

One Pot Synthesis of Cyclophane with Imidazolium Skeleton

An Improved Method

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We report herein a feasible study concerning one pot synthesis of cyclophane with imidazolium skeleton. To our knowledge, this is the first one pot synthesis of a cyclophane with imidazolium skeleton. Comparative with the existing methods, our method has several indisputable advantages: is a one pot synthesis, requires a shorter period of time and small amounts of solvents, low energetically consumption. Consequently, this method could be considered an eco-friendly method. The structure of the newly compound was assigned by elemental and spectral analysis: ¹H NMR, ¹³C NMR, 2D-COSY, 2D-HMQC, 2D-HMBC and X-ray.

Keywords: Imidazolium cyclophane, one pot synthesis, eco-friendly, X-ray

The chemistry of cyclophanes is an important, a widely discussed area within the branch of modern supramolecular chemistry [1, 2]. More and more attention has been paid to cyclophanes chemistry since they have been promoted to act as molecular recognition reagents in host-guest interactions [1-3]. Since the first two papers appear within the area of imidazolium linked cyclophanes [4, 5], there is a growing interest in design and synthesis of cyclophanes with imidazolium skeleton, these compounds being of great interest in obtaining stable *N*-heterocyclic carbene complexes, particularly in the area of catalysis [6-8] and biologically active compounds [9, 10]. On the other hand, diaza heterocycles became representative structure types in medicinal chemistry, opto-electronics and agriculture [11-14].

In continuation of our work in the field of supramolecular chemistry [15,16] and biologically active compounds [11, 17, 18], we report here the synthesis and structural characterization of cyclophane with imidazolium skeleton with potential interest for both supramolecular and medicinal chemistry.

Experimental part

All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus (MELTEMP II) and are uncorrected. The ¹H- and ¹³C-NMR spectra and two-dimensional 2D-COSY, 2D-HMQC, 2D-HMBC experiments were recorded on a Bruker Avance III 500 MHz spectrometer operating at 500 MHz for ¹H and 125 MHz for ¹³C. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.15; H, ± 0.10; N, ± 0.30. X-Ray analysis was recorded with an Agilent SuperNova Dual diffractometer equipped with a

Cu (Kα radiation, λ = 1.5418 Å) fine-focus sealed X-ray tube and a graphite monochromator.

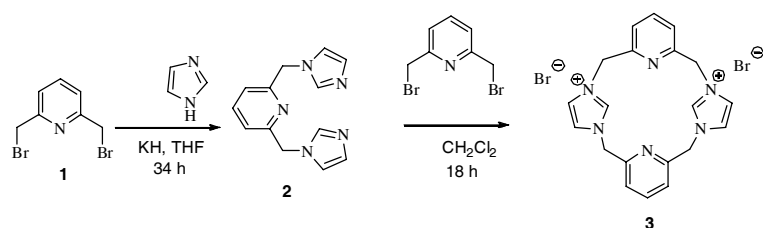
One pot synthesis of cyclophane with imidazolium skeleton, bis(imidazolium) dibromine cyclophane (3).

Imidazole (1.5 mmol, 0.102 g) in 5 mL DMF (dimethylformamide) was added dropwise to NaH (1.6 mmol, 0.039 g) in 5 mL DMF while stirring at 0 °C (ice). Then 2,6-bis(bromomethyl)pyridine (1 mmol, 0.265 g) in 8 mL DMF was added dropwise. The resulting solution was stirred for additional 24 h at ambient temperature. The solution was concentrated on rotary evaporator, then precipitated with methanol. The white precipitate that formed was collected by filtration to yield (3) as a white powder. Mp > 300 °C. Yield: 40%. ¹H-NMR (DMSO-d₆, δ, ppm): 5.62 (8H: 4xCH₂, s); 7.61 (4H: H₃, d, *J*_{3,4} = 9.5); 7.67 (4H: H₄ and H₅, overlaped doublet, *J*_{4,5} = 1.5); 8.01 (2H: H₆, t, *J*_{4,3} = 9.5); 9.17 (2H: H₂, s). ¹³C-NMR (DMSO-d₆, δ, ppm): 52.26 (4xCH₂), 122.39 (4xC₃), 123.24 (2xC₄, 2xC₅), 136.97 (2xC₂), 138.47 (2xC₄), 153.28 (4xC₂).

Results and discussions

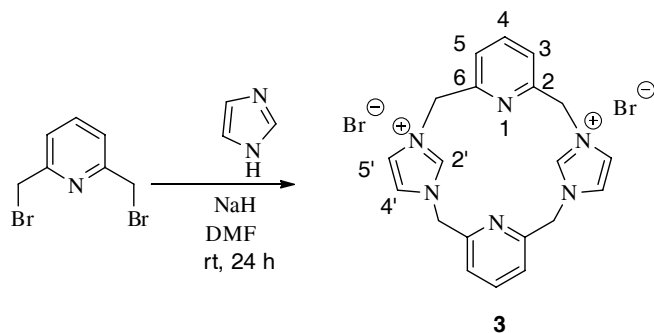
The first synthesis and structural characterization of a cyclophane with imidazolium skeleton was made by the group of Youngs [19]. The Youngs synthesis of the ionic bis(imidazolium) cyclophane (3), involve two steps: reaction of imidazole with 2,6-bis(bromomethyl)pyridine (1), followed by an alkylation of the resulting 2,6-bis(imidazoliummethyl)pyridine (2), with other molecule of 2,6-bis(bromomethyl)pyridine, scheme 1.

This method for synthesis of cyclophanes with imidazolium skeleton has a series of major disadvantages: two steps, moderate yields, very long reactions time, huge amounts of solvents, highly energetically consumption, unfriendly ecologically.



Scheme 1. Reaction pathway (multi pot) to obtain cyclophane with imidazolium skeleton

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Scheme 2. One pot reaction pathway to obtain cyclophane with imidazolium skeleton

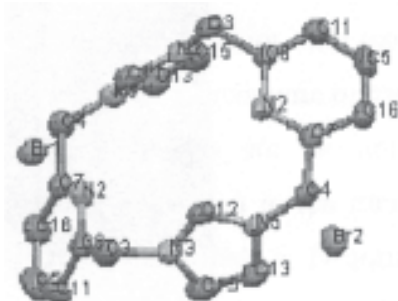


Fig. 1. The molecular structure of $C_{20}H_{20}Br_2N_6$. Displacement ellipsoids are drawn at 50% probability level. H atoms are omitted for clarity

Having in view the above considerations, we decide to find an alternatively route for synthesis of cyclophanes with imidazolium skeleton. On our research we find that the best way of synthesis for cyclophanes with imidazolium skeleton type (**3**), is a *one pot* synthesis as we described in scheme 2.

Comparative with the Youngs method of synthesis, our method have several incontestable advantages. First of all, it is a one pot synthesis and, to our knowledge, this is the first *one pot* synthesis of a cyclophane with imidazolium skeleton. Moreover, the reaction conditions are mild, require short period of time, small amounts of solvents and it is a low energetically consumption pathway. Having in view these considerations, our method of synthesis could be considered an ecologically friendly method.

The structure of the compound was proven by elemental (C, H, N) and spectral analysis (1H NMR, ^{13}C NMR, 2D-COSY, 2D-HMQC and 2D-HMBC) and is in accordance with the proposed structure. In order to establish unambiguously the structure of the cyclophane with imidazolium skeleton (**3**), we performed the X-ray analysis, (fig.1).

The X-ray structure of (**3**) also confirms the proposed structure. We may notice for (**3**) a bowl shape, with the two nitrogen atoms of pyridine moieties inside of the bowl.

The literature results [11,17,18] encourage us to claim that the obtained cyclophane with imidazolium skeleton type (**3**), will probably have similar biological activity with the related structural compounds (the tests are ongoing).

Conclusions

We report herein a feasible study concerning synthesis and structure of cyclophane with imidazolium skeleton. To our knowledge, this is the first *one pot* synthesis of a cyclophane with imidazolium skeleton. Comparative with the existing methods of synthesis which require two steps and harsh conditions (very long reactions time, huge amounts of solvents, highly energetically consumption), our method have several incontestable advantages: is a *one pot* synthesis, require short period of time, small amounts of solvents, low energetically consumption. Consequently, this method could be considered an eco-friendly method. The structure of the newly compound was assigned by elemental and spectral analysis: 1H NMR, ^{13}C NMR, 2D-COSY, 2D-HMQC, 2D-HMBC and X-ray.

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