Novel Synthesis and Characterization of a Chiral Functionalized Pyrido[1,2-*a*]benzimidazole

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Introduction

Pyrido[1,2-*a*]benzimidazole was initially prepared in the late 1930s;[1] however, it has not received much attention until the past decade when some of its derivatives have found pharmaceutical applications.[2] This in part can be attibuted to the difficulty in the preparation of these heterocycles, often requiring a lengthy and low yielding synthesis.[3]

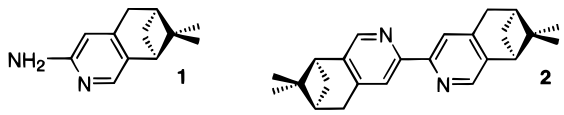
As part of our program to develop new chiral chelation agents for the stereochemical control of coordination complexes,[4] we desired to prepare the α-pinene-functionalized aminopyridine **1** as an intermediate in the synthesis of "super chiragen" **2** (Chart 1).[5] Following a standard Kröhnke-type scheme, the major product proved not to be **1** but a chiral pyrido[1,2-*a*]benzimidazole (**5**).

Results and Discussion

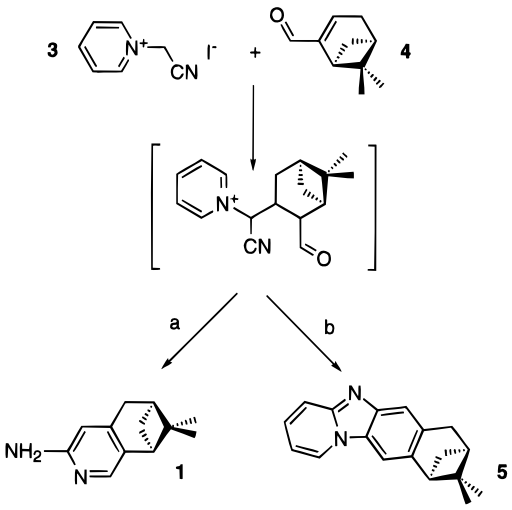
While attempting to prepare **1**, a standard Kröhnke-type reaction was undertaken, combining (cyanomethyl)-pyridinium iodide (**3**) with (1*R*)-(−)-myrtenal (**4**), in the presence of ammonium acetate in formamide.[6] While there were detectable quantities of the desired adduct **1**, surprisingly the major product of the reaction was aromatic and demonstrated strong fluorescence, and NMR analysis indicated that it retained the pinene moiety.

Unfortunately, the connectivity of the aromatic and pinene functionality could not be determined by a range of both 1- and 2-dimensional NMR techniques. However, after slow crystallization from pyridine, crystals suitable for X-ray structural determination were grown, revealing the product to be 7,8,9,10-tetrahydro-9,9-dimethyl-8,10-methanonaphtho[2,3′:4,5]imidazo[1,2-*a*]pyridine (**5**). This

Chart 1. Pinene-Functionalized 2-Aminopyridine and the Chiral Chelation Agent "Super Chiragen"



Scheme 1[a]



[a] (a) NH_4OAc, glacial acetic acid, elimination of pyridine and water, 80 °C, 24 H;[5a] (b) **3** and NH_4OAc (or NaOAc), formamide, 60 °C, elimination of pyridine, water, and hydrogen cyanide, 79% (71%) yield.

14π electron system, containing an aromatic bridgehead nitrogen, adopts the expected planar configuration, with the chiral pinene group projecting out of the plane (ORTEP plot available as Supporting Information). All other physical data are in accordance with this determination. Surprisingly, the Cambridge X-ray crystallographic database revealed only one similar structure that has been described.[7]

A Kröhnke-type reaction is initiated by the loss of a proton from the methylene group adjacent to the pyridinium nitrogen in **3** followed by a Michael addition of the nitrogen ylid to the β-unsaturated carbonyl moiety of **4** (Scheme 1). The preparation of the pyrido[1,2-*a*]-benzimidazole **5** must involve a second addition of a nitrogen ylid to the aldehydic carbonyl. A double cyclization then ensues with the elimination of pyridine, hydrogen cyanide, and water to form the 14π-aromatic system.

The reaction was repeated several times under different conditions to investigate its reproducibility. Due to the supposition that two (cyanomethyl)pyridinium moieties are involved in the synthesis, a 2:1 stoichiometric ratio of **3**:**4** was used. A reduction in reaction temperature from 80 to 60 °C caused the yield to increase from 35% to 79% and, in so doing, eliminated the production of a higher order, as yet unidentifiable, aromatic product. Further, the role of the basic salt (ammonium acetate) in the reaction was explored. In the absence of any salt, only small quantities of the product **5** were detected; however, the use of a large excess of sodium acetate afforded a reaction, and the product was isolated in good yield (71%) without the presence of α-pinene-functional-

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ized aminopyridine **1**. If a more alkaline salt was used, such as NaOH, $NaHCO_3$, or K_2CO_3,, a black tarlike residue resulted and no product **5** could be detected by ^1H NMR. Using methanol, ethanol, and/or glacial acetic acid as the reaction solvent (all typical for Kröhnke-type reactions) reduced the amount of **5** to between 0% and 10% while increasing the percentage of **1** present in the reaction product.[5]

Initial studies on the photophysical character of **5** revealed a strong series of absorbencies in the UV spectrum (see Experimental Section). Irradiation of any of these peaks led to a very strong emission in the visible region. It is noted that similar species have undergone investigation as potential laser dyes, due to these fluorescent properties.[8]

In conclusion, we demonstrate here a simple high-yield synthesis of **5** using cheap and readily available starting materials, the chirality of such a species being derived from the naturally occurring terpene (1*R*)-(−)-myrtenal (**4**). Due to the possible medicinal properties of such compounds, a sample of **5** has been submitted for screening in both antitumor and anti-AIDS programs.[9] Further studies are in progress to investigate the generality of this reaction for the preparation of high-order aromatic species.

Experimental Section

NMR spectra were recorded as previously described.[5a] UV/vis data were recorded on a Varian CARY 5E instrument. Optical rotation values were obtained on a Perkin-Elmer MC 141 instrument. The elemental analyses were performed in The Research-Centre, Marly, Ciba AG. Emission spectra were measured on a Perkin-Elmer LS 50B spectrometer.

(1*R*)-(−)-Myrtenal (**4**) was obtained from Fluka, >97%, $[\alpha]^{20}_D$ −14.6. The preparation of (cyanomethyl)pyridinium iodide (**3**) was according to a previously described method.[5a] Unless otherwise stated, commercial grade reagents were used without further purification.

7,8,9,10-Tetrahydro-9,9-dimethyl-8,10-methanonaphtho[2,3′:4,5]imidazo[1,2-*a*]pyridine (5). (1*R*)-(−)-Myrtenal (**4**) (0.500 g, 3.33 mmol), (cyanomethyl)pyridinium iodide (**3**) (2.504 g, 9.48 mmol), and ammonium acetate (2.10 g, 27.2 mmol) were gently stirred in formamide (puriss 50 mL) for 24 h at 60 °C. To this was added 2 M NaOH (50 mL), and the mixture was extracted with toluene (5 × 100 mL). The extract was dried ($MgSO_4$) and evaporated to a brown oil. This was further purified by column chromatography on silica gel eluting with dichloromethane, containing 1% methanol and 1% triethylamine. The major product was collected and, after removal of the solvent, yielded the product as a brown solid: Yield 0.690 g (79%). Colorless crystals can be obtained by slow crystallization from pyridine/dichloromethane: mp 161.5−162.5 °C; $[\alpha]^{25}_D$ +55.9. ^1H NMR ($CDCl_3$): δ 8.31 (d, 1H, J = 6.8 Hz, H-1), 7.64 (s, 1H, H-6), 7.61 (d, 1H, J = 9.3 Hz, H-4), 7.39 (s, 1H, H-11), 7.29 (dd, 1H, J = 8.7, 6.3 Hz, H-3), 6.74 (dd, 1H, J = 6.7, 6.7 Hz, H-2), 3.19 (d, 2H, J = 1.6 Hz, H-7), 2.92 (dd, 1H, J = 5.5, 5.5 Hz, H-10), 2.69 (ddd, 1H, J = 5.8, 5.8, 9.4 Hz, CH_{2a}-8,10), 2.13 (m, 1H, H-8), 1.39 (s, 3H, Me_a-9), 1.30 (d, 1H, J = 9.6 6 Hz, CH_{2b}-8,10), 0.63 (s, 3H, Me_b-9). ^{13}C NMR: δ 147.7, 143.2, 141.0, 133.7 (Q), 128.2 (CH), 126.3 (Q), 124.9, 118.7, 117.8, 110.1, 107.2 (CH), 48.8, 40.4 (CH), 39.7 (Q), 33.4, 32.5 (CH_2), 26.3, 21.5 (CH_3). MS (EI, *m*/*z*): 262 (M^+). UV/vis absorption peaks (nm (ϵ)): 248 (53 500), 256 (51 200), 265 (13 200), 275 (11 100), 308 (5500), 320 (6900), 348 (6000), 363 (5500), 381 (2600). Emission (nm): 419, 442, 470 (sh), 505 (sh).

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Supporting Information Available: Experimental details of the X-ray crystal structure refinement along with tables of atomic positional parameters and distances (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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