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Bromine-Promoted Cyclization of an Olefinic α-Aminonitrile: A Practical Synthesis of 5-Aminocarbonyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (ADCI)

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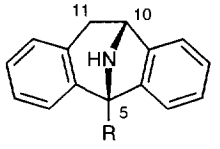
Abstract: The 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine ring system, bearing electron-withdrawing substituents at either C5, or C5 and C11, is synthesized via electrophilic cyclization of an olefinic α-aminonitrile. Copyright © 1996 Elsevier Science Ltd

ADCI (**1**, 5-aminocarbonyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine) is a selective, low-affinity noncompetitive antagonist of the NMDA receptor which has emerged as a promising anticonvulsant with a higher therapeutic index than the PCP receptor ligand, MK-801 (**2**).[1] In the course of investigating compounds related to ADCI, we discovered an electrophile-promoted cyclization reaction that led to the nitrile **3**, which could be readily converted to ADCI.

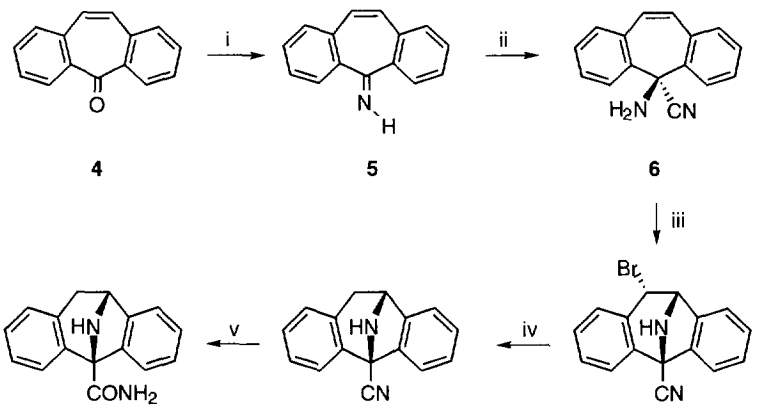


1, R = $CONH_2$ (ADCI)
2, R = CH_3 (MK-801)
3, R = CN

Our approach to the synthesis of **3** starting from dibenzosuberenone is outlined in Scheme 1. Direct addition of ammonia or benzylamine and hydrogen cyanide to ketone **4** using Strecker methodology[2] gave no conversion under a variety of conditions. However, treatment of the known dibenzosuberenone imine **5**[3] with acetone cyanohydrin in ethanol using a catalytic amount of NaCN afforded the α-aminonitrile **6**, which crystallized from the reaction mixture.[4]

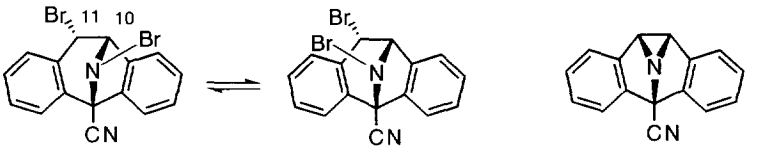
Upon treatment with bromine in methylene chloride, compound **6** cyclized smoothly to the hydrobromide salt of **7**.[5] Examination of the mother liquors from the crystallization of the free base **7** from ethyl ether revealed a 1:1 mixture of unreacted **6** and a cyclized perbromo compound, **8**. Treatment of the mother liquors with excess of bromine afforded **8** in 22% yield. Compound **8** exists as a mixture of invertomers that are in slow exchange on the ^1H NMR timescale, as evidenced by four broadened methine resonances for H10 and H11. Dibromide **8** underwent facile reduction to **7** upon treatment with aqueous thiosulfate; thus, the yield of **7** was improved by simply washing the reaction mixture with this reducing agent.[6]

Scheme 1



4 **5** **6** **1** **3** **7**

Reagents: (i) $TiCl_4$, NH_3, toluene, 25 °C, 16 h (93%); (ii) $(CH_3)_2C(OH)CN$, EtOH, NaCN (5 mole%), 25 °C, 2 h (88%); (iii) Br_2, CH_2Cl_2, 25 °C, 1 h; workup with $Na_2S_2O_3$ and Na_2CO_3 (aq), repeat (88%); (iv) $NaBH_3CN$, NMP, 100 °C, 40 min (83%); (v) PPA, 110 °C, 30 min, then Na_2CO_3 (aq) (77%) or KOH, *tert*-BuOH, reflux, 5 min (66%); steps iii–v involved basic aqueous workups.



8 **9**

The stereochemical assignment of the carbon-bromine bond in **7** is based on the observation of a 5.5 Hz coupling constant between H10–H11. In this bicyclic system, a $J_{H10-H11}$ of ~0 Hz is observed for 11β-substituted compounds, and a $J_{H10-H11}$ of ~5–6 Hz is observed for the corresponding 11α epimers.[7] The α stereochemistry observed in **7** is consistent with a mechanism involving intramolecular displacement of a bromonium ion intermediate by nitrogen (Figure 1). The 11β epimer of **7**, the product expected from intramolecular displacement of a vicinal dibromide, was not observed.

Reduction of the benzylic carbon-halogen bond in **7** was effected cleanly using sodium cyanoborohydride in either *N*-methylpyrrolidinone (NMP) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at 80–100 °C, affording **3**.[8] Two intermediates were observed early in the reduction, one of which has been identified as the aziridine **9**.[9,10] This compound, obtained in 79% yield when **7** is treated with triethylamine in CH_3CN, is a useful building block for C11-substituted analogs of this ring system.[11]

Thus, the key nitrile **3** was obtained in 4 steps and 60% overall yield from dibenzosuberenone (**4**). The synthesis was performed on a 0.1-mole scale without the need for chromatographic purification. Partial saponification of **3** using either polyphosphoric acid[12] or potassium hydroxide in *tert*-butanol[13] afforded **1** in

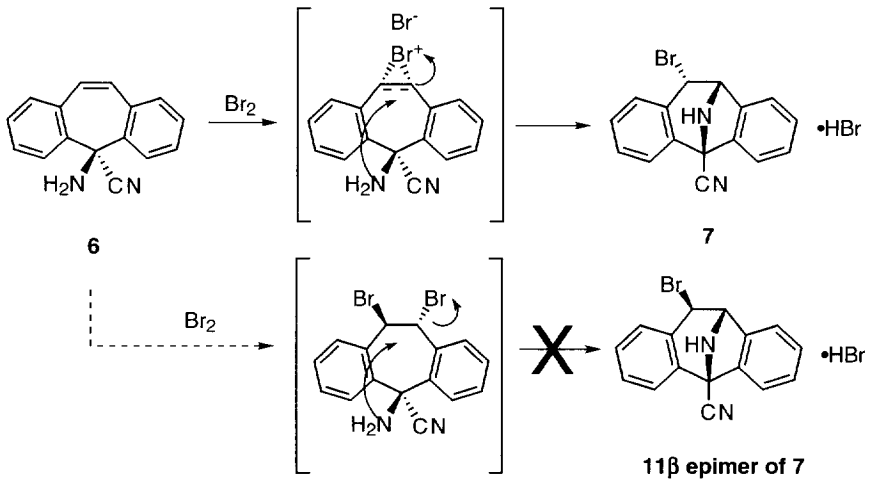


Figure 1. Mechanistic rationale for the observation of α-stereochemistry in **7**.

good yield. The ^{1}H NMR spectrum and melting point of this product were identical to those of a sample prepared by the reported method.[1b] Nitrile **3** will also be useful as a starting material for C5-substituted analogs of this bicyclic system.

In summary, the route described in Scheme 1 provides a facile entry into the 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine ring system that is expected to be complementary to existing routes involving base-promoted ring-closure conditions.[14] To the best of our knowledge, this is also the first example of a cyclization of an olefinic α-aminonitrile promoted by an electrophilic reagent.

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References and Notes

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4. Alternatively, exposure of **5** to sodium cyanide in the presence of chlorotrimethylsilane, pyridine and potassium iodide in acetonitrile at 25 °C for 16 h afforded **6** in 67% yield after a basic aqueous workup. Similar conditions have been used in the synthesis of trimethylsilylcyanide: Duboudin, F.; Cazeau, P.; Moulines, F.; Laporte, O. *Synthesis* **1982**, 212.
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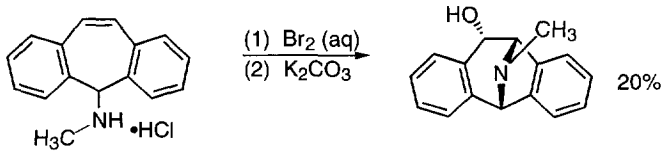

6. **11α-Bromo-5-cyano-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (7)** To a suspension of aminoalkene **6** (19.01 g, 0.0818 mol) in methylene chloride (100 mL) at -65 °C ± 5 °C was added bromine (4.4 mL, 0.085 mol) in methylene chloride (20 mL) over 5 min, and the mixture allowed to warm to room temperature over the course of 1 h. The resulting yellow slurry was stirred with 10% aqueous Na_2CO_3 (50 mL), and 20% aqueous $Na_2S_2O_3$ (50 mL). The mixture was transferred to a separatory funnel with the aid of methylene chloride (100 mL), and the organic phase separated and dried over Na_2SO_4. The volume was reduced by 50% by concentration *in vacuo*, and the resulting thick slurry diluted with cyclohexane (100 mL). The slurry was filtered, and the cake washed with 1:1 methlene chloride/cyclohexane (3 x 30 mL), and dried, affording 14.21 g of **7**. The filtrate was evaporated and treated with bromine as described above, affording an additional 8.17 g of product, resulting in a combined yield of 22.38 g (88%) of **7**. mp 156-157 °C; R_f 0.6 (1:4 ethyl acetate/petroleum ether + 1% saturated NH_3/CH_3OH); ^1H NMR ($CDCl_3$) δ 7.61-7.27 (m, 8H, ArH), 5.72 (d, *J* = 5.5 Hz, 1H), 4.87 (d, *J* = 5.5 Hz, 1H), 3.47 (br s, 1H, NH).
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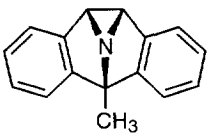

10. The ^1H NMR spectrum of the other intermediate is consistent with an 11β-substituted 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine. However, the structure of this intermediate has not been determined.
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