m, 1 H, $C\underline{H}NH_2$) ; 3.70-4.13 (m, 2 H, benzylic H) ; 6.56-7.40 (m, 4 H, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 25.11, 25.56, 26.12, 27.16, 29.83 (aliph. C) ; 41.39, 50.71, 51.70 (benzylic C) ; 120.93, 121.39, 126.25, 127.46 (arom. C) ; 145.91, 146.75 (C=O). UV (MeOH) λmax (log ε) : 263.5 (3.10) ; 267.9 (3.32) ; 273 (3.41). Analysis : $C_{14}H_{19}N$: % Calc : C 83.52 ; H 9.51 ; N 6.95. Found : C 82.97 ; H 9.32 ; N 7.01.

General procedure for the preparation of 6

To a NiCRA prepared from $Ni(OAc)_2$ (10 mmol) as previously described,[7] was added over a period of 2-3 min, 5 mmol of chloroamines in THF (10 ml). After completion of the reaction, the excess of NaH was carefully destroyed by dropwise addition of a cold 10% solution of HCl in water, up to the end of hydrogen evolution. The product was then isolated by flash chromatography after acidic extraction from ether.

7a : ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.10-1.80 (m, 3 x CH_2) ; 1.90-2.60 (m, $N(CH_2)_2$, C<u>H</u>-N) ; 3.35-3.90 (m, $O(CH_2)_2$, 2 H, benzylic H) ; 7.00-7.35 (m, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 27.50, 28.82, 29.65 (aliph. C) ; 47.91, 46.10, 48.95 (benzylic C) ; 65.94, 67.50 ; 121.11, 122.81, 126.26, 126.93 (arom. C) ; 147.24, 147.89 (C=O). UV (MeOH) λmax (log ε) : 261 (3.15) ; 265 (3.30); 273.5 (3.25). Mp (petroleum ether) : 206°C. Analysis : $C_{16}H_{21}NO$: % Calc : C 78.97 ; H 8.69 ; N 5.75. Found : C 78.58 ; H 8.40 ; N 5.52.

7b : ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.10-2.20 (m, 2 x CH_2) ; 2.40-2.90 (m, $N(CH_2)_2$) ; 3.50-3.90 (m, $O(CH_2)_2$, benzylic H) ; 6.90-7.40 (m, arom. H). ^{13}C NMR ($CDCl_3$) δ (ppm) : 24.50, 26.52, 29.50, 29.90, 32.16 (aliph. C) ; 47.70, 51.65, 67.58 ; 75.54 (benzylic C) ; 122.63, 123.20, 126.71, 128.19 (arom. C) ; 145.62, 147.30 (C=O). UV (MeOH) λmax (log ε) : 261.5 (3.19) ; 267 (3.32) ; 273.5 (3.30). Mp (°C) (petroleum ether) : 135°C. Analysis : $C_{17}H_{23}NO$: % Calc : C 79.33 ; H 9.01 ; N 5.44. Found : C 79.10 ; H 9.24 ; N 5.43.

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