A Facile Synthesis of 2,7-Diazapyrene

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2,7-Diazapyrene is synthesized in three high-yield steps from commercially available 1,4,5,8-naphthalene tetracarboxylic dianhydride, which first reacts with concentrated ammonium hydroxide solution at room temperature to give 1,4,5,8-naphthalenetetracarboxylic diimide (96%). The latter compound is subsequently reduced with borane in refluxing tetrahydrofuran to give 1,2,3,6,7,8-hexahydro-2,7-diazapyrene (77%), which in turn is oxidized with manganese dioxide in refluxing benzene giving 2,7-diazapyrene (71%).

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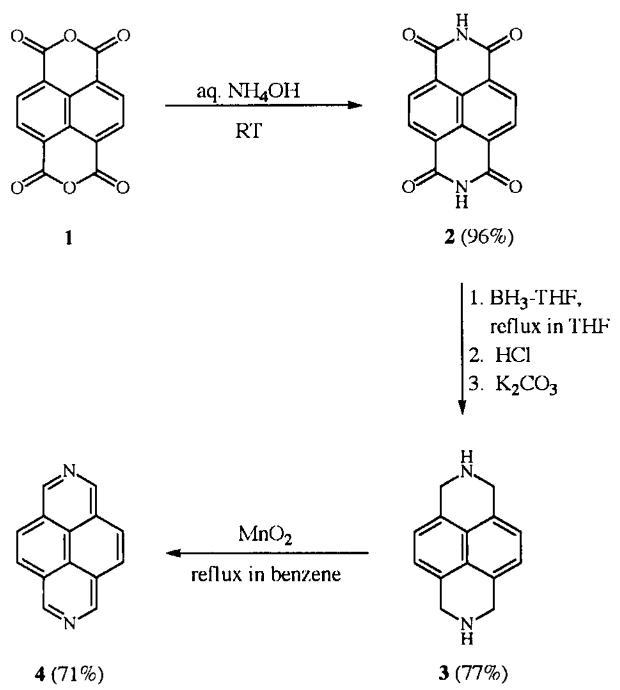
2,7-Diazapyrene and its *N*-methyl cations exhibit interesting photophysical properties, particularly with respect to their interaction with DNA and some of its mononucleotides [1-5]. 2,7-Diazapyrenium dications are attractive subunits for incorporation into macrocyclic structures in order to make photo- and electroactive receptors [6]. Further, 2,7-diazapyrenium dications can function as redox-dependent receptors for aromatic carboxylates and therefore can find applications as electrochemical sensors [7]. Finally, 2,7-diazapyrenium cations, when appropriately derivatized with trimethoxysilyl groups, can covalently bond to sol-gel derived silica and the resulting luminescent materials have shown sensitivity to oxygen [8].

Although other methods exist [9], the synthesis of *N*-alkyl and *N,N'*-dialkyl-2,7-diazapyrenium cations is typically carried out by quaternization of 2,7-diazapyrene [8,10]. However, a convenient and high yield synthesis of 2,7-diazapyrene is still lacking. The first literature method for the synthesis of 2,7-diazapyrene was *via* dehydrogenation of [2.2] (3,5) pyridinophane with palladium on carbon (Pd/C) at 290°, in 30% yield [11]. To make matters worse, [2.2] (3,5) pyridinophane was synthesized in very low yield (~2%) from 3,5-dichloromethylpyridine [12]. On the other hand, the traditional Hünig's method [10] for the synthesis of 2,7-diazapyrene, involves reaction of methylamine (CH_3NH_2) with 1,4,5,8-naphthalenetetracarboxylic acid or, according to Stang's modification [13] of that method, with 1,4,5,8-naphthalenetetracarboxylic dianhydride to *N,N'*-dimethyl-1,4,5,8-naphthalenetetracarboxylic diimide; the latter compound is reduced with lithium aluminum hydride ($LiAlH_4$) to 1,3,6,8-tetrahydro-*N,N'*-dimethyl-2,7-diazapyrene which is subsequently oxidized either with selenium or 10% Pd/C in high temperature melts [10,13]. Both oxidation methods are cumbersome, but the selenium method [10] is also potentially hazardous. Furthermore, the catalytic oxidation with 10% Pd/C is low yield (23%, after extensive product purification by column chromatography, recrystallization and sublimation) [13]. We have found that the oxidation of 1,3,6,8-tetrahydro-*N,N'*-dimethyl-2,7-diazapyrene can be carried out in a sealed tube at 240°, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant, however the yield of 2,7-diazapyrene is also low (32%) [14]. According to Hünig, for the synthesis of *N,N'*-dimethyl-2,7-diazapyrenium dication, the above procedures can be circumvented by a direct but low yield (20%) oxidation of 1,3,6,8-tetrahydro-*N,N'*-dimethyl-2,7-diazapyrene with mercuric acetate in boiling glacial acetic acid [10,15]. The latter method, however, lacks generality as it cannot be carried out when the alkyl groups possess double bonds. Recently, 2,7-diazapyrene was synthesized by oxidation of 1,2,3,6,7,8-hexahydro-2,7-diazapyrene with manganese dioxide (MnO_2) in 49% yield [16]. However, not only is the synthesis of 1,2,3,6,7,8-hexahydro-2,7-diazapyrene lengthy [16], but the starting material for its synthesis, 1,4,5,8-tetrakis(bromomethyl)naphthalene, is not commercially available and needs to be synthesized from 1,4,5,8-naphthalenetetracarboxylic acid in three steps [17].

In this paper, we report an alternative, simple, inexpensive, high-yield procedure for the synthesis of 2,7-diazapyrene (**4**) where commercially available 1,4,5,8-naphthalenetetracarboxylic dianhydride (**1**) can react with concentrated ammonium hydroxide (NH_4OH) solution to give 1,4,5,8-naphthalenetetracarboxylic diimide (**2**), followed by reduction with borane-tetrahydrofuran (BH_3-THF) to give 1,2,3,6,7,8-hexahydro-2,7-diazapyrene (**3**) and aromatization of the later compound with MnO_2.

Scheme 1 summarizes our route for the synthesis of 2,7-diazapyrene. The first step involves preparation of 1,4,5,8-naphthalenetetracarboxylic diimide (**2**) [18] from the reaction of 1,4,5,8-naphthalenetetracarboxylic dianhydride (**1**) with concentrated ammonium hydroxide (29.5%) as a solvent at room temperature for 6 hours. This reaction, a modification of a literature method (yield 89%, product **2** purity 80%) [19], proceeds quantitatively to an insoluble precipitate of analytically pure **2** in excellent yield (96%). The second step involves reduction of **2** with BH_3-THF [20] followed by hydrolysis of the resulting borane intermediate with 6 *M* hydrochloric acid (HCl), addition of a saturated aqueous solution of potassium carbonate (K_2CO_3) until the reaction mixture becomes basic, and soxhlet extraction of the crude diamine **3** with benzene (77% yield). We found that the reduction of diimide **2** with $LiAlH_4$ yields an

Scheme 1



intractable polymeric material, probably *via* proton abstraction from the NH group by $LiAlH_4$ followed by an intermolecular nucleophilic addition of the resulting anion to a carbonyl group of the diimide. On the other hand, the borane method has been used successfully for the reduction of phthalimide to isoindoline [21]. Finally, the 2,7-diazapyrene (**4**) is obtained in 71% yield *via* oxidation of **3** with MnO_2 in refluxing benzene with azeotropic removal of water. Most of the product can easily be obtained in pure form after removal of MnO_2 by filtration. It appears, however, that a significant amount of the product remains adsorbed on the MnO_2 surface, so a subsequent soxhlet extraction of MnO_2 with benzene increases the overall yield of **4** to 71% from the 49% literature value [16]. We have also found that DDQ can be used to oxidize **3** to **4** in glacial acetic acid, at room temperature for 12 hours. However, the yield of **4** is only 18%.

In summary, we report a convenient new method for the rapid, inexpensive and high-yield synthesis of 2,7-diazapyrene.

EXPERIMENTAL

^1H and ^{13}C nmr spectra were obtained with a newly purchased INOVA 400 MHz spectrometer of Varian Corporation (Palo Alto, CA). Elemental analyses were performed by Oneida Research Services, Inc. Melting points were determined with an Electrothermal Melting Point Apparatus and are uncorrected. Starting materials, reagents, and solvents were purchased from Aldrich or Fisher and used as received unless otherwise stated.

1,4,5,8-Naphthalenetetracarboxylic Diimide (**2**).

1,4,5,8-Naphthalenetetracarboxylic dianhydride **1** (12.5 g, 46.6 mmol) was dissolved in a stirred concentrated aqueous solution of ammonium hydroxide (625 mL, 29.5%, w/w). The reaction mixture was stirred at room temperature for 6 hours under nitrogen. During that time, analytically pure diimide **2** precipitated as a pale yellow product, which was filtered, washed with distilled water, and dried under vacuum at 60° overnight. Yield: 11.9 g (96%); mp > 350° (> 320° [19]); ^1H nmr (400 MHz, D_2SO_4): δ 8.10 (s, 4H, ArH); ^{13}C nmr (100 MHz, D_2SO_4): δ 165.5, 134.9, 127.8, 125.4.

Anal. Calcd for $C_{14}H_6O_4N_2$: C, 63.17; H, 2.27; N, 10.52. Found: C, 62.98; H, 2.28; N, 10.48.

1,2,3,6,7,8-Hexahydro-2,7-diazapyrene (**3**).

An oven-dried, 250-mL, three-neck flask equipped with a magnetic stirrer, reflux condenser, addition funnel, nitrogen inlet, and a gas vent, was flushed with nitrogen, and then was charged with diimide **2** (2 g, 7.52 mmol) and anhydrous THF (40 mL). To this suspension was added slowly, *via* the dropping funnel, 1 *M* solution of BH_3-THF (80 mL), at room temperature. The reaction mixture was then refluxed for 60 hours. During that time there was hydrogen evolution and the color of the reaction mixture turned to orange. After cooling to 0°, the reaction mixture was quenched by addition of 8 mL of methanol. After stirring for 30 minutes at room temperature, 10 mL of 6 *M* HCl was added and the mixture was refluxed for 3 hours. *Caution:* At that time the mixture may foam strongly so the stirring must be kept vigorous. The liquid was then evaporated under reduced pressure. The residue was cooled to 0° and aqueous saturated potassium carbonate solution was added with stirring until the pH was basic (>10). All of the liquid was evaporated under reduced pressure and the solid was dried completely under vacuum at 40°. The dry solid was extracted with refluxing benzene in a soxhlet extractor for a week (for best results, the solid should be taken out of the thimble, dried, ground and placed back in the soxhlet extractor, once a day). After this period, the benzene was removed *in vacuo* to yield 1.22 g (77%) of pure diamine **3** which can be recrystallized from benzene to give off-white powder; mp 218° (214° [16]); ^1H nmr (400 MHz, deuteriochloroform): δ 7.17 (s, 4H, ArH), 4.21 (s, 8H, CH_2); ^{13}C nmr (100 MHz, DMSO-d_6): δ 132.9, 127.9, 120.3, 48.9.

2,7-Diazapyrene (**4**).

A 500-mL round-bottom flask, equipped with a magnetic stirrer, reflux condenser, a dean stark trap (for azeotropic removal of water), nitrogen inlet, and a gas vent, was flushed with nitrogen, and then was charged with benzene (250 mL). To the solution was added **3** (1 g, 4.76 mmol) and MnO_2 (10 g, 115.02 mmol, activated grade, Aldrich). After the addition, the solution was refluxed for 24 hours. The hot solution was filtered and the benzene solution was kept. The filtered MnO_2 was dried under vacuum and subjected to a soxhlet extraction with the benzene solution of the filtrate for 3 days (for best results, MnO_2 should be taken out of the thimble, dried, ground and placed back in the soxhlet extractor, once a day). After removal of the benzene *in vacuo*, 0.69 g (71%) of pure **4** was obtained as yellow crystals. Mp 282-284° (283-284° [10]; 284-287° [13]); ^1H nmr (400 MHz, deuteriochloroform): δ 9.38 (s, 4H, ArH), 8.06 (s, 4H, ArH); ^{13}C nmr (100 MHz, deuteriochloroform): δ 144.3, 125.3, 125.2, 124.8.

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