P23

Synthesis of Quinolin-2-ones and Cinnamamides from Derivatives of Malonanilic Acid

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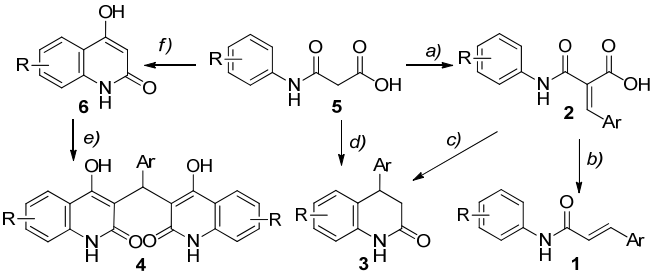
It is well known that avenanthramides – cinnamoyl antranilates – demonstrate a wide range of biological activities; antioxidant and antiradical activities are the most commonly studied ones. We were interested in clarifying the effect of substituents in both aniline and cinnamic acid rings on the antiradical activity: we already described the influence of position of carboxylic group (in aniline ring), as well as the effect of hydroxy and methoxy groups (in the aromatic moiety of cinnamic acid) on the antiradical activity of compounds **1** [1]. Herein, the impact of electron donor substituents in the aniline ring of compounds **1** on the antiradical activity of cinnamoyl anilines will be analyzed; besides, their close structural analogues **2** containing carboxylic group will also be discussed. According to literature data, 4-aryl-3,4-dihydro-1*H*-quinolin-2-ones **3 –** cyclization products of compounds **1** and **2** – demonstrate atypical antipsychotic, antiproliferative and anticonvulsant activities, act as inhibitors of p38 MAP kinase and blood coagulant factor Xa and as antidepressants. This encouraged us to establish how the cyclization of cinnamic anilides **1** leading to quinolinones **3** affect the antiradical activity of these compounds. Moreover, radical scavenging activity of similar 2,4-(1*H*,3*H*)-quinolinediones **4** was tested.

We used as raw material for synthesis of target compounds **1-4** *N*-aryl-malonmonoamides **5**, which were obtained by acylation of correspondingly substituted aniline with Meldrum's acid in water under reflux. This method has two important advantages: first, decarboxylation of products **5** is negligible (experiments with various polar and nonpolar solvents at different reaction temperatures showed that compounds **5** easily underwent decarboxylation forming corresponding acetanilides) and, secondly, in case of aminophenols, monoanilides **5** were formed as major products.

Anilides **2** were synthesized from malonanilic acids **5** and aromatic aldehydes *via* Knoevenagel condensation. We carried out this procedure in glacial acetic acid at 75°C. The duration of reaction varied from 7 up to 40 hours and the isolated yield of 2-arylidenemalonanilic acids **2** was approximately 70%; decarboxylation of compounds **5** in acetic acid was minimal. We established that compounds **2** could be easily converted to cinnamoyl anilines **1** in good yields by reflux in pyridine.

The treatment of compounds **2** with trifluoroacetic acid provided 4-aryl-3,4-dihydro-1*H*-quinolin-2-ones **3**. For the first time, the Knoevenagel condensation of malonanilic acids **5** with aromatic aldehydes and following intramolecular cyclization and decarboxylation of intermediates was carried out as one-pot procedure.

The target heterocycles of our interest - bis(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)arylmethanes **4** were obtained by condensation of quinolinediones **6** with aromatic aldehydes in pyridine under reflux. Compounds **6** were prepared by heating of malonanilic acids **5** in Eaton's reagent at 60°C.



Scheme 1. Synthetic transformations of malonanilic acids

DPPH test of radical scavenging activity of compounds **1-4** was carried out. We established that the inhibition of DPPH (molar ratio antioxidant: DPPH = 1:1) in case of compounds containing as Ar group vanillin moiety and methoxy group in *p*-position of aniline ring decreased in the following order: **4** > **1** > **2** > **3**. It was observed that IC_{50} value increased as follows: **1** < **2** < **4**. The negligible antiradical activity for quinolinone **3** was unexpected in comparison with other vanillin derivatives; for it these compounds demonstrated some antioxidant-prooxidant effect depending on concentration. Compounds **1** and **2** apparently acted as classical phenol type antioxidants; the increased activity of compounds **4** (the IC_{50} value was 2.5 to 3 times greater than that for compounds **1** and **2**, respectively) was most likely due to synergism of two characteristic functional groups of antioxidants – polyphenolic and enolized 1,3-dicarbonyl fragment. We conclude that all compounds **1-4** are riveting due to their antiradical activity, but quinolinone derivatives **3** and **4** are particularly interesting.

Supervisor: Dr.chem., prof. M.Jure.

ACKNOWLEDGEMENTS

The authors thank *JSC Olainfarm* for scholarship granted to A. Stikute.

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