Scientific and technical report

Financing contract

Project title: The synthesis of new hybrid [2.2]paracyclophane-flavonoids systems with potential antimicrobial activity

Project code: PN-III-P1-1.1-PD-2016-0962

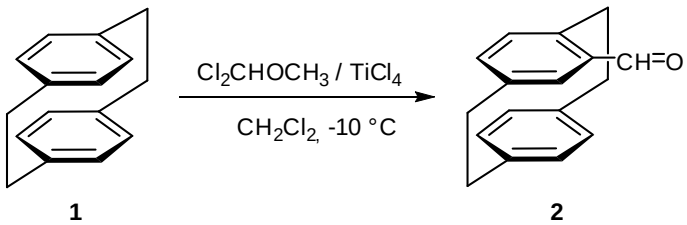
Acronym: [2.2]PC-Flav

No. 48/2018

Synthesis of 1,3-dithiolium flavonoids linked to [2.2]paracyclophane moiety and evaluation of their stability

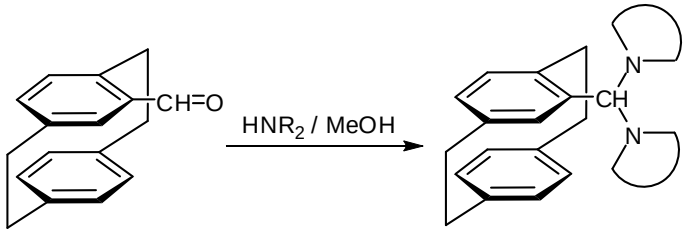
Stage 1 2018

The first step in the synthetic pathway of 1,3-dithiolic flavonoids consists in the functionalization of [2.2]paracyclophane in the sense of introducing the formyl group according to the Rieche method. Thus, treatment of [2.2]paracyclophane **1** with dichloromethyl-methylether in the presence of Lewis acid ($TiCl_4$) at -10 °C gives 4-formyl[2.2]paracyclophane **2** (Scheme 1).



Scheme 1

One of the methods of activating the formyl function is to convert it into an aminal by treatment with a secondary amine. Following this strategy, the reactivity of 4-formyl[2.2]paracyclophane **2** against different secondary amines, i.e. morpholine, piperidine, pyrrolidine, diethylamine and dimethylamine, was tested in accordance with Scheme 2.



2 **3**

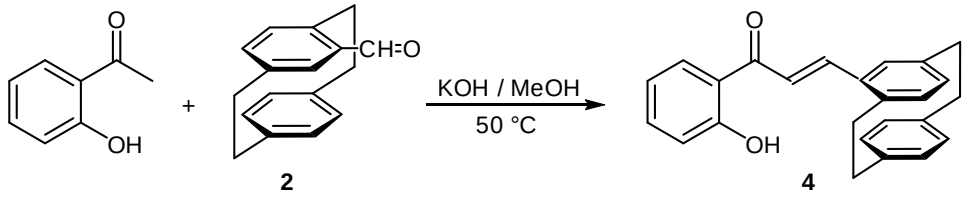
Scheme 2

In contrast to the general chemical behavior of the carbonyl group when reacted with secondary amines, 4-formyl[2.2]paracyclophane **2** exhibits low reactivity when subjected to the same type of reaction. This is most likely due to steric hindrance generated by the ethylene bridge in the proximity of the formyl group. Thus, in situations when morpholine, piperidine, pyrrolidine and diethylamine did not give the corresponding aminal 3, *N*,*N*-dimethylamine proved to be an option worth investigating. When a 2M *N*,*N*-dimethylamine methanol solution was used, it was observed that the corresponding aminal formed slowly, the yield after 8 days being of about 4-5%. The low yield of this reaction has generated two different strategic approaches for the synthesis of tricyclic flavonoids:

- The first consists in the catalyzed synthesis of bis(*N*,*N*-dimethyl)aminal **3** in order to increase the yield for the optimization of the production of the target compounds. These investigations are ongoing.

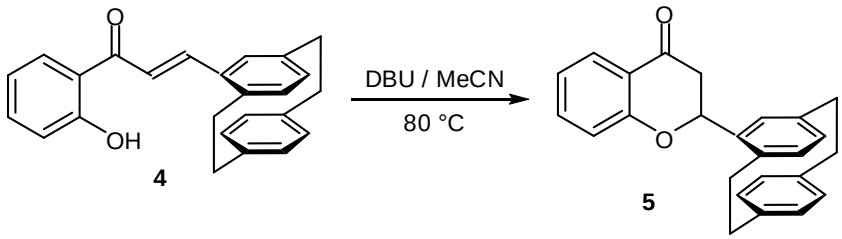
- Use of an alternative synthetic strategy avoiding the use of aminals through direct condensation of 2-hydroxyacetophenones with 4-formyl[2.2]paracyclophane **2**.

Treatment of 2-hydroxyacetophenone with 4-formyl[2.2]paracyclophane in methanolic potassium hydroxide solution yields the corresponding chalcone **4** (Scheme 3). The E configuration for this compound has been attributed as a result of the coupling constants of the olefinic protons around the newly formed double bond.



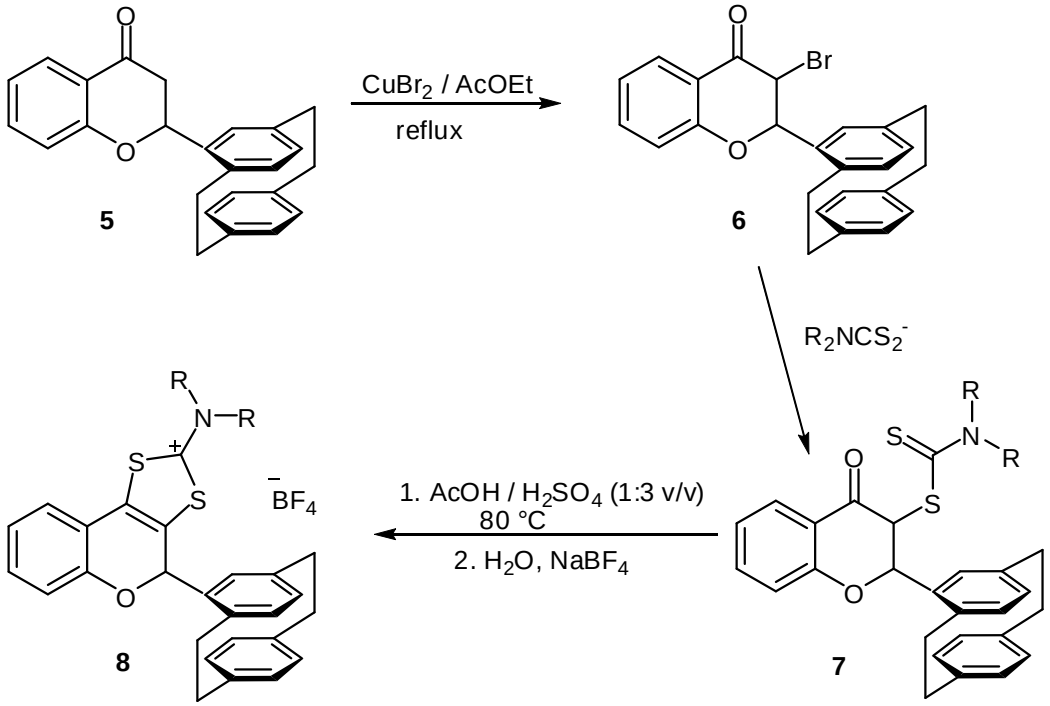
Scheme 3

According to literature data, the intramolecular condensation of type **4** chalcones should lead to the corresponding benzopyrans, important precursors for the synthesis of the tricyclic flavonoids. Preliminary optimization of the reaction conditions showed that the benzopyrane **5** heterocyclization takes place in low yield using DBU as catalyst (Scheme 4).



Scheme 4

Selective bromination of benzopyran **5** with $CuBr_2$ in ethyl acetate gave bromoderivative **6** which was subjected to treatment with various salts of dithiocarbamic acid, to give dithiocarbamates **7** (Scheme 5). Five different dithiocarbamates, morpholinium 4-morpholinyldithiocarbamate, piperidinium 1-piperidinyldithiocarbamate, pyrrolidinium 1-pyrrolidinyldithiocarbamate, sodium *N,N* -diethyldithiocarbamate and dimethylammonium *N,N*-dimethyldithiocarbamate were used for further evaluation of their biological activity.



Scheme 5

The 3-dithiocarbamylbenzopyranes **7** were cyclized in the presence of a sulfuric acid - acetic acid mixture (1:3 v/v) in order to obtain tricyclic flavonoids **8**. These were isolated as tetrafluoroborates to avoid any solubility problems in order to perform biological tests.