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Reactions of 3-functionalized chromones with triacetic acid lactone

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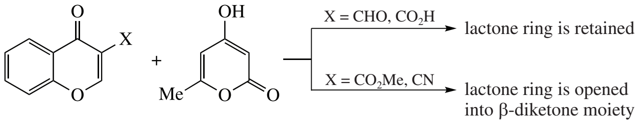
Reaction of 3-formylchromones and triacetic acid lactone proceeds with retention of the chromone skeleton and cyclization into pyrano[3′,4′:5,6]pyrano[2,3-*b*]chromene system. The crystal structure of the reaction product from unsubstituted 3-formylchromone has been determined from X-ray data. Other chromone analogues bearing CO_2H, CO_2Me and CN substituents react with triacetic acid lactone affording an *o*-hydroxychalcone heteroanalogue, pyrano[3,2-*c*]chromene and chromeno[2,3-*b*]pyridine derivatives, respectively.

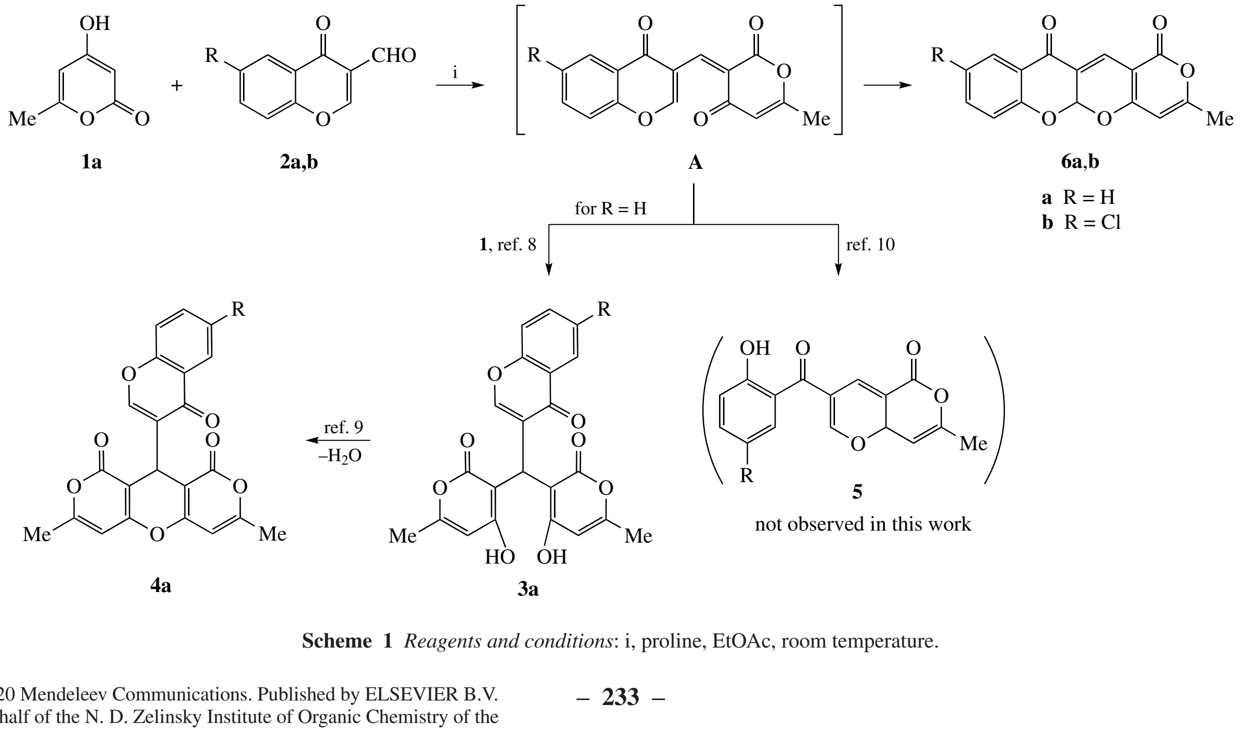


Keywords: chromones, triacetic acid lactone, nucleophilic reactions, heterocyclization, pyrano[3′,4′:5,6]pyrano[2,3-*b*]chromenes, pyrano[3,2-*c*]chromenes, chromeno[2,3-*b*]pyridines.

Chromone and its derivatives, especially flavones and isoflavones, belong to one of the most common natural heterocyclic systems. They exhibit various types of biological activity and are widely used as building blocks in the preparation of new pharmaceuticals and more complex heterocycles with useful properties.[1] The reactivity of the chromone system is determined mainly by the nature and position of a substituent in the pyrone ring and depends on spatial availability and electrophilicity of the C^2 atom. In this regard, chromones with electron-withdrawing group in 3-position and no substituent at the C^2 atom are the most reactive ones towards nucleophiles.[2]

On the other hand, triacetic acid lactone **1** is known to have diverse reactivity.[3] Its reactions with electrophiles are successfully employed in the synthesis of natural and bioactive compounds.[3,4] Recently we reported, that the reaction of lactone **1** with amines afforded carbamoylated amino enones,[5] which reacted with 3-formylchromone and methyl chromone-3-carboxylate through the acetamide moiety and gave functionalized α-pyridones.[6]

Data on the reactions of lactone **1** itself with 3-substituted chromones are scarce and concern mainly 3-bromochromone, from which 2-salicyloyl-6-methyl-4*H*-furo[3,2-*c*]pyran-4-one was formed,[7] and 3-formylchromone **2a** (Scheme 1). The latter



Scheme 1 *Reagents and conditions*: i, proline, EtOAc, room temperature.

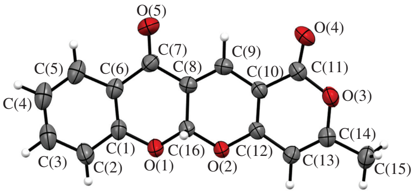
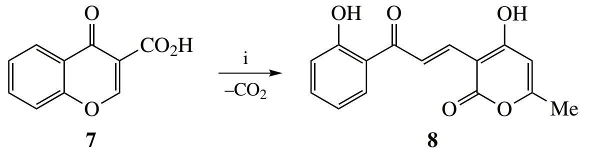


Figure 1 Molecular structure of **6a** as ORTEP drawing with 50% probability level.

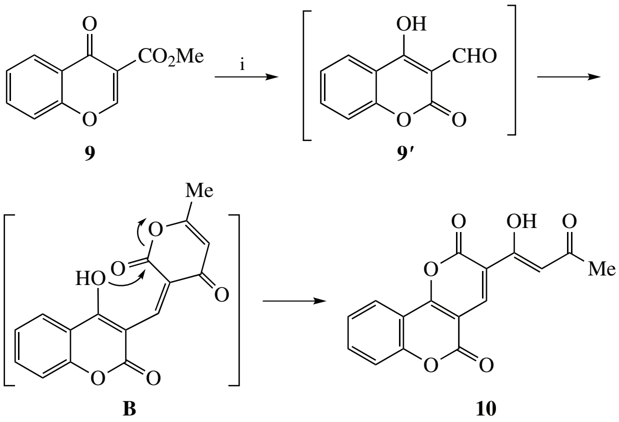
upon boiling in methanol reacted with two equivalents of lactone **1** affording compound **3a**,[8] while in the presence of camphor-10-sulfonic acid dipyranopyran **4a** was obtained.[9] It was reported as well,[10] that the products of a reaction between 3-formylchromones **2a**,**b** and lactone **1** have structure **5** arising from intermediate **A** (see Scheme 1). In our hands, an attempt to reproduce this procedure under the same conditions, namely proline, EtOAc and room temperature, afforded pyranochromenes **6a**,**b** in 60–66% yields. Compounds **6a**,**b** can be formed in the course of 6π-electrocyclization of intermediate **A**, in a good agreement with published data on the reaction of lactone **1** with α,β-enals.[11] 3-Formyl-6-methylchromone **2b** reacted with lactone **1** similarly, however, the electrocyclization product could not be isolated in pure form. The structure of compound **6a** was confirmed by X-ray diffraction analysis (Figure 1).[†]

The reaction of lactone **1** with chromone-3-carboxylic acid **7** in pyridine at 60 °C for 2 h leads to α,β-enone **8** in 63% yield. Compound **8** is formed as a result of an attack of the nucleophilic center of lactone **1** at the C^2 atom of the chromone system, followed by ring-opening and decarboxylation (Scheme 2). Note that under these conditions, unsubstituted chromone itself does not react with lactone **1**, this indicates the important role of the carboxy group, which additionally activates the 2-position. In the ^{1}H NMR spectrum of compound **8**, the doublets at 8.03 and 8.15 ppm are present with $J = 15.2$ Hz, which confirms the *trans*-configuration of the double bond.[12]



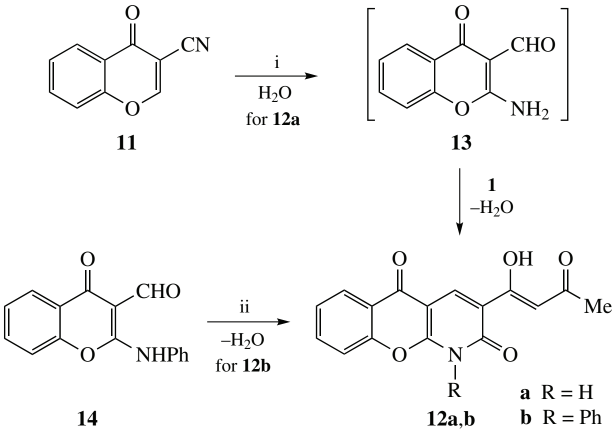
Scheme 2 *Reagents and conditions*: i, **1**, pyridine, 60 °C, 2 h.

Chromone-3-carboxylic acid methyl ester **9** in the reaction with lactone **1** upon boiling in toluene in the presence of pyridine behaves as a synthetic equivalent of 3-formyl-4-hydroxycoumarin **9′** (*cf.* Ref. 6) and affords pyranocoumarin **10** in 36% yield as a result of recyclization of intermediate **B** (Scheme 3). Previously this product, which existed mainly in enol form (80%), was obtained by boiling 3-formyl-4-hydroxycoumarin with lactone **1** in ethanol for 0.5 h (yield 72%).[13]



Scheme 3 *Reagents and conditions*: i, **1**, PhMe, pyridine, reflux, 4 h.

3-Cyanochromone **11** and lactone **1**, when boiled in absolute ethanol in the presence of catalytic amounts of piperidine, resulted in chromenopyridone **12a** (51% yield), previously obtained from 2-amino-3-formylchromone **13**.[14] In our case, chromone **13** was formed as a result of hydration and rearrangement of 3-cyanochromone **11**. We also found that the reaction of 3-formyl-2-(phenylamino)chromone **14** with lactone **1**, when boiling in ethanol in the presence of triethylamine, led to *N*-phenylchromenopyridone **12b** in 27% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: i, **1**, EtOH, piperidine, reflux, 2 h; ii, **1**, EtOH, Et_3N, reflux, 7 h.

In summary, the reactions of 3-substituted chromones with triacetic acid lactone are controlled by the nature of the substituent in 3-position of the chromone moiety and can proceed with either preservation or opening of the lactone ring. In reactions of 3-formyl- and 3-carboxychromones, this ring of triacetic acid lactone is retained, while for 3-methoxycarbonyl- and 3-cyanochromones it opens into synthetically significant β-diketone moieties. It is important that methyl chromone-3-carboxylate behaves as the synthetic equivalent of 3-formyl-4-hydroxycoumarin, whereas 3-cyanochromone appears to be the equivalent of 2-amino-3-formylchromone.

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[†] *Crystal data for* **6a**. $C_{16}H_{10}O_5$, $M = 282.24$, monoclinic, space group $P2_1/c$, at 295 K: $a = 6.5620(5)$, $b = 12.7913(9)$ and $c = 14.8370(11)$ Å, $V = 1244.57(16)$ Å^3, $Z = 4$, $d_{\text{calc}} = 1.506$ g cm^{-3}, μ(MoKα) = 0.113 mm^{-1}, $F(000) = 584$. Total of 7340 reflections were measured and 3296 independent reflections ($R_{\text{int}} = 0.0358$) were used for further refinement. The refinement converged to $wR_2 = 0.1949$ and GOF = 1.001 for all independent reflections [$R_1 = 0.0596$ was calculated against F for 1520 observed reflections with $I > 2\sigma(I)$].

CCDC 1921358 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.035.

References

1 (*a*) R. S. Keri, S. Budagumpi, R. K. Pai and R. G. Balakrishna, *Eur. J. Med. Chem*., 2014, **78**, 340; (*b*) A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte and F. Borges, *Chem. Rev*., 2014, **114**, 4960; (*c*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev*., 2003, **103**, 893.

2 (*a*) M. Yu. Kornev and V. Ya. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2016, **52**, 71 (*Khim. Geterotsikl. Soedin*., 2016, **52**, 71); (*b*) M. A. Ibrahim, N. M. El-Gohary and S. Said, *Heterocycles*, 2015, **91**, 1863; (*c*) C. K. Ghosh and A. Chakraborty, *ARKIVOC*, 2015, (**vi**), 417; (*d*) M. Yu. Kornev, V. S. Moshkin, O. S. Eltsov and V. Ya. Sosnovskikh, *Mendeleev Commun.*, 2016, **26**, 72.

3 D. L. Obydennov, A. I. El-Tantawy and V. Ya. Sosnovskikh, *Mendeleev Commun.*, 2019, **29**, 1.

4 (*a*) J. Yu, J. Landberg, F. Shavarebi, V. Bilanchone, A. Okerlund, U. Wanninayake, L. Zhao, G. Kraus and S. Sandmeyer, *Biotechnol. Bioeng.*, 2018, **115**, 2383; (*b*) L. Song, H. Yao, L. Zhu and R. Tong, *Org. Lett.*, 2013, **15**, 6.

5 D. L. Obydennov, A. I. El-Tantawy and V. Ya. Sosnovskikh, *New J. Chem*., 2018, **42**, 8943.

6 D. L. Obydennov, A. I. El-Tantawy, M. Yu. Kornev and V. Ya. Sosnovskikh, *Mendeleev Commun.*, 2019, **29**, 234.

7 R. Uddin and A. Zaman, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1995, **34**, 639.

8 (*a*) Z. N. Siddiqui, T. N. M. Musthafa and S. Praveen, *Med. Chem. Res.*, 2013, **22**, 127; (*b*) M. Asad, C.-W. Oo, R. S. Kumar, H. Osman and M. A. Ali, *Acta Pol. Pharm. – Drug Res.*, 2013, **70**, 221.

9 D. Kumbhar, R. Patil, D. Patil, A. Patravale, D. Chandam, S. Jadhav and M. Deshmukh, *Synth. Commun.*, 2016, **46**, 85.

10 A. Bari, S. S. Ali, A. Kadi, I. A. Hashmi and S. W. Ng, *Chem. Heterocycl. Compd.*, 2014, **49**, 1723 (*Khim. Geterotsikl. Soedin*., 2013, 1860).

11 (*a*) D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet and P. K. Chiang, *J. Org. Chem.*, 1997, **62**, 6888; (*b*) R. P. Hsung, H. C. Shen, C. J. Douglas, C. D. Morgan, S. J. Degen and L. J. Yao, *J. Org. Chem.*, 1999, **64**, 690; (*c*) J. Moreau, C. Hubert, J. Batany, L. Toupet, T. Roisnel, J.-P. Hurvois and J.-L. Renaud, *J. Org. Chem.*, 2009, **74**, 8963.

12 M. Yu. Kornev, V. S. Moshkin and V. Ya. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2015, **51**, 858 (*Khim. Geterotsikl. Soedin*., 2015, **51**, 858).

13 Z. N. Siddiqui and M. Asad, *Indian J. Chem*., *Sect. B: Org. Chem. Incl. Med. Chem.*, 2006, **45**, 2704.

14 (*a*) Z. N. Siddiqui, G. Khuwaja and M. Asad, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2006, **45**, 2341; (*b*) Z. N. Siddiqui, S. Praveen and F. Farooq, *Chem. Pap.*, 2010, **64**, 818.

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