Synthesis of 2,8-diamino-5-hydroxy-4*H*,10*H*-pyrano[2,3-*f*]chromene-3,9-dicarbonitriles

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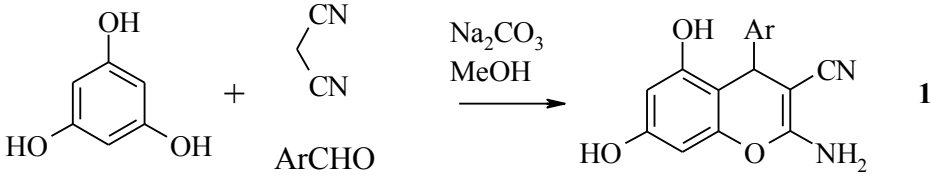
Abstract: The reactions of phloroglucinol with α,β-unsaturated dinitriles (or malononitrile and carbonyl compounds) lead to the formation of hitherto unknown 2,8-diamino-5-hydroxy-4H,10H-pyrano[2,3-*f*]chromene-3,9-dicarbonitriles. The reaction conditions and the structure of the products were studied in details.

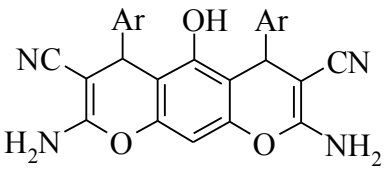
Keywords: phloroglucinol, malononitrile, isatin, NMR studies, X-ray studies, 2-amino-4H-pyran-3-carbonitrile, pyrano[2,3-*f*]chromene.

The great interest in the chemistry of 2-amino-4*H*-chromenes, especially those bearing the nitrile group at the 3-position is essentially inspired by the availability of this class of compounds – on the one hand, and biological activity of many 2-amino-4*H*-chromenes – on the other. The chemistry of 2-amino-4*H*-chromenes have been reviewed [1-3]. As it was reported in the literature [4], the reaction of benzaldehydes and malononitrile with phloroglucinol taken in the ratio 1 : 1 :1 leads to the formation of 2-amino-3-cyano-4H-chromenes **1**:



1

Since phloroglucinol could be considered as a tautomeric form of cyclohexan-1,3,5-trione, one may suggest that phloroglucinol may react with activated nitriles to form three- or tetracyclic pyran compounds. We decided to study the reaction in order to obtain products with the proposed structures **2-4**:



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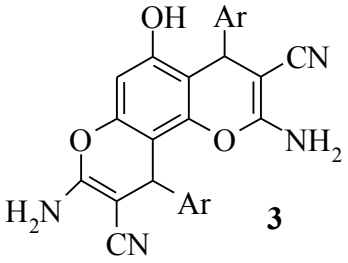

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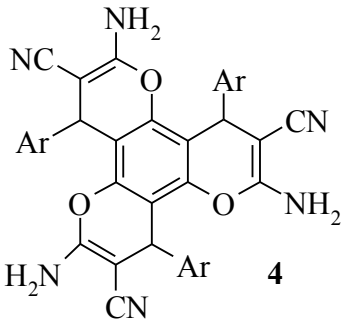
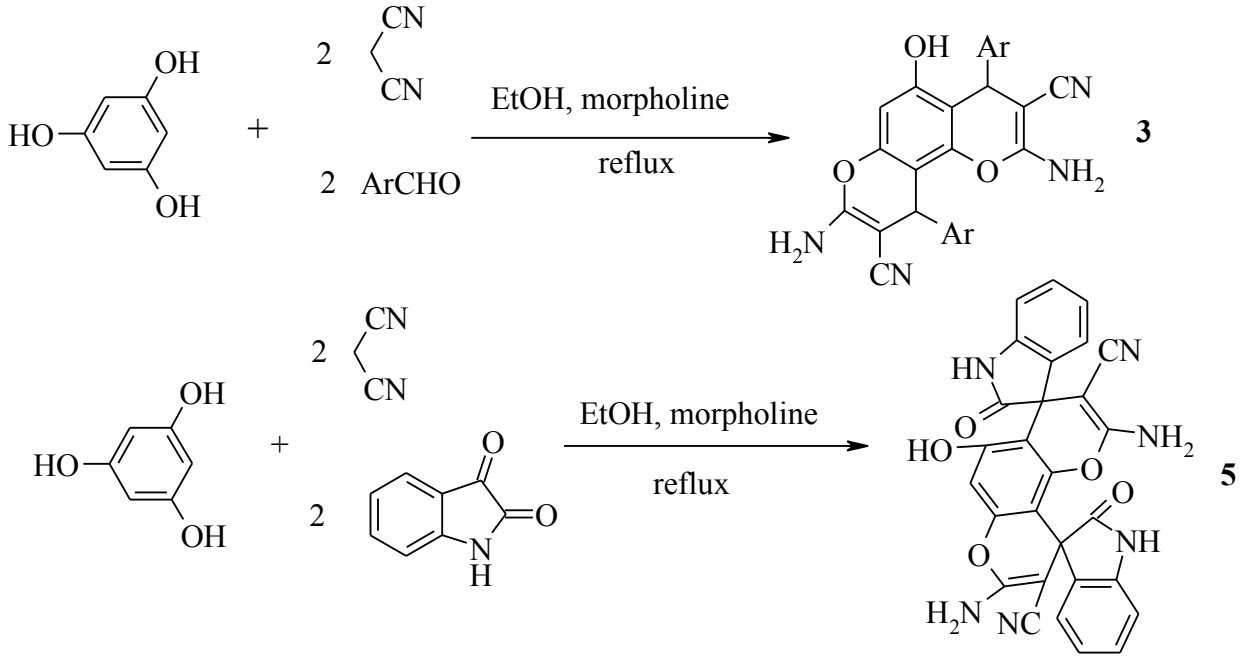


4

It was found that when phloroglucinol reacted with malononitrile and aromatic aldehydes taken in a ratio of 1 : 2 : 2, or with arylmethylene malononitriles in a ratio of 1 : 2, both in the presence of catalytic amounts of morpholine in boiling EtOH – the same products with the possible pyranochromene structures **2** and **3** were formed. The choice between two possible structures – linear **2** and angular one **3** – was made in favor of the angular structure **3** on the basis of NMR spectroscopy. Isatin as an active carbonyl compound was reacted with malononitrile and phloroglucinol in hot EtOH to afford spirocyclic pyranochromene **5** in 47% yield.



Ar = 4-$MeOC_6H_4$, 3-pyridyl.

Thus, the ^{1}H NMR spectrum of crude compound **3a** (obtained from the reaction of 2 eq. 4-(methoxybenzylidene)malononitrile with phloroglucinol) revealed the doubling of both the aryl protons signals and chromene proton H-4. Such a spectrum is impossible for symmetric linear structures like pyranochromene **2**. Figure 1 shows a fragment of the ^{1}H NMR spectrum of crude compound **3a**. Thus, the presence of two different signals for H-4 protons of 4H-pyran ring at δ 4,45 ppm and 4.68 ppm clearly indicates their non-equivalence, and thus confirms the asymmetric structure of the product. It should be noted that only one signal corresponding to OH group was observed at δ 10,00 ppm, and one signal of an aryl

proton only was observed at δ 6,28 ppm, whereas the signals of the aromatic substituents are doubled. Pyridine-3-carbaldehyde as well as it's condensation product with malononitrile were found to react the same way. Thus, compound **3b** was obtained in 70% yield when phloroglucinol was reacted with two equivalents of malononitrile and pyridine-3-carbaldehyde.

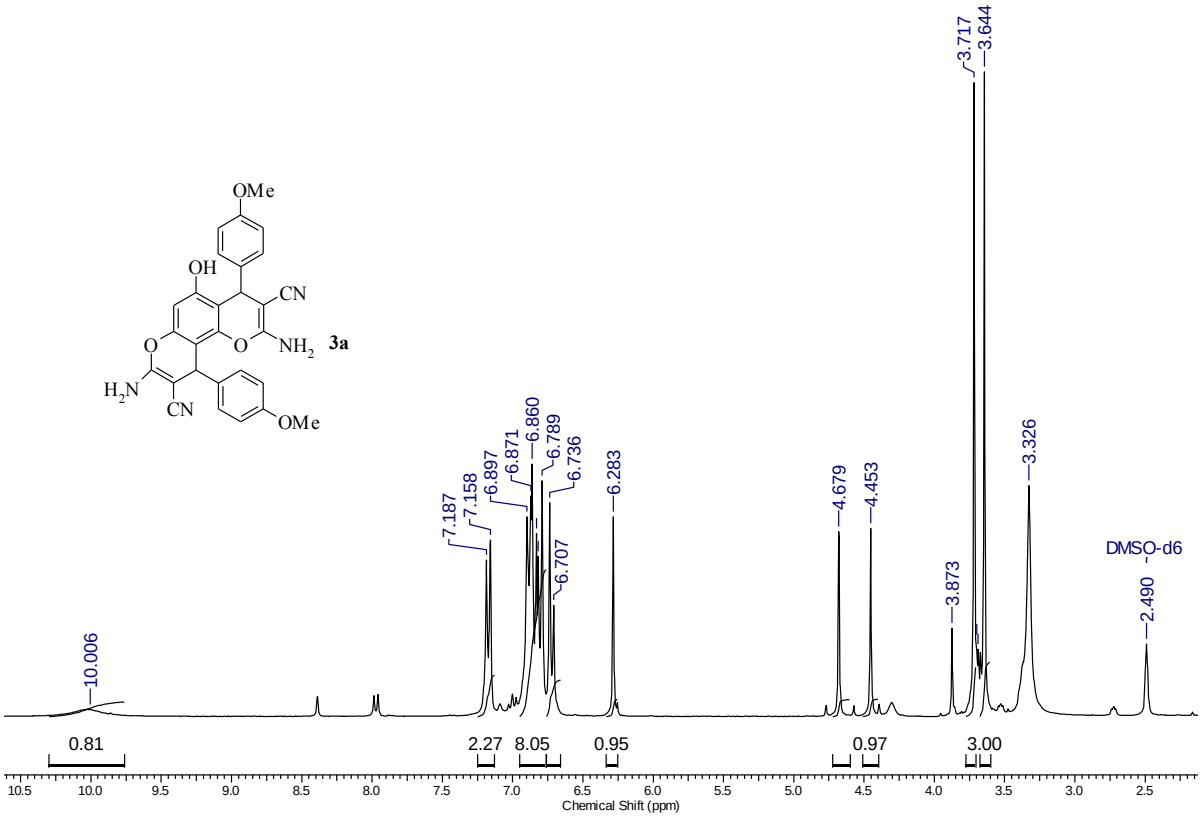
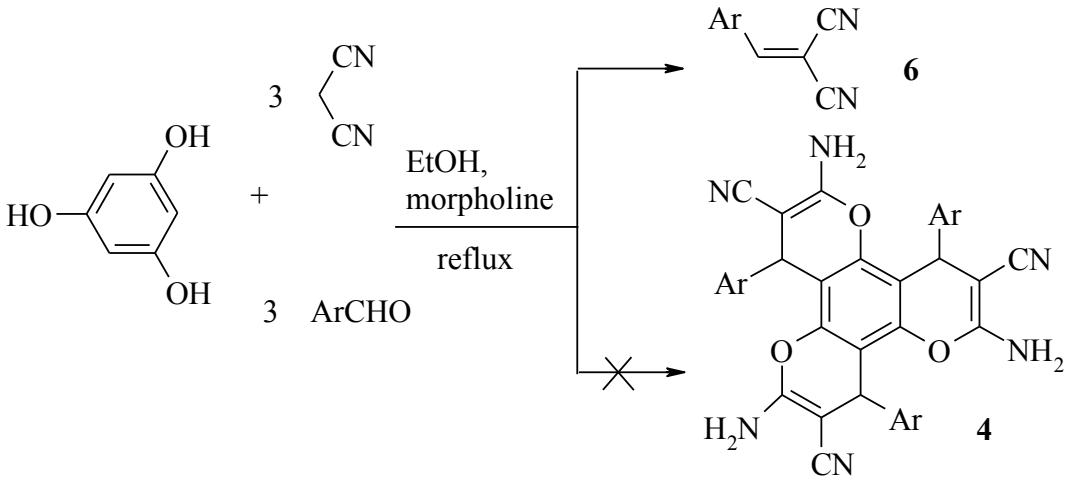


Fig. 1. The fragment of the ^{1}H NMR spectrum of crude **3a**.

We failed to obtain tetracyclic compounds **4** from the reaction of phloroglucinol with malononitrile and aromatic aldehydes taken in a ratio of 1 : 3 : 3 under the same conditions. In this case, the sole products isolated were arylmethylene malononitriles **6**.



6 Ar = Ph, 4-AcNHC$_6$H$_4$, 2-furyl.

Aliphatic aldehydes do not react under these conditions to give pyranochromenes. The structure of the obtained compounds was confirmed by means of NMR, FTIR and LCMS. The structure of the condensation product **6b** was studied by X-ray analysis (Figure 2).

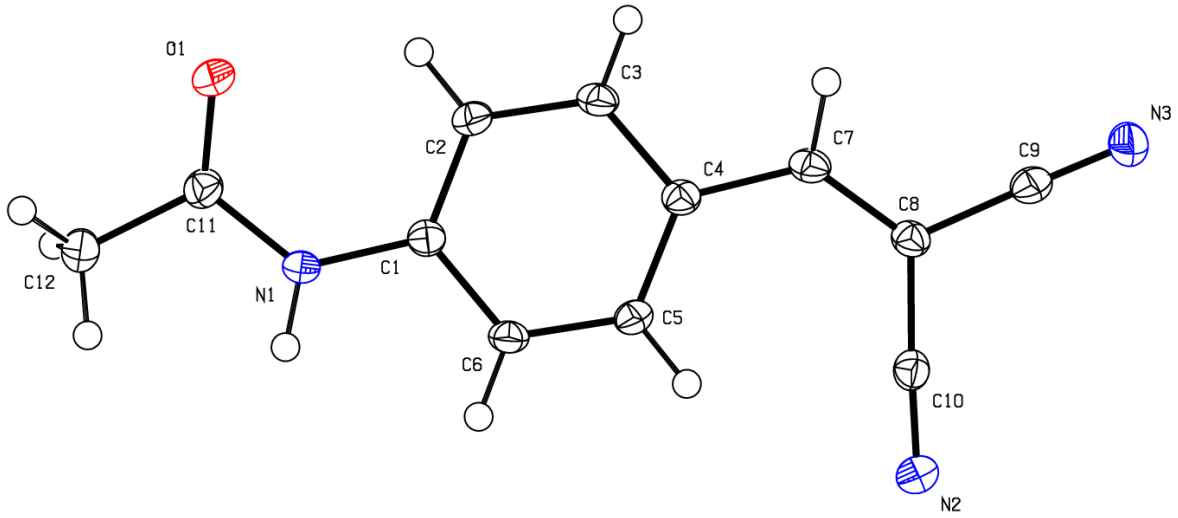
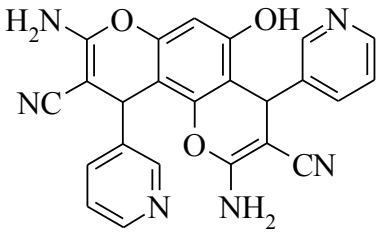


Fig. 2. The structure of 4-AcNHC$_6$H$_4$CH=C(CN)$_2$.

Typical experimental procedure

Synthesis of 2,8-diamino-5-hydroxy-4,10-di(3-pyridyl)-4*H*,10*H*-pyrano[2,3-*f*]chromen-3,9-dicarbonitrile.



A round bottom 50 mL flask was charged with malononitrile (0.4 g, 0.00606 mol), pyridine-3-carbaldehyde (0.57 ml, 0.00606 mol) and EtOH (10 mL). Then 2 drops of morpholine were added, and, after 5 minutes – 0.38 g (0.00303 mol) of phloroglucinol. The reaction mixture was refluxed for 6 h. Upon cooling, the beige solid precipitated. The precipitate was filtered off and washed with EtOH and BuOH to give 0.96 g (70%) of **3b**.

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