Research Article

New Catalytic Method for the Synthesis of 2,7-Dicycloalkyl-hexaazaperhydropyrenes

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An efficient method for the synthesis of 2,7-dicycloalkyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes by the NiCl$_2$\cdot$6$H$_2$O-catalyzed ring transformation reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 1,4,5,8-tetraazadecaline has been successfully developed.

1. Introduction

The interest in diazapyrenes is related to their practical applicability as drug candidates for the development of analgesics [1] and antibacterial [2] and antitumor [3, 4] drugs agents. Polyazapyrenes are actively used in supramolecular chemistry for the design of molecular devices [5], host-guest type molecules [6], and macrocyclic squares incorporating mixed transition metal systems and a main group element [7]. Currently, quite a number of isomeric diazapyrenes [8] and polyazapyrenes [9] with different arrangements of the peripheral nitrogen atoms in the pyrene ring have been synthesized. As previously reported [10], 2,7-diazapyrenes can be obtained by the reaction of dihydroazaphenalen with sym-triazine in polyphosphoric acid. There is little information about methods for the synthesis of azaperhydropyrenes. For instance, stereoisomeric tetraazaperhydropyrenes can be synthesized by the reaction of 1,4,5,8-tetraazadecaline with methyl acrylate [11]. Hexaazaperhydropyrenes are prepared by the three-component cyclocondensation of amines with formaldehyde and 1,4,5,8-tetraazadecaline in the presence of a strong acid cation exchanger [12] or by the intermolecular heterocyclization of 1,4,5,8-tetraazadecaline with $N,N$-bis(methoxymethyl)-$N$-alkylamines in the presence of the lanthanide catalyst [13].

Herein, we report a new efficient synthesis of 2,7-dicycloalkyl-2,3a,5a,7,8a,10a-hexaazaperhydropyrenes through the ring transformation reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 1,4,5,8-tetraazadecaline catalyzed by NiCl$_2$\cdot$6$H$_2$O.

2. Materials and Methods

The NMR spectra, including two-dimensional homonuclear (COSY and NOESY) and heteronuclear (HSQC and HMBC) spectra, were recorded on a Bruker Avance 500 spectrometer at 500.17 MHz for $^1$H and 125.78 MHz for $^{13}$C according to standard Bruker procedures. CDCl$_3$ was used as the solvent, and tetramethyldilane was used as the internal standard. The MALDI TOF/TOF mass spectra (positive ion detection, 2,5-dihydroxybenzoic acid matrix) were obtained on a Bruker AutoflexTM III Smartbeam mass spectrometer. Samples were prepared by the dried drop technique. Solutions of matrix and substrate were mixed at a ratio of 50 : 1 to 100 : 1, and a drop of the mixture was applied onto a target and dried in a stream of warm air. The sample was vaporized from the target by laser pulses (200 pulses with a frequency of 100 Hz) generated by a solid state UV laser ($\lambda$ 355 nm). The melting points were determined on a Carlo Erba 1106 analyzer. The elemental analyses were obtained on a Carlo Erba 1106 analyzer. The melting points were determined on a PHMK 80/2617 melting point apparatus. The reaction progress was controlled by TLC using Sorbfil plates (PTSH-AF-V); spots were visualized by treatment with iodine vapor. Column chromatography was performed on KSK silica gel (100 – 200 $\mu$m). 1,4,5,8-Tetraazadecaline (I) was obtained as described previously [14].
Ring Transformation Reaction of 1,3,5-Tricycloalkyl-1,3,5-triazines with 1,4,5,8-Tetraazadecalin (1) (General Method). A round bottom flask equipped with a magnetic stir bar was charged with MeOH (10 mL), the corresponding 1,3,5-tricycloalkyl-1,3,5-triazine (2.00 mmol), obtained in situ by the reported procedure [15], and NiCl₂·6H₂O (0.012 g, 0.05 mmol). The mixture was stirred at room temperature for 30 min. Next, 1,4,5,8-tetraazadecalin (1) (0.14 g, 1.00 mmol) in H₂O (1 mL) was added to the mixture. The mixture was stirred at 20°C for 3 h and evaporated. The residue was separated by column chromatography on silica gel (SiO₂). Products 2–8 were obtained as colorless crystals (recrystallized from MeOH). The final products 2–8 were identified by spectral methods.

2,7-Dicyclopentyl-2,3a,5,7,8a,10a-hexaazaheptyroperylene (2). Rf = 0.63 (MeOH); m.p. = 195–197°C; 1H NMR (500.17 MHz, CDCl₃): δ = 0.35 (d, Jₕ₋ₖ = 6 Hz, 4H; CH₃); δ = 2.60–2.64 (m, 4H; CH₂); δ = 3.77 ppm (d, Jₕ₋ₖ = 10 Hz, 4H; CH₂; δ = 71.8 (C-1, C-3, C-5-b) 71.3, C-1, C-3, C-5 (8), 82.5 ppm (C-10b, C-10c); MS (MALDI TOF/TOF): m/z (%): 303 [M⁺–H]–; elementary analysis calcld (%) for C₁₄H₂₆N₆O₂: C 69.18; H 10.65; N 20.17; found: C 69.09; H 10.60; N 20.08.

2,7-Dicyclopentyl-2,3a,5,7,8a,10a-hexaazaheptyroperylene (3). Rf = 0.65 (MeOH); m.p. = 224–226°C; 1H NMR (500.17 MHz, CDCl₃): δ = 1.33–1.41 (m, 4H; CH₂; δ = 2.60–2.64 (m, 4H; CH₂); δ = 3.77 ppm (d, Jₕ₋ₖ = 10 Hz, 4H; CH₂; δ = 71.8 (C-1, C-3, C-5-b) 71.3, C-1, C-3, C-5 (8), 82.5 ppm (C-10b, C-10c); MS (MALDI TOF/TOF): m/z (%): 303 [M⁺–H]–; elementary analysis calcld (%) for C₁₄H₂₆N₆O₂: C 69.18; H 10.65; N 20.17; found: C 69.09; H 10.60; N 20.08.

2,7-Dicyclooctyl-2,3a,5,7,8a,10a-hexaazaheptyroperylene (4). Rf = 0.71 (MeOH); m.p. = 225–227°C; 1H NMR (500.17 MHz, CDCl₃): δ = 1.13–1.18 (m, 6H; CH₃); δ = 2.52–2.56 (m, 4H; CH₂); δ = 3.65 ppm (d, Jₕ₋ₖ = 10 Hz, 4H; CH₂; δ = 71.8 (C-1, C-3, C-5-b) 71.3, C-1, C-3, C-5 (8), 82.5 ppm (C-10b, C-10c); MS (MALDI TOF/TOF): m/z (%): 303 [M⁺–H]–; elementary analysis calcld (%) for C₁₄H₂₆N₆O₂: C 69.18; H 10.65; N 20.17; found: C 69.09; H 10.60; N 20.08.

2,7-Dicyclooctyl-2,3a,5,7,8a,10a-hexaazaheptyroperylene (5). Rf = 0.75 (MeOH); m.p. = 230–232°C; 1H NMR (500.17 MHz, CDCl₃): δ = 1.45–1.49 (m, 10H; CH₂; δ = 2.52–2.56 (m, 4H; CH₂); δ = 3.65 ppm (d, Jₕ₋ₖ = 10 Hz, 4H; CH₂; δ = 71.8 (C-1, C-3, C-5-b) 71.3, C-1, C-3, C-5 (8), 82.5 ppm (C-10b, C-10c); MS (MALDI TOF/TOF): m/z (%): 303 [M⁺–H]–; elementary analysis calcld (%) for C₁₄H₂₆N₆O₂: C 69.18; H 10.65; N 20.17; found: C 69.09; H 10.60; N 20.08.
2,7-Dicyclo[2.2.1]hept-2-yl-3a,5a,7a,8a,10a-hexaazaperhydropyrene (8). Rf = 0.75 (MeOH); m.p. = 261–263°C; 1H NMR (500.17 MHz, CDCl3): δ = 1.05–1.12 (m, 6H; CH2; H-2, 3, 3‘, 3″), 2.71–3.10 and 3.76–3.84 ppm (m, 4H; CH2; H-4, 5, 9, 10), 3.81–3.84 ppm (m, 4H; CH2; H-2, 3, 3‘, 3″), 1.99 (d, Jba = 10 Hz, geminal) corresponding to the methylene protons (44%) CuCl (82%), FeCl3 (78%), NiCl2 (69.86%; H 9.77; N 20.37; found: C 69.77; H 9.71; N 20.29).

3. Results and Discussion

To develop a new preparative method for the synthesis of 2,7-dicycloalkyl-2,3a,5a,7a,8a,10a-hexaazaperhydropyrenes, which are difficult to obtain by other methods, we have studied the ring transformations in the reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 1,4,5,8-tetraazadecalin (1). 1,3,5-Triazine was chosen as a new aminomethylating reagent for the synthesis of target hexaazaperhydropyrenes resorting to the reported [16] ring transformation reaction of 1,3,5-triazines-2-one induced by compounds having active hydrogen atoms (S–H). 1,4,5,8-Tetraazadecalin was hypothesized to serve as a compound containing active N–H bonds by analogy with 1,2-ethanediol used in the ring transformation of 1,3,5-triazin-2-one [16].

Our preliminary experiments have shown that noncatalyzed reaction of in situ generated 1,3,5-tricyclopropyl-1,3,5-triazine [15] with 1,4,5,8-tetraazadecalin at 20°C in MeOH afforded 2,7-dicyclopropyl-2,3a,5a,7a,8a,10a-hexaazaperhydropyrene (2) in no more than 10% yield. Conducting the reaction in refluxing methanol increased the yield of hexaazaperhydropyrene to 35%.

To achieve a higher yield of the target heterocycle 2, we have performed the reaction of 1,3,5-tricyclopropyl-1,3,5-triazine with 1,4,5,8-tetraazadecalin in the presence of the catalysts that showed high activity in the ring transformation reactions [17–19]. The highest activity was found for catalysts based on transition metal salts and complexes, the yield of 2,7-dicyclopropyl-2,3a,5a,7a,8a,10a-hexaazaperhydropyrene (2) being increased in the series of catalysts (5 mol% toward tetraazadecalin) as follows: Pd[CH3COO]2 (41%), PdCl2 (44%), CuCl2⋅6H2O (65%), Cp2TiCl2 (73%), PtCl2 (75%), FeCl3⋅6H2O (78%), CoCl2⋅6H2O (82%), and NiCl2⋅6H2O (89%). When lanthanide (Er, Sm, Yb, La, In, and Eu) salts were used as the catalysts, the yield of hexaazaperhydropyrenes (2) did not exceed 70%. All experiments were carried out in MeOH at room temperature (~20°C) due to good solubility of the reactants and the target heterocycles.

Under optimized reaction conditions (5 mol% NiCl2⋅6H2O, 20°C, 3 h, MeOH), 1,3,5-tricycloalkyl-1,3,5-triazines react with 1,4,5,8-tetraazadecalin (1) to afford selectively 2,7-dicycloalkyl-2,3a,5a,7a,8a,10a-hexaazaperhydropyrenes 2–8 in 74–89% yield (Scheme 1).

In the 1H NMR spectra (Figure 1) of compounds 2–8, characteristic signals are doublets at 2.71–3.10 and 3.76–3.84 ppm (J = 10 Hz, geminal) corresponding to the methylene protons (H-1, H-3, H-6, and H-8) at the carbon atoms located between two nitrogen atoms. The methylene protons (H-4, H-5, H-9, and H-10) resonate as two doublets at 2.26–2.63 ppm (J = 7 Hz, vicinal). The broadened signals at 2.24–2.72 ppm belong to the cage protons (H-10b and H-10c).

The hexaazaperhydropyrene cage of compounds 2–8 is responsible for three 13C NMR (Figure 2) signals at 48.0–48.4, 70.6–74.4, and 82.4–82.7 ppm with a 2 : 2 : 1 integrated intensity ratio. The signals were assigned based on homonuclear (COSY and NOESY) and heteronuclear (HSQC and HMBC) 2D NMR experiments.

The proposed structures were confirmed by the molecular ion peaks present in the positive ion matrix assisted laser desorption ionization tandem mass spectra (MALDI TOF/TOF MS, resolution 0.001 a.u.).

The experimental results as well as published data suggest [20–23] that the ring transformation reaction of 1,3,5-tricycloalkyl-1,3,5-triazine with tetraazadecalin I represents a multistaged chemical process. It comprises the successive steps of coordination of the tertiary nitrogen atom to the catalyst central ion, ring opening of the starting heterocycle, nucleophilic addition of secondary amine to a carbocation, and subsequent intermolecular cyclization to give the target hexaazaperhydropyrenes (Scheme 2). The GC/MS analysis of the
Figure 1: $^1$H NMR spectra of compound 4.

Figure 2: $^{13}$C NMR spectra of compound 4.
reaction products formed from 1,3,5-tricyclohexyl-1,3,5-triazine and tetraaza[2 × 6]decalin I showed the fragment ion at m/z 127 [M–C6H11] formed upon fragmentation of N,N-dicyclohexylmethyldiamine [CH2(NH-cyclo-C6H11)2], resulting from ring transformation of 1,3,5-tricyclohexyl-1,3,5-triazine, which provides evidence for the proposed reaction pathway.

4. Conclusion

Polyheterocyclic structural architectures occur in many bioactive natural products and synthetic drugs, and these structural units serve as important intermediates in organic synthesis. Therefore, organic chemists have been making extensive efforts to produce polyheterocyclic compounds by developing new and efficient synthetic transformations. Among the variety of new synthetic transformations, catalyzed reactions are some of the most attractive methodologies for synthesizing polyheterocycles. In summary, we have developed an efficient method for the synthesis of 2,7-dicycloalkyl-2,3a,5a,7,8a,10a-hexaaza[2,3]pyridine derivatives, difficult to prepare previously, via the NiCl2·6H2O-catalyzed ring transformation reaction of 1,3,5-tricycloalkyl-1,3,5-triazines with 1,4,5,8-tetraaza[2 × 6]decalin.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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