

Synthesis of new benzo-fused macrocycle diamides

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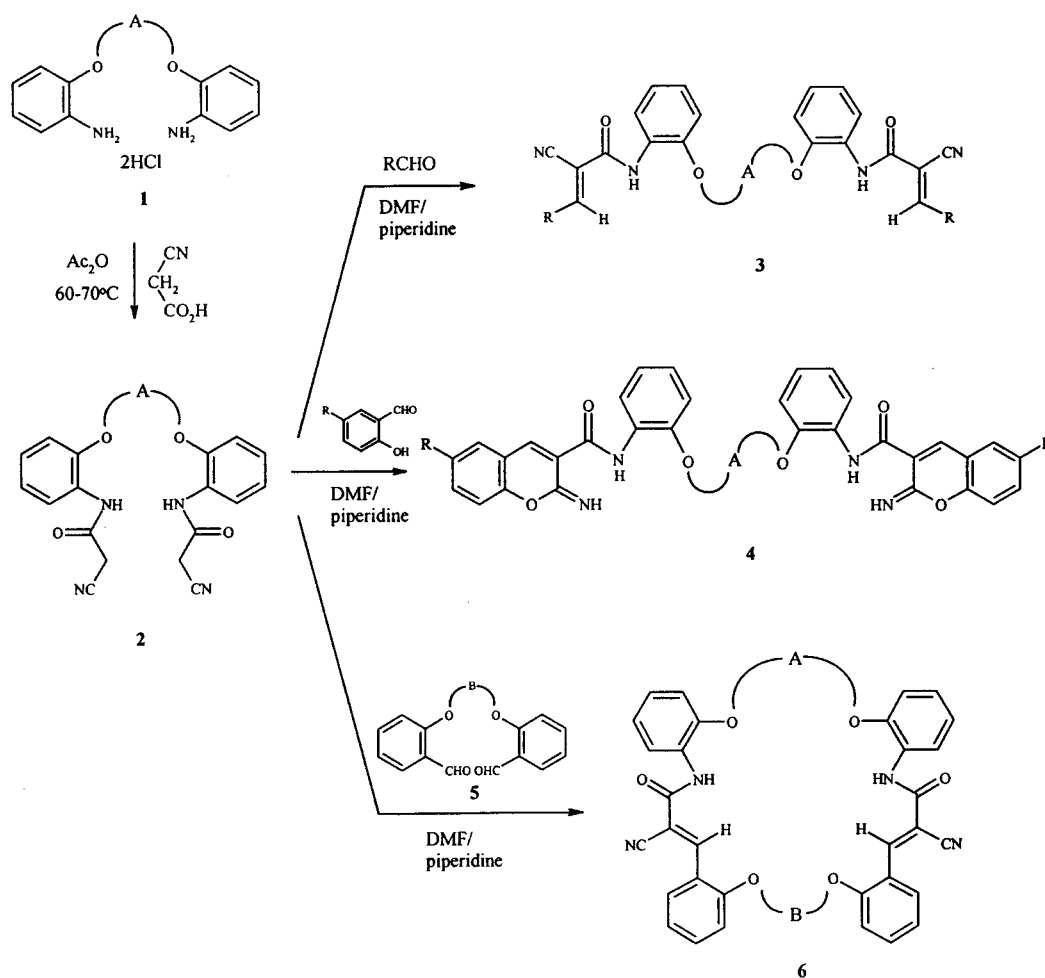
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A facile synthetic approach was adopted towards the synthesis of 26–28 membered benzo-fused macrocycle diamides **6a–d** via the base-catalyzed condensation reaction of 2,2'-[alkylbis(oxy)]bisbenzaldehydes **5** with bis-cyanoacetanilides **2** which had been obtained by the reaction of cyanoacetic acid with 2,2'-[alkylbis(oxy)]bisbenzenamines **1**.

Interest has progressively increased over the last few years in the chemistry of macrocycles, particularly oxa–aza macrocycles, due to their successful utility as ligands forming complexes with many metal ions (e.g. nickel,^{1–6} cobalt,^{4–8} copper,^{4–6, 9, 10} cadmium^{4,9} and mercury⁴). In the light of the previous reports, it is intended in the present work to investigate

the synthesis of new benzo-fused macrocycle diamides by a simple and facile synthetic approach.

Reaction of 2,2'-[alkylbis(oxy)]bisbenzenamine hydrochlorides **1a,b** with cyanoacetic acid in acetic anhydride at 60–70°C afforded exclusively the corresponding biscyanoacetanilide derivatives **2a,b**. The structure **2** was established



1a, 2a, 5a; A = (CH₂)₃

1b, 2b, 5b; A = (CH₂)₄

3a; R = Ph, A = (CH₂)₃

3b; R = Ph, A = (CH₂)₄

3c; R = 4-ClC₆H₄, A = (CH₂)₃

3d; R = 4-ClC₆H₄, A = (CH₂)₄

3e; R = 4-H₃COC₆H₄, A = (CH₂)₃

3f; R = 4-H₃COC₆H₄, A = (CH₂)₄

4a; R = H, A = (CH₂)₃

4b; R = H, A = (CH₂)₄

4c; R = Cl, A = (CH₂)₃

4d; R = Cl, A = (CH₂)₄

6a; A = B = (CH₂)₃

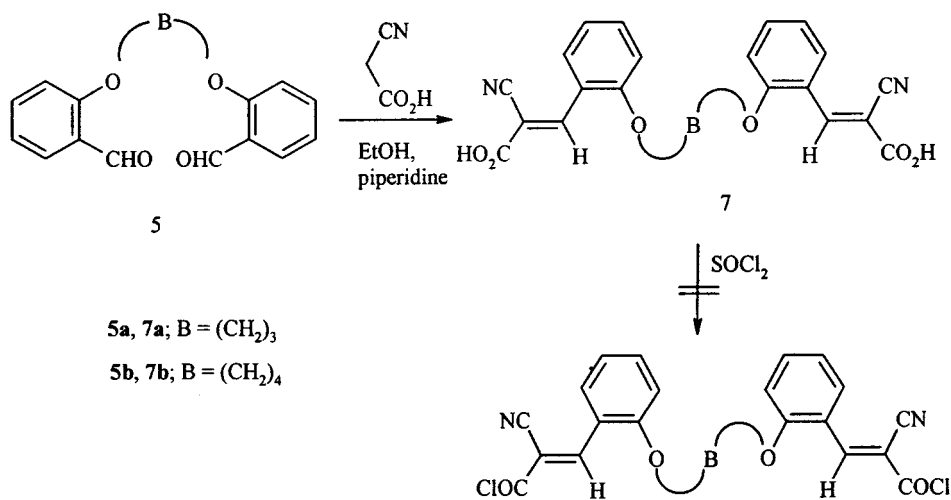
6b; A = (CH₂)₃, B = (CH₂)₄

6c; A = (CH₂)₄, B = (CH₂)₃

6d; A = B = (CH₂)₄

Scheme 1

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Scheme 2

through IR, ¹H-NMR, mass spectra as well as elemental analysis data. The IR spectra of **2a,b** reveal the presence of the stretching vibration bands of both the nitrile and carbonyl functions. Also, ¹H-NMR spectra of **2** exhibit the presence of the methylene protons at (δ) 3.99.

Reaction of **2a,b** with a variety of aromatic aldehydes (namely benzaldehyde, *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde) in the presence of piperidine as a basic catalyst gave the corresponding arylidenes **3a-f**. The structure **3** was inferred from different spectroscopic and analytical analysis data. The ¹H-NMR spectra of **3a-f** reveal the absence of the activated methylene group and exhibit the presence of the ylidene olefinic protons at (δ) 8.3–8.41. The appearance of the olefinic proton signal at this chemical shift value indicates that the methine proton is located in a *trans* position to the nitrile group.¹⁹

On the other hand, reaction of **2a,b** with (un)substituted salicylaldehydes afforded the corresponding bis(2-imino-2H-[1]benzopyran) derivatives **4a-d**. The reaction probably takes place by condensation of the aldehydic group with the methylene function followed by nucleophilic attack of the hydroxyl group on the neighbouring nitrile residue giving eventually **4**. The absence of the nitrile group in the IR spectra of **4** confirms its involvement in the cyclization process. The isolation of the benzopyrans **4** from the reaction confirms the intermediacy of the geometrical isomer **3** during the reaction course. In other words, the nitrile group must be in a *trans* position to the olefinic proton in the intermediate ylidene structure as only this geometrical isomer can easily undergo cyclization to the corresponding benzopyran **4**.

Meanwhile, reaction of **2a,b** with acyclic dialdehydes **5a,b** in dimethylformamide solution in the presence of a catalytic amount of piperidine (under the high dilution technique which was often used as the most versatile procedure) gave the corresponding macrocyclic diamides **6a-d**. The structure **6** was established through IR, ¹H-NMR, mass spectra and elemental analysis data. The downfield shift of the olefinic proton resonance in **6** (δ = 8.92–8.96) compared with the corresponding **3** could be attributed to the effect of the alkoxy group attached to the *ortho*-position of the olefinic linkage¹⁹.

An attempt was made to prepare the oxa-aza macrocycles **6** by an alternative pathway by the reaction of bisbenzenamines **1** with the appropriate acid chloride. Thus, the bis-2-propenoic acids **7** (prepared by condensation of the corresponding aldehyde **5** with cyanoacetic acid) were boiled under reflux with thionyl chloride for a prolonged time but failed to give the corresponding acid chlorides and the acids **7** were recovered unchanged (Scheme 2).

Techniques used: Elemental analysis, IR, ¹H-NMR and MS.

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