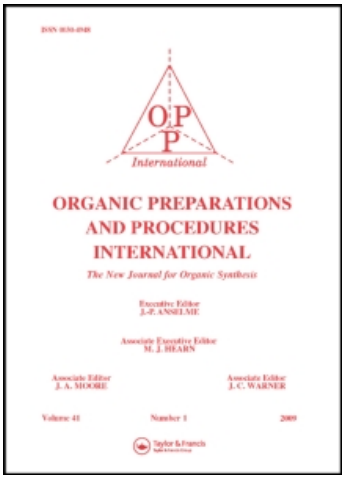

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SYNTHESIS OF BENZO[c][2,7]NAPHTHYRIDINES AND 2,13-DIAZABENZO[b]CHRYSENE

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dichloromethane was used for the preparation of BTCFH yield 69%, mp. 148-149°,[7] ^{1}H NMR (CD_3CN): δ 2.06 (m, 4, CH_2), 3.88 (m, 4, CH_2N).

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SYNTHESIS OF BENZO[c][2,7]NAPHTHYRIDINES AND 2,13-DIAZABENZO[b]CHRYSENE

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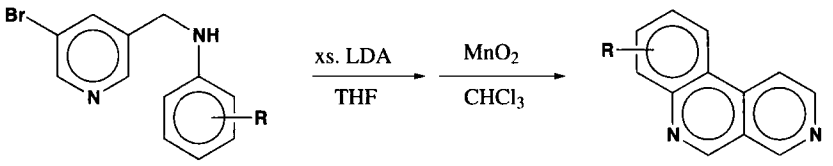
Over the past fifteen years marine organisms have furnished a number of biologically active natural products that contain the benzo[c][2,7]naphthyridine subunit.[1] In 1992 we reported a divergent synthesis of substituted benzo[c][2,7]naphthyridines that utilized an intramolecular pyridyne cyclization strategy.[2]



Alkylation of a variety of anilines with 5-bromo-3-chloromethylpyridinium hydrochloride, prepared in four steps from commercial 5-bromonicotinic acid,[3] provided the requisite pyridyne precursors. In order to minimize polyalkylation byproducts, a five-fold molar excess of the aniline was employed, necessitating cumbersome and often capricious chromatographic purification to separate unreacted aniline from the secondary amine product. Furthermore, this process would not be desirable for anilines that are either expensive or difficult to prepare. In order to circumvent these drawbacks an alternate procedure, based on reductive alkylation of substituted anilines with 5-bromonicotinaldehyde, has been developed, and is now reported.

Acid-catalyzed condensation of 5-bromonicotinaldehyde and the requisite substituted aniline followed immediately by reduction with sodium borohydride in methanol affords the pyridine cyclization products in 65-86% yield for the two-step process (Table). As the intermediate imines had a propensity to hydrolyze, they were not purified prior to reduction.

TABLE. Preparation of 5-Bromo-3-[(N-aryl)aminomethyl]pyridines

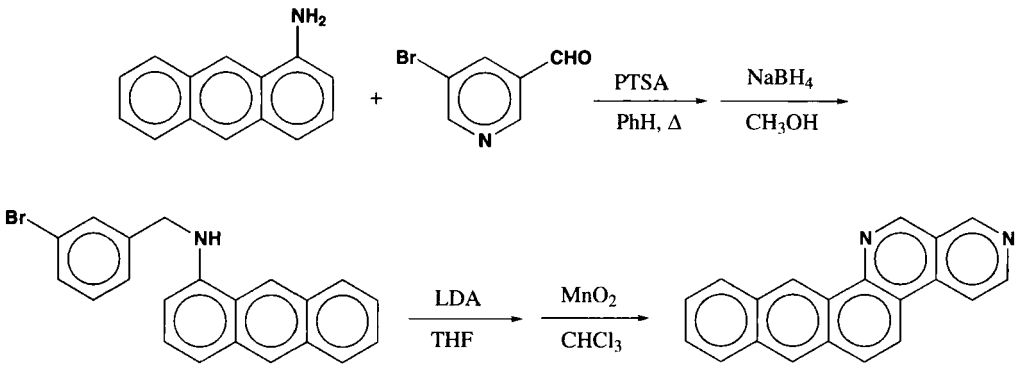
Substrate	Aniline	4-Methoxyaniline	3,4,5-Trimethoxyaniline	4-Methylaniline
Yield (%)[a]	79	86	65	85

a) Yields after flash chromatography. All products gave physical and spectral data identical to those previously reported.[2]

These yields compare favorably with those obtained from the alkylation of anilines with 5-bromo-3-chloromethylpyridinium hydrochloride (49-73%).[2] Although slightly lower overall yields from 5-bromonicotinic acid were obtained (19-25% for the present method; 24-35% for the previously reported procedure), the ease of preparation of 5-bromonicotinaldehyde versus 5-bromo-3-chloromethylpyridinium hydrochloride, the equimolar stoichiometry of the condensation reaction, and the ease of chromatographic purification should render the current procedure the method of choice for the preparation of 5-bromo-3-[(N-aryl)aminomethyl]pyridines.

The utility of this strategy is further exemplified by the synthesis of 2,13-diazabenzo[b]chrysene, a previously unreported ring system. Thus, acid catalyzed condensation of 1-aminoanthracene and 5-bromonicotinaldehyde followed by sodium borohydride/methanol reduction affords 5-bromo-3-[(N-1-anthryl)aminomethyl]pyridine in 52% yield. Cyclization with excess LDA followed by manganese dioxide dehydrogenation gives 2,13-diazabenzo[b]chrysene in 48% yield.

This improved procedure for the preparation of 5-bromo-3-[(N-aryl)aminomethyl]pyridines should be widely applicable to the synthesis of benzo[c][2,7]naphthyridines as well as more complex polyaza polycyclic aromatic hydrocarbon ring systems.



EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°), and all lithiation reactions were performed under nitrogen. Lithium diisopropylamide was purchased from Aldrich as a 2M solution in heptane/THF/ethylbenzene. Tetrahydrofuran was distilled from sodium/benzophenone. Thin layer chromatography was performed on precoated (0.25 mm) silica gel 60 F_{254} plastic sheets and were visualized with 254 nm ultraviolet light. Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Norcross GA. Proton and carbon NMR spectra were recorded on a Bruker ACE300 FT-NMR spectrometer.

Preparation of 5-Bromonicotinaldehyde.- A mixture of 5-bromo-3-hydroxymethylpyridine[3] (3.70 g, 19.7 mmol) and activated manganese dioxide (16.9 g, 194 mmol) in chloroform (300 mL) under nitrogen was magnetically stirred at 25° for 5 days. The manganese dioxide was removed by vacuum filtration and washed with acetone (75 mL); the washings were combined with the original filtrate. The filtrate was concentrated *in vacuo* with direct adsorption onto silica gel. Flash chromatography (ether) gave 5-bromonicotinaldehyde (2.00 g, 55%) as a white solid, mp. 94-95°, lit.[4] mp. 95-96°.

General Procedure. Preparation of 5-Bromo-3-[(N-1-anthryl)aminomethyl]pyridine.- A magnetically stirred solution of 1-aminoanthracene (0.354 g, 1.83 mmol), 5-bromonicotinaldehyde (0.344 g, 1.85 mmol), and p-toluenesulfonic acid monohydrate (.003 g, 0.016 mmol) in benzene (50 mL) was refluxed for 17 hrs with water removal via a Dean-Stark trap. The reaction was allowed to cool to 25°, the benzene was removed *in vacuo*, and the oily residue was dissolved in methanol (50 mL). Sodium borohydride pellets (1.98 g, 52.3 mmol) were added over a period of 2 hrs and the reaction was magnetically stirred at 25° for 24 hrs. The methanol was removed *in vacuo* and the resulting yellow solid was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark brown solid. Flash chromatography (2.5:1 hexanes/ether) gave 5-bromo-3-[(N-1-anthryl)aminomethyl]pyridine (0.344 g, 52%) as a yellow/orange solid: mp. 178-180° (methylene chloride/ hexane); ^{1}H NMR ($CDCl_3$): δ 8.64-8.62 (m, 2H), 8.38 (s, 2H), 8.01-7.96 (m, 3H), 7.48-7.45

(m, 3H), 7.29 (t, 1H), 6.44 (d, 1H), 4.94 (br, 1H), 4.56 (br s, 2H); ^{13}C NMR ($CDCl_3$): δ 150.0, 147.3, 142.0, 137.7, 136.5, 132.4, 131.6, 131.0, 128.3, 127.8, 126.8, 125.8, 125.7, 125.3, 123.5, 121.1, 118.8, 118.5, 103.0, 45.5.

*Anal.*Calcd for $C_{20}H_{15}BrN_2$: C, 66.13; H, 4.16; Br, 22.00; N, 7.71
Found: C, 65.89; H, 4.17; Br, 22.25; N, 7.63

Preparation of 2,13-Diazabenzo[b]chrysene.- To a magnetically stirred solution of 5-bromo-3-[(N-1-anthryl)aminomethyl]pyridine (0.308 g, 0.848 mmol) in dry THF (15 mL) at -78° under nitrogen was added *via* syringe over 3 min 2M lithium diisopropylamide (1.70 mL, 3.4 mmol). After 5 min at -78°, the dark purple solution was allowed to warm to 25° and stirred at 25° for 20 hrs. The reaction mixture was poured into saturated brine (50 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting dark oily residue was dissolved in chloroform (25 mL), manganese dioxide (0.53 g, 6.1 mmol) was added and the black suspension was magnetically stirred at 25° under nitrogen for 24 hrs. The insoluble manganese dioxide was removed by vacuum filtration and washed with acetone (50 mL); the washings were combined with the original filtrate. The filtrate was concentrated *in vacuo* with direct adsorption onto silica gel. Flash chromatography (1:5 hexanes/ether) gave 2,13-diazabenzo[b]chrysene (0.115 g, 48%) as a yellow/brown solid: mp. 238-239° (methylene chloride/hexane); ^{1}H NMR ($CDCl_3$): δ 9.89 (s, 1H), 9.57 (s, 1H), 9.50 (s, 1H), 8.91 (d, 1H), 8.46 (s, 1H), 8.34-8.23 (m, 3H), 8.12-8.06 (m, 2H), 7.62-7.59 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 152.8, 150.7, 148.0, 136.6, 132.8, 132.3, 131.7, 129.6, 129.3, 129.2, 127.8, 126.7, 126.4, 126.1, 125.0, 122.0, 119.0, 118.9, 115.4.

Anal. Calcd for $C_{20}H_{12}N_2$: C, 85.69; H, 4.31; N, 9.99. Found: C, 85.47; H, 4.26; N, 10.03

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