Synthesis of new pyrano[3,2-c]chromenes

Alina A. Machukha[1], Victor V. Dotsenko[1,2]*, Gennady D. Krapivin[3], Inna V. Aksenova[4], Nikolai A. Aksenov[4], Vladimir D. Strelkov[1,5]

[1]Kuban State University, 149 Stavropolskaya str, Krasnodar, 350040 Russia
e-mail: victor_dotsenko@bigmir.net
[2]ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, Lugansk, 91034 Russia
[3] Kuban State Technological University, 2 Moskovskaya st., 350072 Krasnodar, Russia
[4]Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia
[5]All-Russian Research Institute of Biological Plant Protection, Laboratory of plant growth regulators, 350039 Krasnodar, Russia

Abstract

The reaction of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione with aldehydes and malononitrile afforded new pyrano[3,2-c]chromenes. Upon treatment of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione with anilines and triethyl orthoformate, new 3-anilinomethylidene 7,8-dihydro-2H-chromen-2,4,5(3H,6H)-triones were synthesized.

Keywords

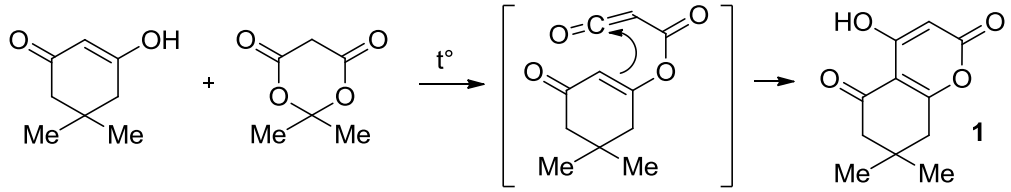
malonyl heterocycles, Meldrum's acid, dimedone, 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione, pyrano[3,2-c]chromenes

Cyclic malonates/malonamides and related compounds (such as barbituric acids, Meldum's acid, 4-hydroxypyran-2-ones) which are known under common name of "malonyl heterocycles" – have been recognized as very useful reagents in the field of organic synthesis [1-5]. While continuing research in the chemistry of 2-amino-3-cyano-4H-pyrans, we decided to study the reactivity of certain malonyl heterocycles with aldehydes and malononitrile (or their Knoevenagel-type products). Interest in the chemistry of 2-amino-4*H*-pyrans, especially those bearing the nitrile group at the 3-position is essentially inspired by their availability on the one hand, and

biological activity of many 2-amino-3-cyano-4*H*-pyrans – on the other. The chemistry of 2-amino-4*H*-pyrans have been reviewed [6-8].

We have focused our attention primarily on the chemistry of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1**. Compound **1** was first prepared by Ziegler, Junek and Herzog [9] by fusing dimedone with Meldrum's acid for 10 min. However, in our hands the described procedure was found to be inconvenient and hardly reproducible, and product **1** have been prepared in broadly varying yields and purity. We have developed the conditions that gave the desired 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** in very good yields (up to 90%, Scheme 1); the full experimental details will be reported elsewhere.

Scheme 1



The compound **1** could be recrystallized from ethyl acetate to form very nice, large orange crystals (Figures 1, 2). The structure of compound **1** was studied by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, HPLC-MS, and confirmed by X-ray data (Fig. 3).

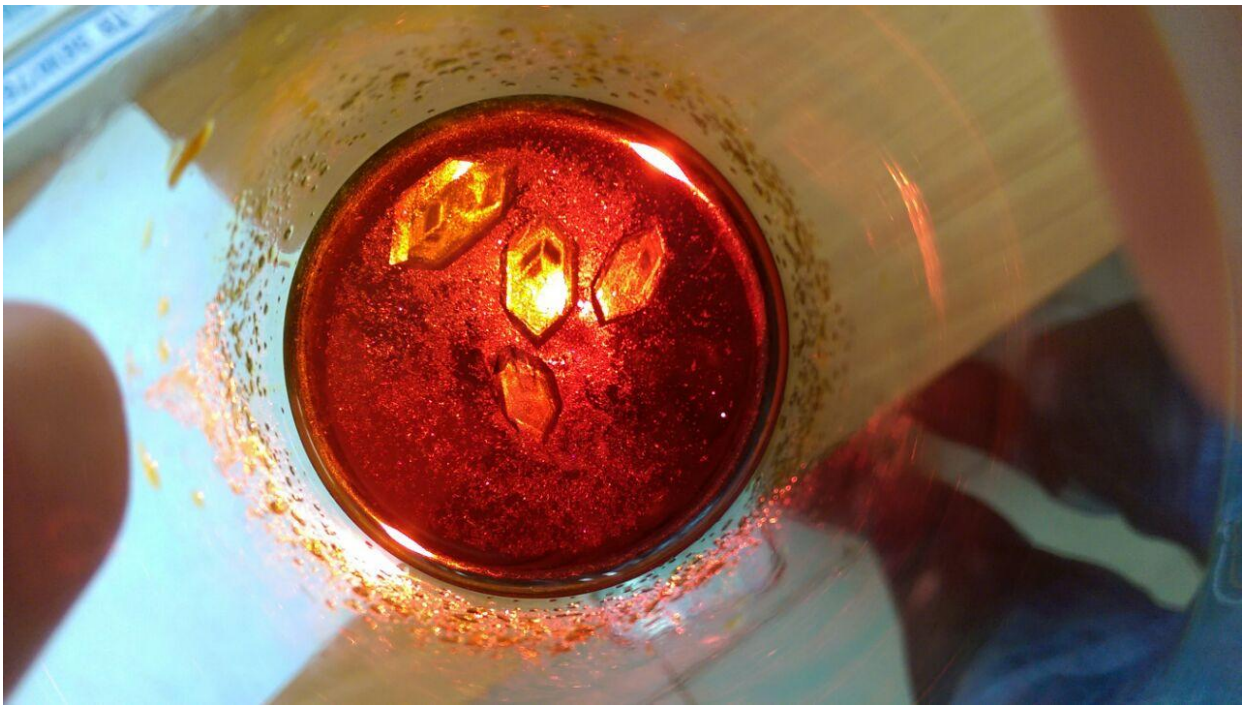


Figure 1. The crystals of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** precipitated from EtOAc solution.

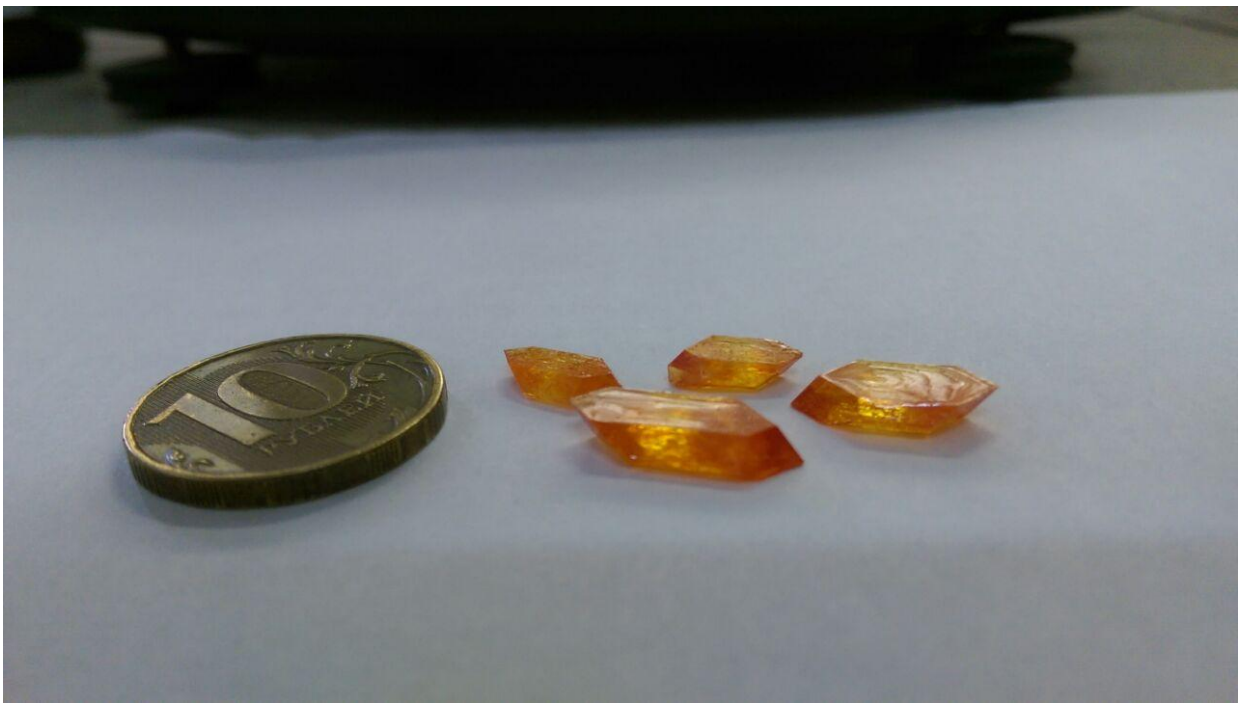


Figure 2. The crystals of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** in comparison with a ten rubles coin (diameter – 22 mm).

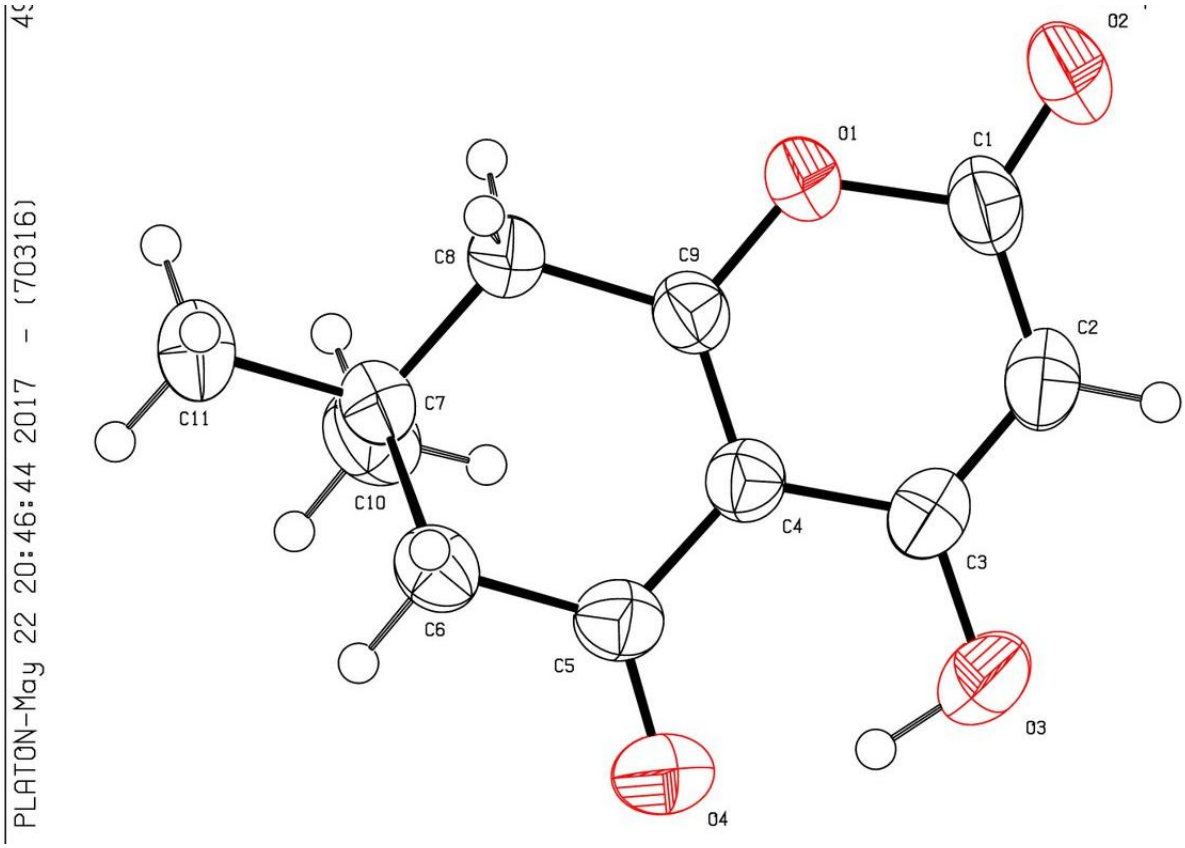
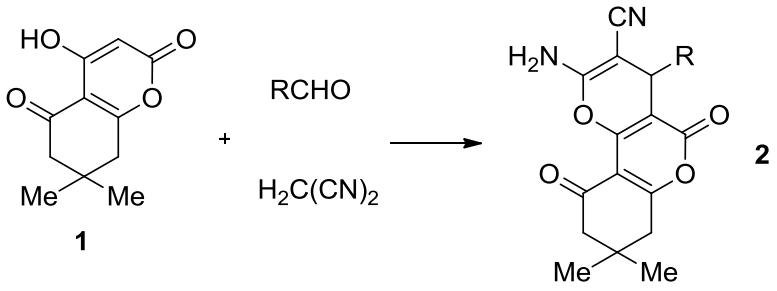
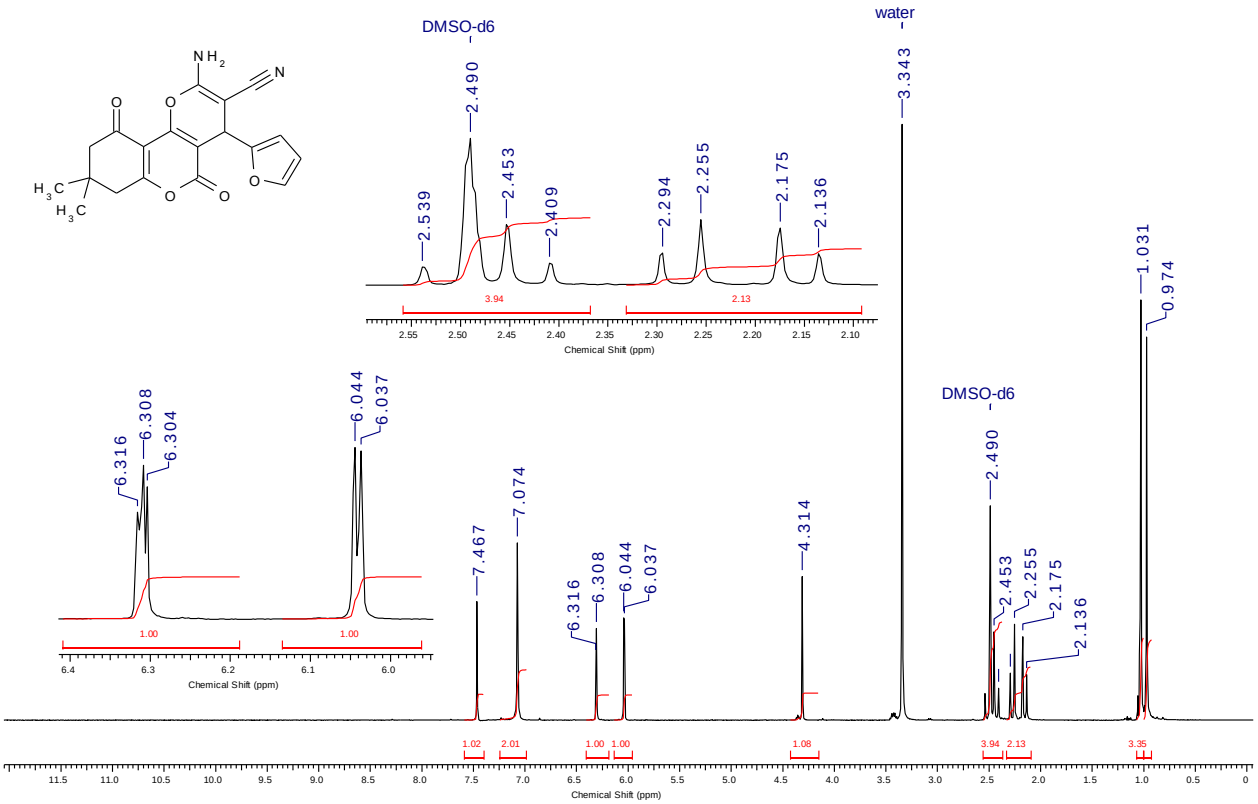


Figure 3. The structure of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** (by X-ray).

With a convenient procedure for the preparation of compound **1** in hands, we have studied the synthesis of condensed analogs of 2-amino-3-cyano-4H-pyrans. When compound **1** was reacted with malononitrile and aldehydes in the presence of amines as a base, new pyrano[3,2-c]chromenes were obtained.



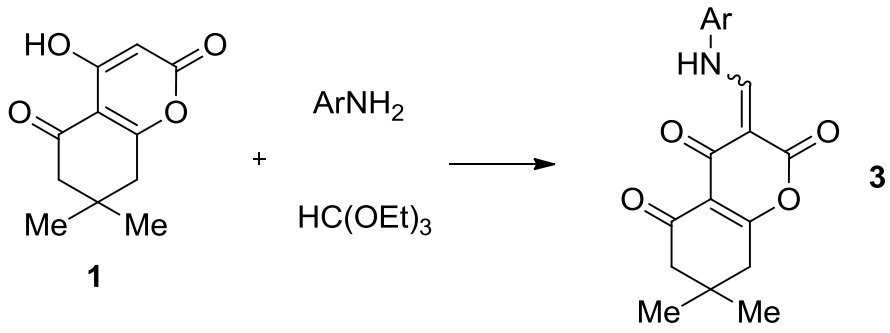
The structure of compounds **2** were confirmed by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy (Fig. 4), HPLC-MS data.



^{1}H NMR spectrum (400 MHz, DMSO-d_6) of 2-amino-4-(2-furyl)-8,8-dimethyl-5,10-dioxo-7,8,9,10-tetrahydro-4*H*,5*H*-pyrano[3,2-c]chromene-3-carbonitrile

Next we studied the reaction of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** with triethylorthoformate and primary amines. The reaction of active methylenes $HC(OEt)_3$ and RNH_2 was first described by Snyder and Jones [10] in 1946. To date, this approach has proven to be simple and excellent method for the synthesis of various β-enamino-carbonyls and -

nitriles. When **1** was fused with $HC(OEt)_3$ and anilines, yellow products **3** were isolated in good yields. The structure of compounds **3** were confirmed by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy.



Experimental

*Preparation of pyrano[3,2-c]chromenes **2***

A 10-ml round bottom flask was charged with malononitrile (0.86 g, 1.2 mmol), EtOH (3 mL), aldehyde (1.2 mmol), 2 drops of morpholine (or Et_3N), and 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** (1.2 mmol). The mixture was stirred until complete dissolution of the starting reagents, then refluxed for 10-30 min (a white precipitate is formed). The solid was filtered off, washed with cold EtOH and petroleum ether to give **2**.

*Synthesis of enamines **3***

A mixture of 4-hydroxy-7,7-dimethyl-7,8-dihydro-6H-chromen-2,5-dione **1** (0.416 g, 2.0 mmol), $HC(OEt)_3$ (3.0 mmol) and corresponding aniline (2.0 mmol) were melted for 1 min, the hot melt was treated with n-BuOH. The obtained yellow/orange solid was filtered off, washed with n-BuOH and petroleum ether to give pure **3**.

References

1. W. Stadlbauer, E.-S. Badawey, G. Hojas, P. Roschger and Th. Kappe. Malonates in Cyclocondensation Reactions // Molecules, 2001, 6, 338-352.

2. D. V. Novikov, I. P. Yakovlev, V. E. Zakhs, and A. V. Prep'yalov. Synthesis, Properties, and Biological Activity of 4-Hydroxy-2H-Pyran-2-ones and Their Derivatives // Russian Journal of General Chemistry, Vol. 72, No. 10, 2002, pp. 1601-1615.

3. Bang-Chi Chen. Meldrum's acid in organic synthesis // Heterocycles. Vol. 32, No. 3, 1991. Pp 529-597.

4. V. V. Lipson, N. Yu. Gorobets. One hundred years of Meldrum's acid: advances in the synthesis of pyridine and pyrimidine derivatives // Molecular Diversity, 2009, Vol. 13, pp 399–419.

5. A. V. Moskvin, N. R. Reznikova, and B.A. Ivin. Condensation of Hydroxypyrimidines with Carbonyl Compounds: I. Barbituric Acids // Russian Journal of Organic Chemistry, Vol. 38, No. 4, 2002, pp. 463-474

6. Yu A Sharanin, M P Goncharenko, V P Litvinov. Reactions of carbonyl compounds with a,b-unsaturated nitriles as a convenient pathway to carbo and heterocycles// Russian Chemical Reviews – 1998, Vol. 67. – No. 5. –pp. 393 – 422.

7. Ahmed M. El-Agrody and Tarek H. Afifi. The reactivity of 8-hydroxyquinoline and its derivatives toward α-cyanocinnamonitriles and ethyl α-cyanocinnamates: synthesis, reactions, and applications of 4H-pyrano[3,2-h]quinoline derivatives // Heterocycles – 2014, Vol. 89 - №. 7. - pp. 1557-1584.

8. Yuri M. Litvinov and Anatoliy M. Shestopalov. Synthesis, Structure, Chemical Reactivity, and Practical Significance of 2-Amino-4H-pyrans. In Advances in Heterocyclic Chemistry (ed. A. R. Katritzky), 2011, Vol. 103, p. 175.

9. E. Ziegler, H. Junek and U. Herzog. Zur Chemie der Meldrumsäure. Synthesen von Heterocyclen, 157. Mitt. // Monatshefte für Chemie, 1971, Vol 102, Issue 5, pp 1626–1630.

10. H. R. Snyder, R. Jones, Synthesis of 4-Hydroxyquinolines. A Direct Synthesis of p-Substituted Acrylic Esters // J. Am. Chem. Soc., 1946, 68 (7), pp 1253–1255.