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Preparation of 9,9-Disubstituted 4,5-Diazafluorenes Useful as Cognitive Enhancers

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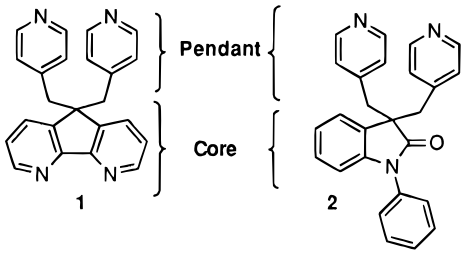
Abstract:

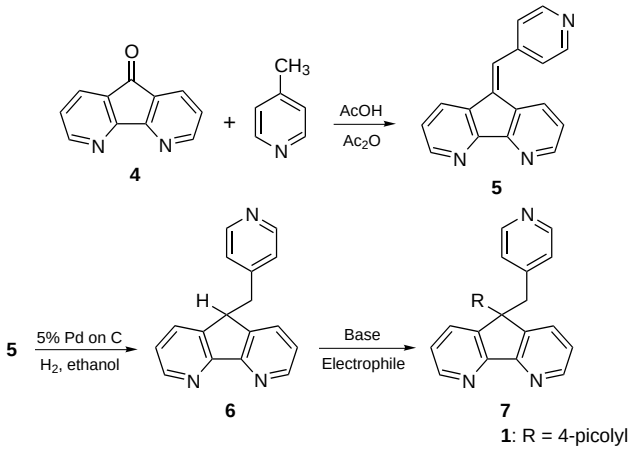
A novel synthesis of symmetric and nonsymmetric 9,9-disubstituted 4,5-diazafluorenes has been developed. These compounds have activity in both an *in vitro* acetylcholine release assay and *in vivo* rodent models of learning and memory. Preparation of these compounds involves a unique aldol condensation between 4,5-diazafluoren-9-one (4) and 4-picoline. Reduction of aldol product 5 (5-(4-pyridinylmethylene)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]dipyridine) provides monoalkylated diazafluorene 6 (5-(4-pyridinylmethyl)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]dipyridine) which proved to be a key intermediate for synthesis of nonsymmetric analogs.

Introduction

The development of agents to treat Alzheimer's disease is one of the most critical problems facing the pharmaceutical and medical community. Our efforts center on the development of compounds that increase endogenous stimulus-induced acetylcholine release.[1] Agents with this profile are expected to provide a palliative treatment by improving the cognitive abilities of Alzheimer's patients. Previous work on the structure−activity relationship (SAR) has allowed for the division of our cognition enhancers into two portions, a heteroaromatic core and pendant or side-chain substituents.[2] Compound **1** (EXP-9121) was a crucial lead showing good activity both *in vitro* and *in vivo* with a core chemically distinct from that of our former clinical candidate linopirdine (**2**, DuP996).



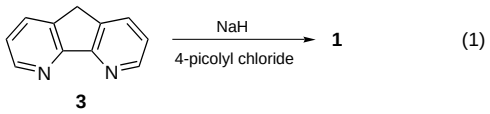
Scheme 1



In order to support preclinical development, an efficient and economical synthesis of **1** was needed. The inclusion of an intermediate that would allow rapid SAR development of unsymmetrical pendant groups would be beneficial to the development of future clinical candidates.

Discussion

Initial preparation of **1** involved gem-dialkylation of 4,5-diazafluorene (**3**)[3] (eq 1).



(1)

Several complications were identified in the direct scale-up of the initial route. First, the reduction of **4** to **3** required a large excess of hydrazine (10 equiv), resulting in handling and waste disposal problems. Second, the use of sodium hydride as a base requires strictly anhydrous conditions. Third, a fairly large excess (10−20%) over the 2 mol stochiometric amount of picolyl chloride was required. In addition, the picolyl chloride had to be prepared from the commercially available hydrochloride salt in a separate step and was unstable as the free base. These considerations increased the cost of the final drug significantly.

A longer but overall more efficient route to **1** was developed through intermediate **5** (Scheme 1). Treatment of 4,5-diazafluoren-9-one (**4**)[4] with picoline in a mixture of

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(1) (a) Nickolson, V. J.; Tam, S. W.; Myers, M. J.; Cook, L. *Drug Dev. Res.* **1990**, *19*, 285−300. (b) Cook, L.; Nickolson, V. J.; Steinfels, G. F.; Rohrbach, K. W.; DeNoble V. J. *Drug Dev. Res.* **1990**, *19*, 301−314. (c) Tam, S. W.; Rominger, D.; Nickolson, V. J. *Mol. Pharmacol.* **1991**, *40*, 16.

(2) Earl, R. A.; Myers, M. J.; Johnson, A. L.; Scribner, R. M.; Wuonola, M. A.; Boswell, G. A.; Wilkerson, W. W.; Nickolson, V. J.; Tam, S. W.; Brittelli, D. R.; Chorvat, R. J.; Zaczek, R.; Cook, L.; Wang, C.; Zhang, X.; Lan, R.; Mi, B.; Wenting, H. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 851−854.

(3) (a) Kloc, K.; Młchowski, J.; Szulc, Z. *Heterocycles* **1978**, *7*, 849−852. (b) Młochowski, J.; Szulc, Z. *Pol. J. Chem.*, **1983**, *57*, 33.

(4) Kloc, K.; Młochowski, J.; Szulc, Z. *J. Prakt. Chem.* **1977**, *319*, 959−967.

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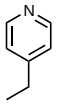
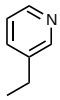
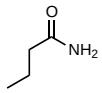
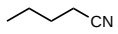
Table 1. **Unsymmetrical analogs of compound 1**

	electrophile	R	base	% yield
1	4-picolyl chloride		NaOH	68
7a	2-cyclohexen-1-one		Triton B	84
7b	3-picolyl chloride		NaH	67
7c	acrylamide		Triton B	72
7d	ethyl bromoacetate		NaH	88
7e	bromobutanenitrile		NaH	93
7f	2-bromoethyl ethyl ether		NaH	88

AcOH/Ac_2O (4:1) provided aldol product **5** in 77% yield.[5,6] Reduction of **5** succeeded with $NaBH_4$, but catalytic hydrogenation proved more efficient at larger scales, affording **6** in 88% yield. Conversion of **6** to **1** was accomplished using 4-picolyl chloride hydrochloride (1.3 equiv) with NaOH in 2-propanol (68%). This scheme reduces the expensive picolyl chloride by half and eliminates the preliminary free base step.

In addition, **6** could be transformed into a wide selection of unsymmetrical analogs by alkylation or Michael addition with several different substrates, demonstrating the utility of **6** as a key intermediate in our cognition program (see Table 1 for representative examples).

The chemistry outlined has successfully provided >10 kg of GMP (good manufacturing practices) **1** for preclinical development and supported an intensive analog program. Details of a large-scale preparation of **1** and representative procedures for preparing unsymmetrical analogs shown in Table 1 are included in the Experimental Section.

The addition of 5% NaOCl during workup and recrystallizations of **6** was key to obtaining high yields. After pH adjustment, the solution was black and visibly "oily". The slow addition of NaOCl produced a bright yellow solution and increased the yield by 10−15%. The exact nature of the oily phase was not determined. However, this phase did contain a significant amount of product which was released as a crystalline material just when the color disappeared. The effect was very dramatic. Copious crystals formed and the temperature increased at the instant the solution changed from black to yellow. Hydrogen peroxide was much less effective. Other reagents were not tried since NaOCl was effective and inexpensive.

(5) Only a few examples of aldol condensations with 2- or 4-picoline and ketones exist. These conditions have proved useful for a number of reactive ketones. For a general discussion of condensation of picolines with aldehydes, see: Tenenbaum, L. E. In *The Chemistry of Heterocyclic Compounds*; Abramovitch, R. A., Ed.; John Wiley and Sons: New York, 1961; Vol. 14, Part 2, p 192.

(6) For additional examples using aldehydes and ketones, see: (a) Klemm, L. H.; Severns, B.; Wynberg, H. *J. Heterocycl. Chem.* **1991**, *28*, 61. (b) Efange, S. M. N.; Michelson, R. H.; Remmel, R. P.; Boudreau, R. J.; Dutta, A. K.; Freshler, A. *J. Med. Chem.* **1990**, *33*, 3133. (c) Williams, J. L. R.; Adel, R. E.; Carlson, J. M.; Reynolds, G. A.; Borden, D. G.; Ford, J. A. *J. Org. Chem.* **1963**, *28*, 387. (d) Sharp, W.; Sutherland, M. M. J.; Wilson, F. J. *J. Chem. Soc.* **1943**, 5. (e) Bryant, W. M., III; Huhn, G. F. U.S. Patent 4,806,651, 1989. (f) Bryant, W. M., III; Huhn, G. F.; Jensen, J. H.; Pierce, M. E.; Stammbach, C. *Synth. Comm.* **1993**, *23*, 1617.

Conclusions

We have developed an efficient, scalable synthesis of disubstituted diazafluorene **1**. The optimized route provided an important intermediate **6** by an aldol condensation between 4-picoline and ketone **4** followed by reductive hydrogenation. The isolation of **6** was useful for preparing unsymmetrical analogs.

A process improvement of using bleach in the workup after neutralization may have practical benefit in other reactions involving 4-picoline.

Experimental Section[7]

5-(4-Pyridinylmethylene)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]-dipyridine (5). 4,5-Diazafluoren-9-one (**4**) (667.4 g, 3.66 mol) dissolved in 743.1 g of acetic anhydride, 1328.4 g of 4-picoline, and 1560 g of acetic acid was heated for 7 h at 120 °C (<2% remaining fluorenone determined by HPLC). The solution was cooled to 50−80 °C and diluted with 11.7 kg of water, followed by 580 mL of 50% NaOH to adjust the pH to 4.9. The solution was cooled to 28 °C and 731 mL of 5% NaOCl added to decolorize the slurry. The solution was cooled to 10 °C and the pH adjusted to 6.7 with 900 mL of 50% NaOH. The cake was filtered and washed with 1625 mL of water. The crude yield was 83%**.** Three such batches (2314 g) were combined and recrystallized from a mixture of acetonitrile (4630 g), water (12 200 g), and 288 mL of 5% NaOCl. A second recrystallization was carried out in the same manner. The cake was dried at 50−70 °C in a vacuum oven to yield 2175 g for an overall yield of 77% as light yellow crystals: mp 195−196 °C; MS *m*/*e* 258 $(M + H)^+$; IR (KBr) (cm^{-1}) 3034, 1592, 1394; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (m, J = unresolved, 3H), 8.68 (dd, J = 1.5, 4.8 Hz, 1H), 8.11 (dd, J = 1.5, 7.7 Hz, 1H), 7.72 (dd, J = 1.5, 8.1 Hz, 1H), 7.64 (s, 1H), 7.46 (dd, J = 0.7, 5.1 Hz, 2H), 7.37 (dd, J = 4.8, 7.7 Hz, 1H), 7.11 (dd, J = 4.8, 8.1 Hz, 1H). Anal. Calcd for $C_{17}H_{11}N_3$: C, 79.36; H, 4.31; N, 16.33. Found: C, 79.25; H, 4.18; N, 16.32.

5-(4-Pyridinylmethyl)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]dipyridine (6). **5** (3130 g, 12.16 mol), 5% Pd/C (690 g), MgO (340 g), and anhydrous ethanol (18.5 L) were charged to a 40 L hydrogenator. Hydrogen pressure (29.4 psig) was maintained for 2.3 h at 50−52 °C. HPLC showed <2%

(7) All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Commercial reagents were used as received without additional purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. ^1H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectral data were recorded on a Finnigan-MAT 8230 instrument. Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Thin-layer chromatography was performed on E. Merck 15719 silica gel plates. HPLC analyses were carried out with Zorbax SB-phenyl 25 × 4.6 mm columns. Sodium octanesulfonate was used in the methanol/water mobile phase. Flash chromatography was carried out using EM Science silica gel 60 (230−400 mesh).

starting material. The catalyst and MgO were removed by filtration at 40 °C, and the cake was rinsed with 7.9 kg of ethanol. Two batches of solution were combined, and the ethanol was replaced with water by distillation to a head temperature of 96.8 °C. The slurry was cooled to below 10 °C, held for 6 h, and filtered. The cake was washed twice with 10 L of water. The wet cake was recrystallized from 4.5 kg of ethanol and 48 kg of water. The cake was washed with 20 kg of water and dried at 50 °C in a vacuum oven, yielding 5.6 kg of off-white product, 88% overall yield: mp 176−177 °C; MS *m*/*e* 260 $(M + H)^+$; IR (KBr) (cm^{-1}) 3012, 1598, 1404; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (dd, J = 1.1, 4.8 Hz, 2H), 8.55 (dd, J = 1.5, 4.4 Hz, 2H), 7.53 (dd, J = 1.1, 7.7 Hz, 2H), 7.24 (dd, J = 4.8, 7.7 Hz, 2H), 7.12 (dd, J = 1.5, 4.4 Hz, 2H), 4.27 (t, J = 7.7 Hz, 1H), 3.14 (d, J = 7.7 Hz, 2H). Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.40; H, 4.94; N, 16.13.

5,5-Bis(4-pyridinylmethylene)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]dipyridine (1). **3** (304 g, 1.17 mol) was dissolved in 1200 mL of 2-propanol, the solution was cooled to <5 °C, and 225 mL of 50% NaOH was added at a temperature below 10 °C. A solution of 212 g of 4-picolyl chloride hydrochloride in 1 L of water was added over 40 min, the temperature being maintained below 10 °C. The solution was allowed to warm to ambient temperature overnight. The product was precipitated with 10 L of water. The solids were washed with 1 L of water and dried in a vacuum oven at ambient temperature (330.3 g, 80% crude yield). Three batches were combined and recrystallized from a mixture of 3500 mL of water and 1500 mL of ethanol, and a second time from 2520 mL of water and 1080 mL of ethanol to give a light yellow powder (840 g, 68% yield): mp 249−250.5 °C; MS *m*/*e* 351 $(M + H)^+$; IR (KBr) (cm^{-1}) 3020, 1598, 1402; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (dd, J = 1.5, 4.8 Hz, 2H), 8.20 (dd, J = 1.5, 4.4 Hz, 4H), 7.79 (dd, J = 1.5, 7.7 Hz, 2H), 7.33 (dd, J = 4.8, 7.7 Hz, 2H), 6.53 (dd, J = 1.5, 4.4 Hz, 4H), 3.41 (s, 4H). Anal. Calcd for $C_{23}H_{18}N_4$: C, 78.83; H, 5.18; N, 15.99. Found: C, 78.67; H, 5.12; N, 15.95.

3-[5-(4-Pyridinylmethyl)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]-dipyridin-5-yl]cyclohexanone (7a) (Triton B Conditions). Triton B (40% in methanol, 10 drops via a disposable pipet) was added to **6** (1.0 g, 3.86 mmol) and 2-cyclohexen-1-one (0.39 g, 4.05 mmol) in methanol (0.5 mL), and the reaction mixture was stirred for 3 h at room temperature and then diluted to 50 mL with chloroform. The chloroform layer was washed with water (1 × 25 mL), saturated $NaHCO_3$ (1 × 25 mL), and brine (1 × 25 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed over silica gel (30 g, 5% methanol/chloroform). The resulting solid was recrystallized from ethyl acetate/hexanes to provide **7a** (1.15 g, 84%) as white crystals: mp 198−199 °C; MS *m*/*e* 356 $(M + H)^+$; IR (KBr) (cm^{-1}) 2932, 1714, 1403; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.69 (m, 2H), 8.10 (m, 2H), 7.88 (dd, J = 7.7, 1.5 Hz, 1H), 7.79 (dd, J = 7.7, 1.5 Hz, 1H), 7.35 (m, 2H), 6.38 (d, J = 6.3 Hz, 2 H), 3.45 (d, J = 12.8 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 2.62−1.21 (m, 9H). Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.42; H, 6.00; N, 11.42.

5-(3-Pyridinylmethyl)-5-(4-pyridinylmethyl)-5*H*-cyclopenta[2,3-*b*:3,4-*b*′]dipyridine (7b) (Metal Hydride Conditions). **6** (1.5 g, 5.78 mmol) suspended in anhydrous THF (15 mL) was added dropwise via pipet to sodium hydride (0.28 g, 60% in mineral oil, 6.94 mmol) in anhydrous THF (20 mL) at room temperature under a stream of nitrogen. After gas evolution was complete, stirring was continued for 0.5 h. The free base of 3-picolyl chloride hydrochloride (1.42 g, partitioned between 20 mL of toluene and aqueous K_2CO_3 at 5 °C, dried over K_2CO_3, 8.68 mmol) was added dropwise over 20 min, and then the mixture was stirred for 3 h. The reaction was quenched with saturated NH_4Cl (20 mL) and transferred to a separatory funnel using water (25 mL) and chloroform (25 mL). After separation and further extraction with chloroform (3 × 40 mL), the combined extracts were washed with water (2 × 30 mL) and brine (1 × 30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (80 g, 5% methanol/ chloroform). Recrystallization from hot ethyl acetate provided the product **7b** (1.36 g) in 67% yield as light tan crystals. mp 193−194 °C; MS *m*/*e* 351 $(M + H)^+$; IR (KBr) (cm^{-1}) 3045, 1605, 1407; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.63 (dd, J = 4.8, 1.5 Hz, 2H), 8.23 (m, 1H), 8.19 (dd, J = 4.4, 1.5 Hz, 2H), 7.99 (d, J = 7.0 Hz, 1H), 7.82 (dd, J = 7.0, 1.4 Hz, 2H), 7.33 (m, 2H), 6.84 (m, 2H), 6.54 (dd, J = 4.4, 1.5 Hz, 2H), 3.43(s, 4H). Anal. Calcd for $C_{23}H_{18}N_4 \cdot 0.25H_2O$: C, 77.83; H, 5.25; N, 15.79. Found: C, 78.01; H, 5.14; N, 15.81.

5-(4-Pyridinylmethyl)-5*H*-cyclopenta[2,1-*b*:3,4-*b*′]dipyridine-5-propanamide (7c) (Triton B conditions): **6** (1.0 g, 3.86 mmol) and acrylamide (0.29 g, 4.05 mmol). Yield = 0.92 g, **7c** (72%): mp 250 °C dec; MS *m*/*e* 331 $(M + H)^+$; IR (KBr) (cm^{-1}) 3348 (broad), 1673, 1402; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.59 (dd, J = 5.1, 1.5 Hz, 2H), 8.20 (dd, J = 4.4, 1.5 Hz, 2H), 7.72 (dd, J = 7.7, 1.1 Hz, 2H), 7.30 (dd, J = 7.7, 4.7 Hz, 2H), 6.55 (dd, J = 4.4, 1.5 Hz, 2H), 5.48 (br s, 1H), 5.12 (br s, 1H), 3.24 (s, 2H), 2.65 (t, J = 7.7 Hz, 2H), 1.45 (t, J = 7.7 Hz, 2H). Anal. Calcd for $C_{20}H_{18}N_4O \cdot 0.25H_2O$: C, 71.73; H, 5.57; N, 16.73. Found: C, 71.74; H, 5.30; N, 16.59.

5-(4-Pyridinylmethyl)-5*H*-cyclopenta[2,3-*b*:3,4-*b*′]dipyridine-5-acetic Acid, ethyl ester(7d) (metal hydride conditions, substituting ethyl bromoacetate): white solid, mp 163-165 °C (hexane/chloroform); 88% yield; MS *m*/*e* 346 $(M + H)^+$; IR (KBr) (cm^{-1}) 1737; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.69 (dd, J = 4.7, 1.5 Hz, 2H), 8.25 (d, J = 5.9, 1.5 Hz, 2H), 7.82 (dd, J = 7.7, 1.5 Hz, 2H), 7.31 (dd, J = 7.7, 4.8 Hz, 2H), 6.63 (dd, J = 4.5, 1.5 Hz, 2H), 3.89 (q, J = 7.4 Hz, 2H), 3.42 (s, 2H), 3.02 (s, 2H), 0.94 (t, 3H). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.01; H, 5.55; N, 12.17. Found: C, 72.87; H, 5.40; N, 12.08.

5-(4-Pyridinylmethyl)-5*H*-cyclopenta[2,3-*b*:3,4-*b*′]dipyridine-5-butanenitrile (7e) (metal hydride conditions, substituting 4-bromobutanenitrile): off-white solid, mp 106−110 °C (hexane/ethyl acetate); 93% yield; MS *m*/*e* 327 $(M + H)^+$; IR (KBr) (cm^{-1}) 2244; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.71 (dd, J = 4.8, 1.1 Hz, 2H), 8.25 (dd, J = 4.4, 1.1 Hz, 2H), 7.73 (dd, J = 7.7, 1.5 Hz, 2H), 7.34 (dd, J = 8.5, 5.5 Hz, 2H), 6.65 (dd, J = 5.8, 4.4 Hz, 2H), 3.24 (s, 2 H), 2.41 (m, 2 H), 2.11 (t, J = 6.6 Hz, 2H), 0.94 (m, 2H).

Anal. Calcd for $C_{21}H_{18}N_4 \cdot 0.5H_2O$: C, 75.20; H, 5.71; N, 16.70. Found: C, 75.34; H, 5.34; N, 16.70.

5-(2-Ethoxyethyl)-5-(4-pyridinylmethyl)-5*H*-cyclopenta-[2,3-*b*:3,4-*b*′]dipyridine (7f) (metal hydride conditions, substituting 2-bromoethyl ethyl ether): off-white solid, mp 128−129 °C (ethanol/ether); 88% yield; MS *m*/*e* 322 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (dd, $J = 4.7$, 0.7 Hz, 2H), 8.25 (d, $J = 5.8$, Hz, 2H), 7.69 (dd, $J = 7.7$, 1.1 Hz, 2H), 7.30 (dd, $J = 7.7$, 4.8 Hz, 2H), 6.60 (d, $J = 5.5$ Hz, 2H), 3.21 (s, 2 H), 3.03 (q, $J = 6.9$ Hz, 2H), 2.79 (t, $J = 6.9$ Hz, 2H), 2.50 (t, $J = 6.9$ Hz, 2H), 0.92 (t, $J = 6.9$ Hz, 2H). Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 75.80; H, 6.29; N, 12.61.

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