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HETEROCYCLES IN FOCUS

Synthesis of 5,6-dihydro-2*H*-pyran-2-ones (microreview)

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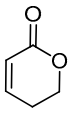
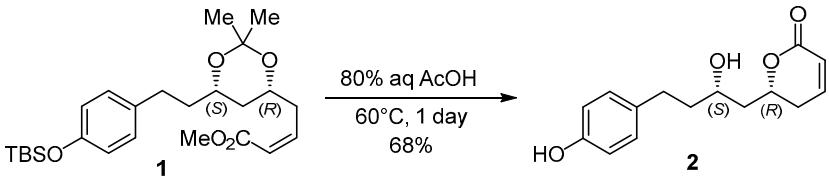


5,6-Dihydro-2*H*-pyran-2-ones constitute an important class of heterocyclic compounds which also may be considered as α,β-unsaturated δ-lactones. These types of heterocycles have shown a wide range of biological and pharmacological activities including human antitumor,[1,2] antifungal,[3,5] antimicrobial,[4] anti-inflammatory,[4] antistress,[4] antibiotic,[5] antituberculosis,[6] antiparasitic,[6] antiviral;[7] 5,6-dihydro-2*H*-pyran-2-ones are also known as the inducer of a colony stimulating factor in bone marrow stromal cells.[5] All this made 5,6-dihydro-2*H*-pyran-2-ones more attractive both for chemists and pharmacologists. For example, (*R*)-rugulactone which was firstly reported in 2009 by Cardellina and coworkers possess interesting anticancer properties.[2] In addition, 5,6-dihydro-2*H*-pyran-2-ones as chemical intermediates have widely been applied to the synthesis of numerous organic compounds including heterocycles.[8] Nowadays, there are several synthetic routes to the preparation of these heterocycles including intramolecular cyclization, *N*-heterocyclic carbene-precatalyst (NHC-precatalyst) reaction of enals and ketones, dicobaltoctacarbonyl-mediated tandem (5+1)/(4+2) cycloaddition, ring-closing metathesis of dienes containing carboxylate group by Grubbs II catalyst, (3+2) cyclo-addition reaction, condensation reaction, and biosynthesis pathway.

Intramolecular cyclization

(+)-Dodoneine (**2**) is a 5,6-dihydro-2*H*-pyran-2-one natural product which has been recently isolated from *Tapinanthus dodoneifolius* that grows in Burkina Faso (West Africa).[9] This heterocycle among other biological activities exhibits vaso-relaxant effect on preconstricted rat aortic rings.[10] Very recently an efficient route to total synthesis of this heterocycle has been reported where in the final step *Z*-configured α,β-unsaturated ester **1** in the presence of AcOH *via* phenol deprotection, ketal removal, and intramolecular cyclization gives pure (+)-dodoneine (**2**) in 68% yield.[11]

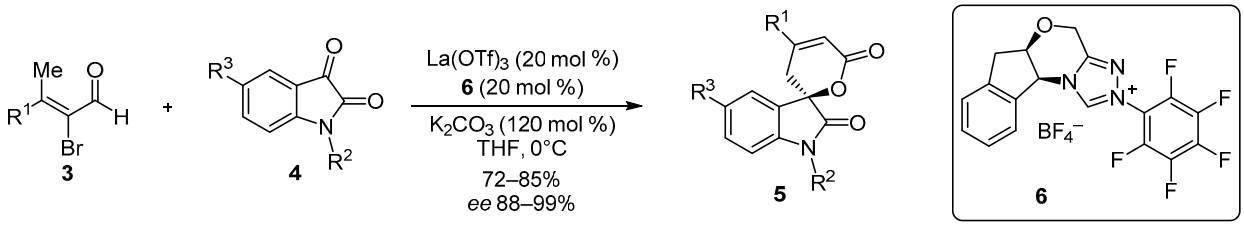


Khalil Eskandari was born in Shahrekord, Iran, in 1984. He obtained his BSc in Pure Chemistry from the Mazandaran University in 2007, MSc in Organic Chemistry from the Kharazmi University, Tehran in 2009, and PhD in Organic Chemistry from the Yasouj University in 2013. He graduated with honor in BSc, MSc, and PhD as distinguished student. He also spent his Postdoctoral career in 2015–2016 in the Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences.

Mahmoud Rafieian-Kopaei was born in Isfahan, Iran, in 1955. He got his Pharm.D. degree from the Isfahan University in 1983 and PhD degree in pharmacology from the Cardiff University, UK. He has published more than 500 papers and at the present time he is professor and head of the Medical Plants Research Center at the Shahrekord University of Medical Sciences, Iran. He works predominantly on pharmacology and therapeutic properties of medicinal plants and their derivatives.

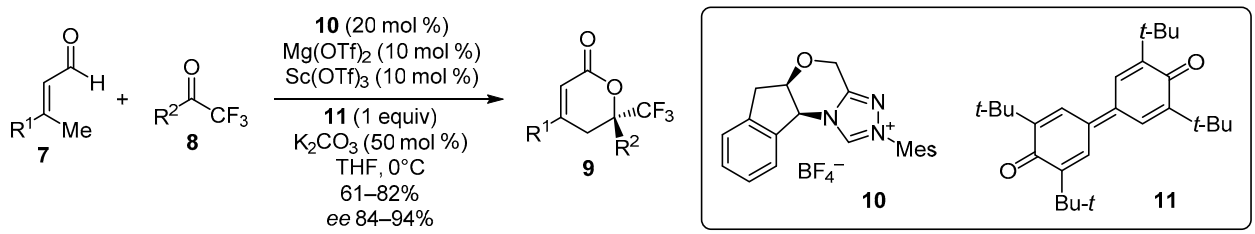
NHC-precatalyst reaction of enals and ketones

Recently, novel spirocyclic oxindole-5,6-dihydro-2*H*-pyran-2-ones **5** have been enantioselectively prepared by the use of catalytic amounts of $La(OTf)_3$ and *N*-heterocyclic carbene (**6**) as precatalyst through the (4+2) annulation between α-bromoenals **3** and isatins **4**.[12]



R^1 = Me, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$; R^2 = Me, Et, allyl; R^3 = H, Me

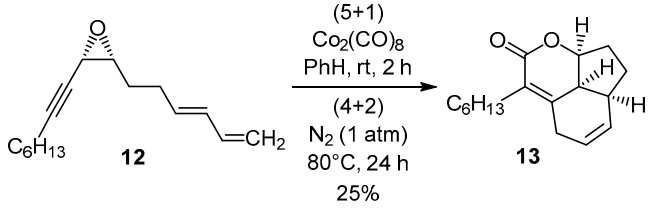
Also, in other recently reported route, 5,6-dihydro-2*H*-pyran-2-ones **9** have been enantioselectively synthesized through an oxidative γ-addition of enals **7** to trifluoroacetophenones **8** by $Mg(OTf)_2/Sc(OTf)_3$ and *N*-heterocyclic carbene **10** cooperative catalysis in the presence of an external oxidant **11**.[13]



R^1 = Ph, 2-thienyl, 2-furyl, 2-Py, 4-$MeOC_6H_4$, 4-BrC_6H_4; R^2 = Ph, 4-MeC_6H_4, 4-BrC_6H_4

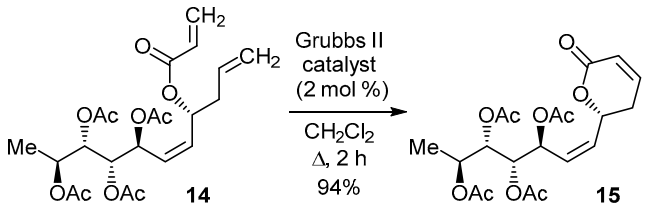
Dicobaltoctacarbonyl-mediated tandem (5+1)/(4+2) cycloaddition

In a newly introduced route to 5,6-dihydro-2*H*-pyran-2-ones, dicobaltoctacarbonyl complex $[Co_2(CO)_8]$ ensures an intramolecular carbonylation of *cis*-epoxyalkynes **12** to generate $Co_2(CO)_6$-stabilized γ-lactonyl allenes which under heating in benzene are transformed into 5,6-dihydro-2*H*-pyran-2-ones **13**. This transformation can be described as a tandem (5+1)/(4+2) cycloaddition between epoxyalkyne, CO, and diene functionalities.[14]



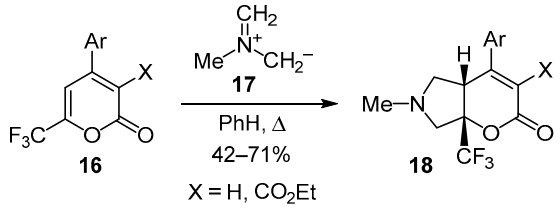
Ring-closing metathesis of dienes containing carboxylate group by Grubbs II catalyst

Synthesis of (–)-spicigerolide **15**, a natural product which has been isolated from *Hyptic spicigera* and has been used in the treatment of gastrointestinal disturbances, skin infections, wounds, and insect bites, is recently reported *via* ring-closing metathesis of acrylate **14** effected by the second generation Grubbs ruthenium catalyst to obtain 5,6-dihydro-2*H*-pyran-2-one **15**.[15]



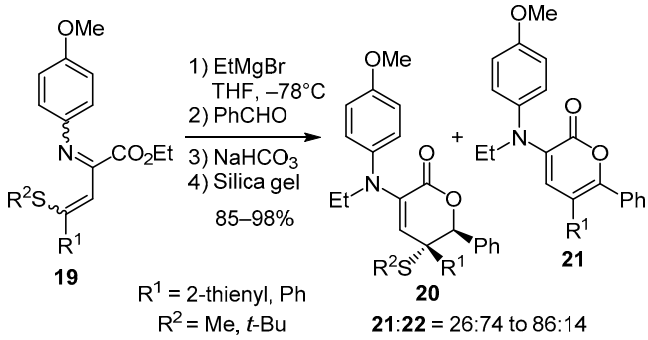
(3+2) Cycloaddition reaction

Novel type of 5,6-dihydro-2*H*-pyran-2-ones **18** have been synthesized *via* (3+2) cycloaddition reaction between azomethine ylide **17** with electron-deficient 4-aryl-6-(trifluoromethyl)-2-pyrones **16**. It should be mentioned that azomethine ylide **17** is *in situ* generated from sarcosine and formaldehyde.[16]



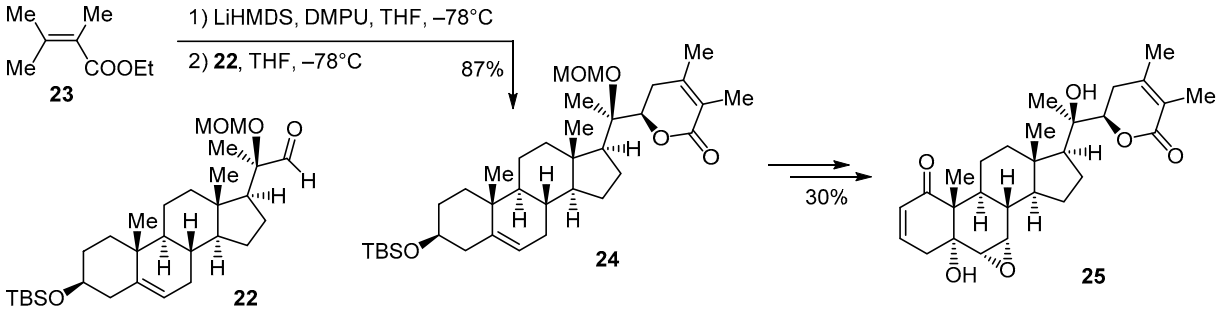
Condensation reaction

In another recent attempt, a novel route to synthesis of 5,6-dihydro-2*H*-pyran-2-ones **20** was described by Shimizu and coworkers. In this newly reported condensation reaction, 3-amino-2-pyrones **20**, **21** are obtained *via* a highly regioselective tandem *N*-alkylation/vinylogous aldol reaction of β,γ-alkenyl-α-iminoesters **19** under given conditions.[17]



Biosynthesis

5,6-Dihydro-2*H*-pyran-2-one scaffold is found also in withanolides, a group of natural products which have shown a variety of biological activities.[18] Gupta and coworkers reported biosynthesis of withanolide A (**25**) using farnesyl diphosphate synthase (FPPS) and squalene synthase (SQS). The key steps in this procedure is FPPS- and SQS-catalyzed transformation of isopentyl diphosphate to farnesyl diphosphate and farnesyl diphosphate to squalene, respectively.[19a,b] 5,6-Dihydro-2*H*-pyran-2-one **24** is formed from reaction of next generated aldehyde **22** with 2,3-dimethylbut-2-enoate **23** and LiHMDS in a mixture of THF and DMPU *via* an aldol condensation reaction. Finally, withanolide A (**25**) is obtained from compound **24** through further multiple steps.[19c]



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