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Triacetic acid lactone as a bioprivileged molecule in organic synthesis

Dmitrii L. Obydennov,[a] Asmaa I. El-Tantawy[a,b] and Vyacheslav Ya. Sosnovskikh*[a]

[a] *Institute of Natural Sciences and Mathematics, Ural Federal University, 620000 Ekaterinburg, Russian Federation. E-mail: vy.sosnovskikh@urfu.ru*

[b] *Department of Physics and Engineering Mathematics, Faculty of Electronic Engineering, Menoufia University, 32952 Menouf, Egypt*

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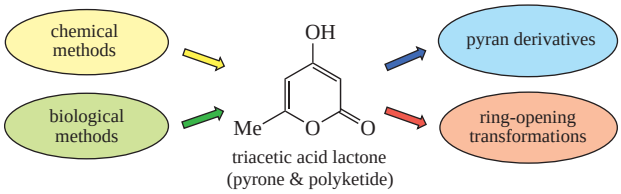
Major methods for the preparation of triacetic acid lactone and its application as a bioprivileged compound in the synthesis of various valuable materials are summarized. Due to its structural features, this lactone belongs to both pyrones and polyketides, which provides opportunities for its obtaining by chemical and biological methods. The presence of several electrophilic and nucleophilic centers in its molecule, as well as its capability of undergoing transformations with both preservation and opening of the ring, ensure its multiple reactivity. Reactions proceeding without the ring opening lead to substituted and fused pyrans, while the ring opening provides N-heterocycles and acyclic derivatives.



Introduction

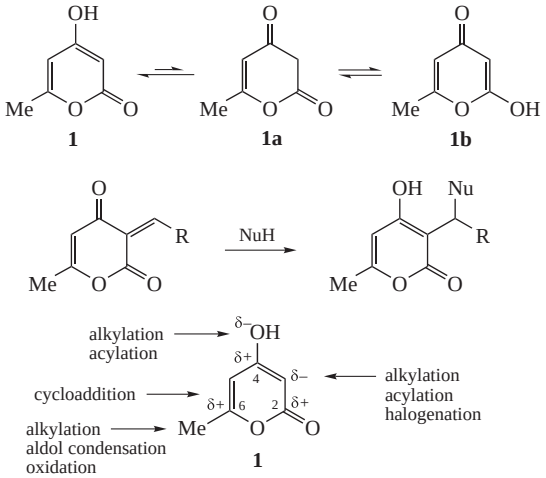
A utilization of plant biomass as the renewable resource for obtaining valuable organic chemicals is an important trend for the evolution of modern human society.[1] One branch of this trend includes an application of multifunctional substrates obtained *via* the processing of carbohydrates and employing them as the convenient building blocks for the organic synthesis. In this context, a significant attention is being paid to furan derivatives.[2] Currently, pyrones extracted from natural sources, including the carbohydrate processing, emerge to be not the less valuable building blocks than furans.[3] Triacetic acid lactone **1** (4-hydroxy-6-methyl-2*H*-pyran-2-one), notable for its availability and chemical properties, can be assigned to the both series of 2-pyrones and 4-pyrones[4] and is recognized as a bioprivileged structure and a potential 'platform molecule'.[5] Moreover, triacetic acid lactone belongs to a polyketide, which makes it available *via* not only chemical, but also biological methods, therefore, the opportunity to combine them in order to obtain various valuable products from carbohydrates, including on the industrial scale,[5(b)] promotes its active studies.

The major tautomeric form of triacetic acid lactone is enol form **1**, which, along with tautomers **1a**,**b**, maintains its high reactivity upon a treatment with the wide range of reagents. This molecule contains three electrophilic centers (C^2, C^4, and C^6), two nucleophilic centers (C^3 and OH), and the methyl group that exhibits nucleophilic properties in a strongly basic medium. The most preferred site to be attacked by electrophiles [aldehydes, trialkyl orthoformates, and $Me_2NCH(OMe)_2$] is the C^3 atom to afford 3-methylidene derivatives. Such products belong to the class of enones and can undergo Michael addition of C-, N- and S-nucleophiles, and react with ambiphiles such as malononitrile. These transformations are usually realized as three-component

Dmitrii L. Obydennov graduated from the Ural State University in 2009 and received his PhD degree in 2012. He currently works as an associate professor at the Ural Federal University. His research focuses on the preparation of both pyrones and polycarbonyl compounds, their reactivity and use in the synthesis of various heterocyclic structures.

Asmaa I. El-Tantawy graduated from the Menoufia University (Egypt) and received her master's degree in 2010. She works as an assistant lecturer at the Faculty of Electronic Engineering, the Menoufia University (Egypt). At the same time, she is a PhD student under the supervision of Professor V. Ya. Sosnovskikh at the Ural Federal University and is currently writing her PhD thesis. Her research interests include the preparation of pyrones and polycarbonyl compounds, their reactivity and application in the synthesis of heterocyclic compounds.

Vyacheslav Ya. Sosnovskikh is Doctor of Chemical Sciences, Professor, Head of Department of Organic Chemistry and High Molecular Compounds at the Institute of Natural Sciences and Mathematics, the Ural Federal University. His current interests cover organic synthesis, oxygen and nitrogen heterocycles, CF_3-containing chromones and pyrones, polyfunctional compounds, 1,3-dipolar cycloaddition.



Scheme 1

reactions proceeding with the preservation of ring and giving either 3-substituted or 3,4-fused 2-pyrones.[6] Reactions of electrophilic halogenation occur at the C^3 atom, alkylation and acylation proceed at C^3 atom and OH group, while in the case of Me group, alkylation, aldol condensation, and oxidation to the aldehyde group have been reported (Scheme 1).[7]

Reactions of lactone **1** with mononucleophiles begin from the attack at C^2 and/or C^6 atoms and are accompanied by the opening of pyrone cycle, while the third electrophilic center C^4 is involved in the reaction with excess of amine. Note that reactions of lactone **1** with dinucleophiles often require harsh conditions and afford mixtures of products due to low selectivity.[8] Hydrolytic ring opening gives triacetic acid or acetylacetone, whose synthetic equivalent under certain conditions can be lactone **1**.

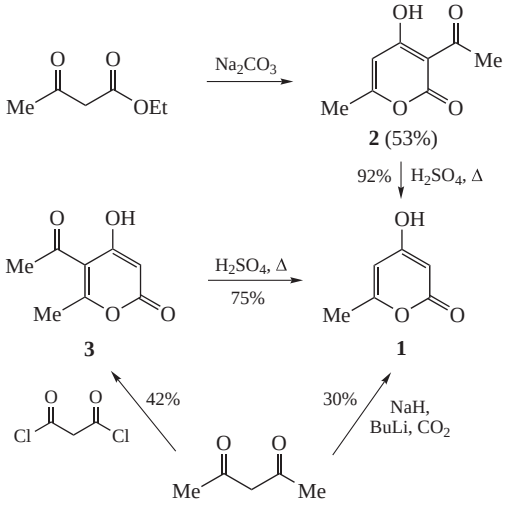
Despite the significant interest shown throughout the world to the triacetic acid lactone, there are no publications, wherein the latest data are summarized, except for one review devoted to its application in multicomponent reactions.[6] These reactions are very characteristic of lactone **1** but do not cover its synthetic potential. Here, the data are classified according to the reactions proceeding either with preservation or opening of the pyrone ring, which allows us to provide a more complete concept of chemical properties of lactone **1** and, at least partially, to fill the blank space formed in this area since 1992.[4]

Synthesis of triacetic acid lactone

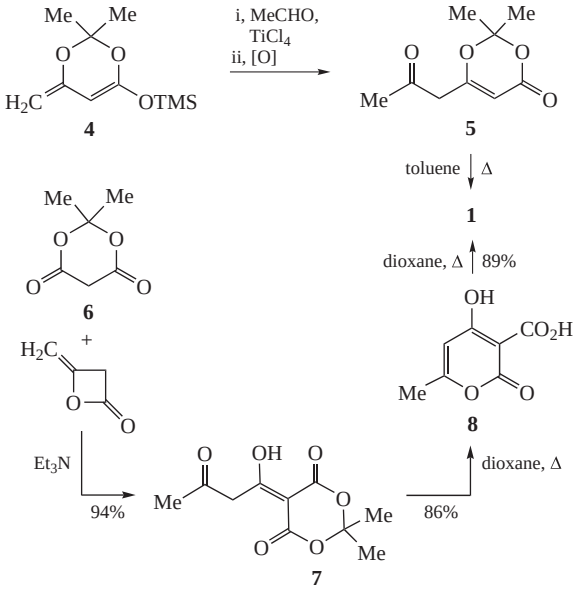
Triacetic acid lactone **1** can be obtained by both chemical and biological methods. The most common approaches are chemical transformations based on carbonyl substrates. The simplest way is an acid-catalyzed deacetylation of dehydroacetic acid **2**,[9(*a*)] which is consequently formed *via* the self-condensation of ethyl acetoacetate in the presence of Na_2CO_3.[9(*b*)] Other methods involve carboxylation of acetylacetone with carbon dioxide and its acylation with malonic acid chloride, which initially leads to 5-acetyl-4-hydroxy-6-methyl-2-pyrone **3** (Scheme 2).[9(*c*)]

A vynilogous aldol condensation of acetaldehyde with acetoacetic equivalent **4** followed by the Dess–Martin oxidation leads to compound **5**, which is recyclized into lactone **1** upon heating in toluene with acetone elimination.[10(*a*)] An acylation of Meldrum's acid **6** with diketene in the presence of Et_3N gives dioxanedione **7** in excellent yield, which rearranges upon heating in dioxane into acid **8**, and the latter is decarboxylated into lactone **1** (Scheme 3).[10(*b*)]

As for biotechnological production, lactone **1** can be obtained from two common precursors, acetyl-CoA **9** and malonyl-CoA **10**, in the presence of polyketide synthase. Biotechnological

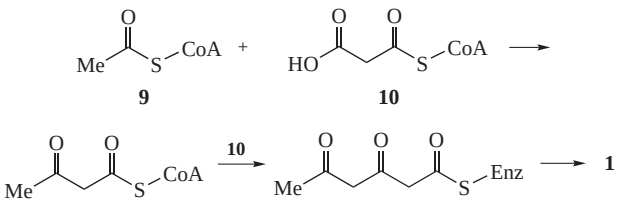


Scheme 2



Scheme 3

methods for the conversion of glucose into lactone **1** are now actively being developed and aimed at the raising concentration and yield of the desired product. Genetically modified microorganisms, such as *Saccharomyces cerevisiae*,[11(*a*)–(*c*)] *Escherichia coli*,[11(*d*)–(*f*)] and the yeast *Yarrowia lipolytica*[11(*g*)] are usually used. The maximum yield achieved currently is 49%,[11(*f*)] which provides great opportunities for its industrial implementation (Scheme 4).

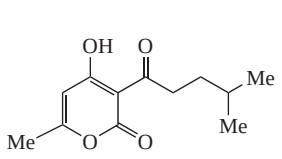


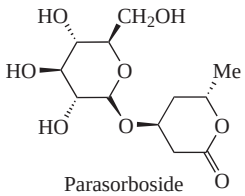
Scheme 4

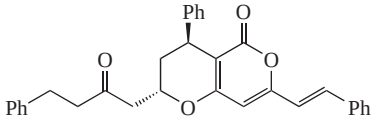
Reactions preserving the pyrone ring

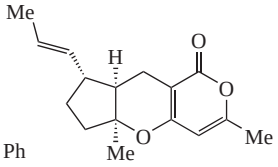
Reactions involving the polyfunctional lactone **1** can be divided into the two large groups: those with the preservation of pyrone ring (usually with electrophiles) and reactions with its opening

(usually with nucleophiles).[4] Transformations without ring opening have been applied in the preparation of many natural and medicinal derivatives of pyran, such as progostone,[12(a)] parasorboside,[12(b)] katsumadain A,[12(c)] and penicipyrone.[12(d)]


Progostone

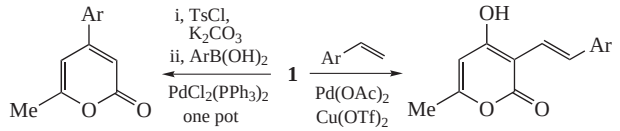

Parasorboside


Katsumadain A


(–)-Penicipyrone

Palladium-catalyzed reactions. The most well studied reactions are C- and O-alkylation,[13] C-acylation and O-tosylation,[14] and 3- and 4-halogenation,[14(c),15] since the products of these reactions can be subjected to the Suzuki, Sonogashira or Heck cross-couplings. In recent years, methods of the C–H functionalization of lactone **1** have been developed, which allowed one to obtain its aryl- and styryl-substituted as well as fused derivatives. The presence of labile proton limits the usage of pyrone **1** in cross-coupling reactions; thus, the replacement of hydroxyl group by substituents such as MeO, TfO, and Br significantly expands its capabilities. First of all, the transformations proceeding directly with the triacetic acid lactone and not requiring the preliminary modification of OH group will be considered.

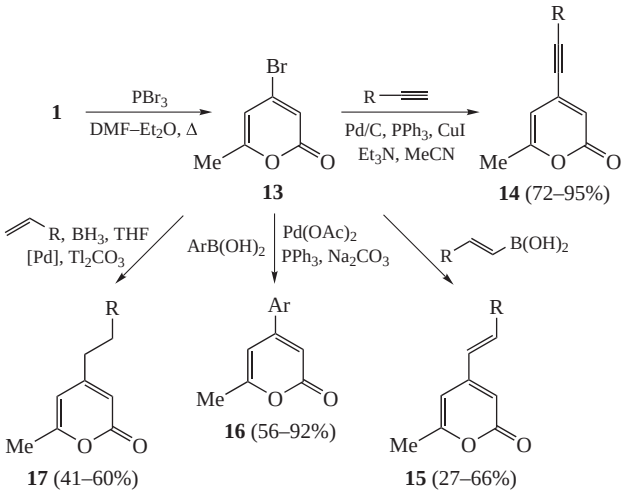
The Heck oxidative reaction[16] between lactone **1** and styrenes occurs in air in the presence of palladium acetate and copper triflate in DMF/DMSO (8 : 2) and gives 3-styryl-2-pyrones **11** in good yields regardless of the nature and position of substituent at the benzene ring (Scheme 5). The selectivity of this reaction is related to the activation of precisely position C^3 by the palladium. Lactone **1** also participates in the Suzuki reaction with arylboronic acids, while the OH group is activated during the process by tosyl chloride, affording finally 4-aryl-2-pyrones **12** (see Scheme 5). 3-Bromo-4-hydroxy-6-methyl-2-pyrone can also be subjected to the Suzuki coupling [$Pd(OAc)_2$, K_2HPO_4] to provide 3,4-diaryl-2-pyrones.[17]


12 (62–91%) **11** (64–70%)

Scheme 5

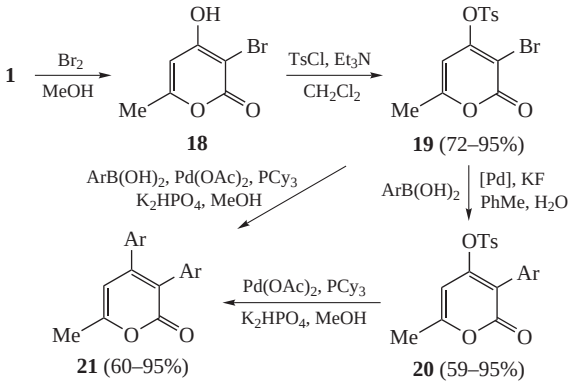
4-Bromo-6-methyl-2-pyrone **13**, which is readily generated from lactone **1**, has been used in a number of works[14(c),15(a),18] to synthesize 4-alkynylpyrones **14** *via* the Sonogashira reaction and 4-alkenyl- (**15**), 4-aryl- (**16**) and 4-alkylpyrones (**17**) *via* the Suzuki reaction (Scheme 6). 4-Tosyloxy-6-methyl-2-pyrone subjected to the Suzuki reaction in the presence of nickel complexes[19] gives 4-arylpyrones **16** in the yields of 76–96%, while its Heck cross-coupling with *N*-vinylacetamide and vinyl butyl ether results in the corresponding 4-vinyl derivatives (yield of 84–91%).[20]

3-Bromo-6-methyl-4-tosyloxy-2-pyrone **19** derived from 4-hydroxy precursor **18** turned out to be a convenient substrate


13 **14** (72–95%) **17** (41–60%) **16** (56–92%) **15** (27–66%)

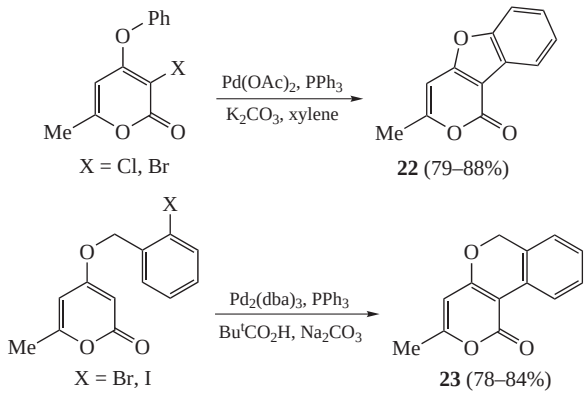
Scheme 6

for the synthesis of 3-arylpyrones **20** and 3,4-diarylpyrones **21** (Scheme 7). The variation of the Suzuki reaction conditions allows one to obtain either mono- or diaryl derivatives *via* a one-pot procedure, while taking pyrone **20** as the starting material makes it possible to synthesize compounds **21** containing different aryl substituents (see Scheme 7).[15(b)] 4-Methoxy(phenoxy)-6-methyl-3-chloro-2-pyrones are also useful for the preparation of the corresponding 3-phenyl-substituted 2-pyrones.[21]


18 **19** (72–95%) **21** (60–95%) **20** (59–95%)

Scheme 7

A method of intramolecular direct arylation has been recently developed for the series of 4-hydroxycoumarin and pyrone **1**, which does not demand the introduction of activating groups and allows one to obtain products **22** and **23** from the corresponding 4-phenoxy(benzyloxy)-2-pyrones in high yields (Scheme 8).[22] 3-Methyl-1*H*-pyrano[4,3-*b*]benzofuran-1-one **22** is also formed from 4-(*o*-iodophenoxy)-6-methyl-2-pyrone in 79% yield,[23] while a double C–H functionalization by palladium acetate in the


X = Cl, Br **22** (79–88%)

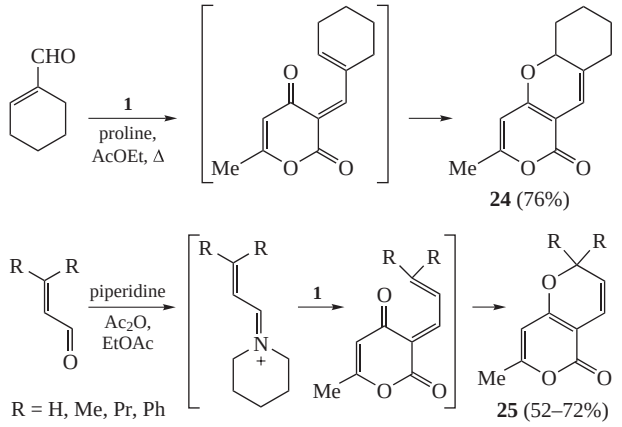
X = Br, I **23** (78–84%)

Scheme 8

presence of Ag_2O and K_2CO_3 provided its obtaining directly from 6-methyl-4-phenoxy-2-pyrone (yield of 56%).[24]

Formal [3 + 3] cycloaddition through 1,2-A_N/electrocyclization. Reactions of lactone **1** with α,β-unsaturated aldehydes and ketones can proceed *via* either the initial Knoevenagel reaction (1,2-A_N) followed by 6π-electrocyclization or the Michael reaction route (1,4-A_N) with the consequent acetalization. The both directions are a formal [3 + 3] cycloaddition leading to 2*H*,5*H*-pyrano-[4,3-*b*]pyran-5-ones in the first case and 4*H*,5*H*-pyrano[4,3-*b*]-pyran-5-ones in the second one.

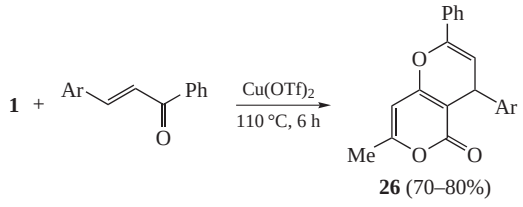
Although in one of the first reports on this topic[25] it was proposed that α,β-enals react with lactone **1** predominantly *via* 1,4-addition route, it was found[26] that in the presence of proline, cyclohex-1-enecarbaldehyde initially gives a 1,2-addition intermediate, which is converted into final product **24** *via* 6π-electronic electrocyclic ring closure. The more general nature of this reaction was demonstrated by Hsung *et al.*,[27] who have found that α,β-enals in the form of iminium cations in the presence of piperidine and acetic anhydride upon heating in ethyl acetate react with lactone **1** *via* the Knoevenagel route and afford products **25** in good yields at the step of electrocyclization (Scheme 9).



Scheme 9

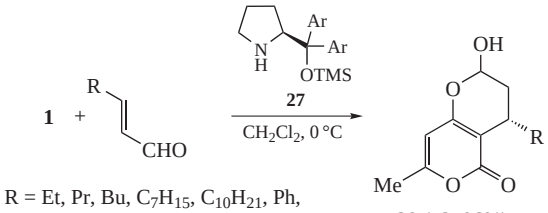
It was later demonstrated that this reaction can be catalyzed by Brønsted acids,[28(a),(b)] Lewis acids,[28(c)] and β-alanine in the presence of $CaSO_4$.[28(d)] The presence of proline or pyrrolidine allows one to involve 2-*C*-formyl galactal in this reaction and to obtain polycyclic fused pyranopyrone acetals.[29]

Formal [3+3] cycloaddition through 1,4-A_N/acetalization. In general, the reactions between α,β-enals and pyrone **1** starts from the Knoevenagel stage, while α,β-enones usually undergo the Michael reaction. Indeed, many recent works confirm this rule, although there are some exceptions. The reaction of lactone **1** with chalcones catalyzed by copper triflate proceeds upon heating without a solvent as the 1,4-addition followed by an attack of hydroxyl group at the carbonyl one, and final dehydration of ketal results in 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones **26** in high yields (Scheme 10).[30] Similar products were obtained when an $AuCl_3$/3AgOTf system was used as the catalyst in boiling toluene for 6 h.[31] If the reaction was carried out in the presence of oxidized graphite powder in water at 80 °C, the dehydration can be avoided.[32]



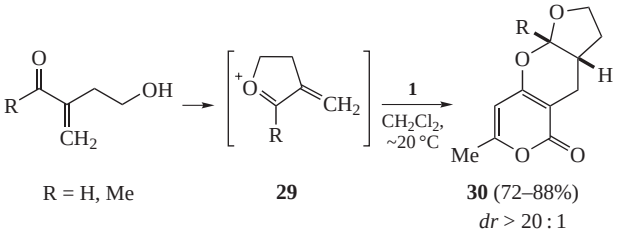
Scheme 10

A very unexpected result was reported[33] on the reaction of lactone **1** with α,β-enals in the presence of diarylprolinol ether **27** in CH_2Cl_2 upon cooling to 0 °C. As in the case of α,β-unsaturated ketones, the cascade of 1,4-A_N/acetalization was therein observed and acetals **28** were obtained with high regio- and enantioselectivity (Scheme 11).



Scheme 11

Later Tong *et al.*[34] reported that the OH group linked *via* a methylene bridge to the moiety of α,β-unsaturated carbonyl compound had the crucial influence on the reactivity and regioselectivity of enone system, directing the reaction towards 1,4-A_N route due to the generation of hypothetical α-methylene cyclic oxonium ion **29**. In this case, acetals **30** are diastereoselectively formed from both the enones and enals (Scheme 12).

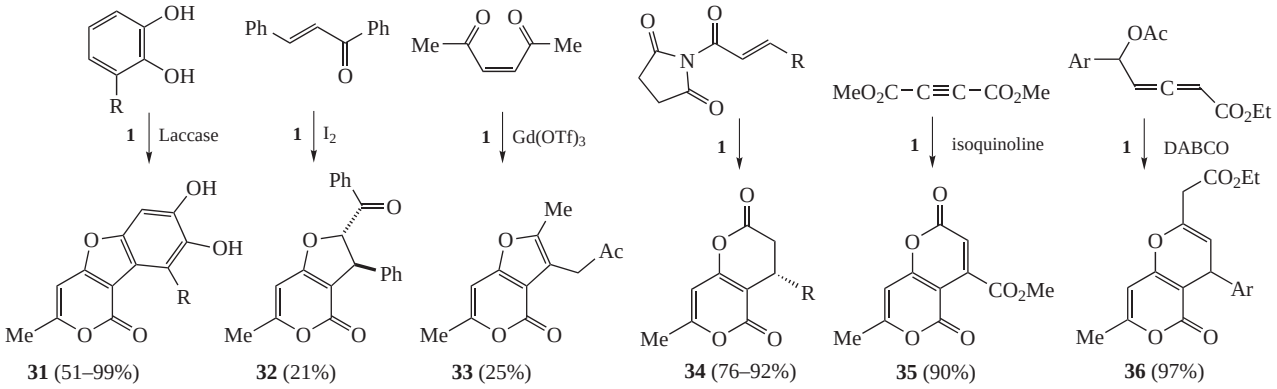


Scheme 12

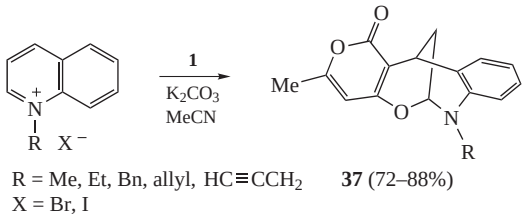
Reactions with 1,2- and 1,3-dielectrophiles. Some works[35] described a domino-reaction catalyzed by laccase enzyme between lactone **1** and pyrocatechols with the participation of atmospheric oxygen, which led to annelated benzofurans **31** (Scheme 13). The reaction proceeds *via* the generation of *o*-benzoquinone acting as a 1,2-dielectrophile. Dihydrofuro[3,2-*c*]pyran-4-one **32** is formed in the case of reaction between lactone **1** and chalcone in the presence of iodine, which iodinated the Michael adduct.[36] (*Z*)-3-Hexene-2,5-dione obtained by a laccase-catalyzed oxidative cleavage of 2,5-dimethylfuran reacts with lactone **1** in the presence of a Lewis acid and gives furopyrone **33**, which can also be directly synthesized from 2,5-dimethylfuran (see Scheme 13).[37]

An enantioselective Michael reaction involving lactone **1** and N-acylated succinimides in the presence of the quinine derivative, squaramide, is completed by the cyclization into compounds **34** (see Scheme 13).[38] The reaction of lactone **1** with dimethyl acetylenedicarboxylate in the presence of isoquinoline yields 7-methyl-2,5-dioxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-4-carboxylate **35**,[39] and its reaction with δ-acetoxyallenoate affords pyrano[4,3-*c*]-pyran **36** (Ar = 4-BrC_6H_4).[40]

There is one interesting example reported,[41] wherein quinoline salts act as the 1,3-dielectrophiles. The reaction starts from an attack at the 4-position of quinolinium by the C^3 atom of lactone **1** and the following cyclization *via* the addition of OH group at



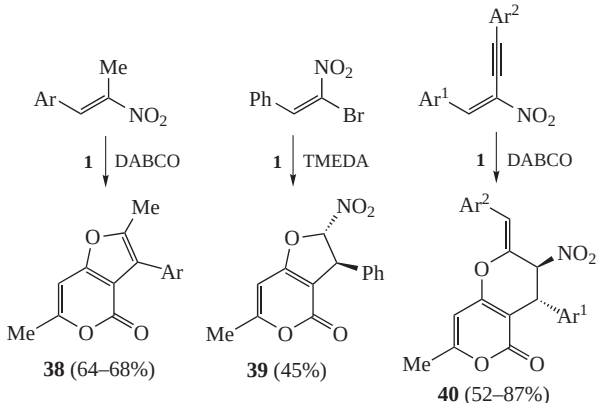
Scheme 13



Scheme 14

the C^2 atom of iminium intermediate leads to bridged system **37** (Scheme 14).

Reactions with β-nitrostyrenes. It is interesting to compare the reactions of lactone **1** with β-methyl- and β-bromo-β-nitrostyrenes. In the first case, the Michael addition with the consequent cyclization into furo[3,2-*c*]pyran-4-one **38** is accompanied by the elimination of nitro group as water and HNO (Scheme 15).[42] In the second case, the leaving group is the bromine atom, which results in compound **39**. Note that the latter product was obtained with 74% *ee* in the presence of chiral catalyst based on urea.[43] An organocatalytic reaction of lactone **1** with β-alkynyl-β-nitrostyrenes in the presence of DABCO and chiral catalyst, a hybrid of squaramide and quinine, gives dihydropyrano[4,3-*b*]pyran-5-ones **40** with 97–99% *ee* (see Scheme 15).[44]

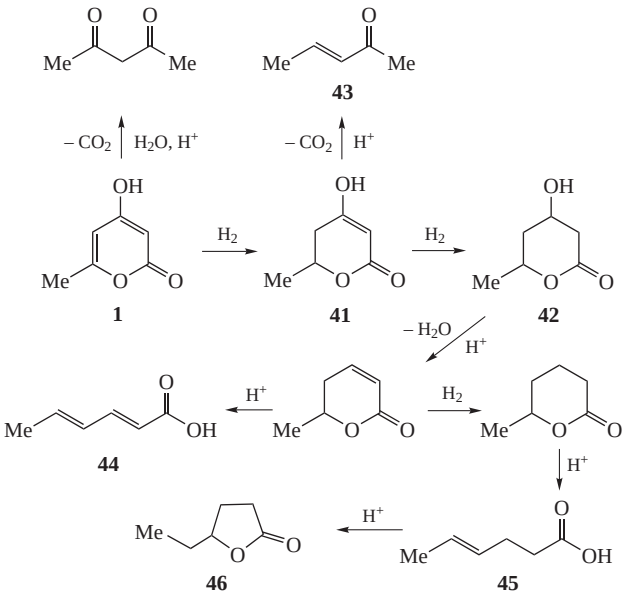


Scheme 15

Ring opening reactions

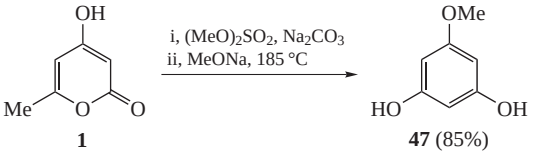
In contrast to the well-studied interaction of lactone **1** with electrophilic reagents, wherein the cycle is preserved, its nucleophilic reactions are almost always accompanied by the pyrone ring opening and are characterized by the formation of either acyclic or cyclic products. However, despite the fact that lactone **1** is under investigations since 1891,[9(a)] this direction has gained momentum only in recent years, which may be attributed to a not always high selectivity because of the need to apply quite harsh conditions in reactions with dinucleophiles.

Reactions with hydrogen and C-nucleophiles. Dumesic *et al*.[45] for the first time paid attention to triacetic acid lactone as the potential 'platform compound' in the study of lactone **1** transformations under conditions of heterogeneous catalysis. It has been shown[45(a)] that in the absence of hydrogen on the acidic catalyst (Amberlist™ 70), the pyrone ring opening and decarboxylation occur in water, which leads to acetylacetone in an almost quantitative yield (Scheme 16). In the case of carrying out the reaction in the presence of hydrogen, one can obtain either product **41** of partial reduction (BuOH, Pd/Nd_2O_5, 92%) or product **42** of complete reduction (THF, Pd/C, 96%) in excellent yields depending on the catalyst nature, and they can be converted into pentenone **43** and sorbic acid **44** in 58 and 67% yields (64% from lactone **1**), respectively, using an acid catalyst. Since sorbic acid is employed as the preservative and its consumption is about 100,000 tons per year, this method can be considered as an alternative for its production from renewable resources. A combination of hydrogenation processes on the palladium and acid catalysts allows one to obtain hexenoic acid **45** and γ-butyrolactone **46**. Although the latter compounds were formed with a low selectivity, this direction enhances the synthetic capabilities of lactone **1**. Thus, one can obtain a variety of valuable products using the acid (ring opening, decarboxylation) and palladium-containing (reduction) catalysts (see Scheme 16).



Scheme 16

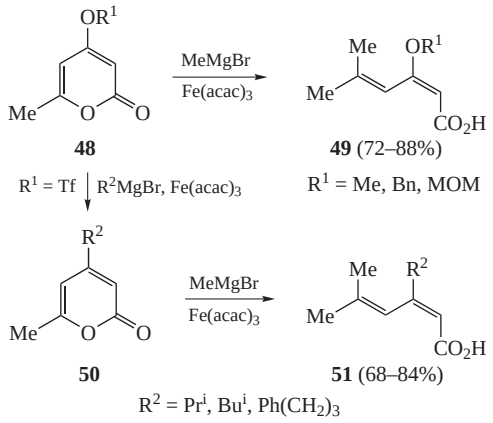
One of the important properties of triacetic acid lactone **1** from the viewpoint of preparation of valuable products is its transformation into functionalized arenes. Lactone itself does not undergo this reaction, but its methylated derivative can rearrange into *O*-methylphloroglucine **47** in the presence of sodium methoxide (Scheme 17).[46]



1 **47** (85%)

Scheme 17

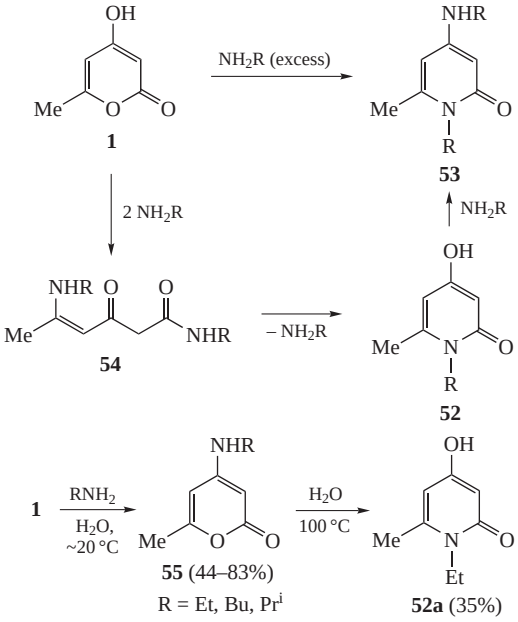
Usually, 2-pyrones react with Grignard reagents at the carbonyl group. However, pyrones **48** alkylated at the OH group react with them at the C^6 atom to open the pyrone ring and to form compounds **49** in the presence of Fe-catalysts, such as iron(III) acetylacetonate[47] or iron(II) chloride (Scheme 18).[48] When triflate **48** is used, it becomes possible to consequently introduce two alkyl groups. In this case, pyrones **50** are initially formed as the result of nucleophilic substitution at 4-position, which are further attacked by the second organomagnesium molecule to give substituted sorbic acids **51** (see Scheme 18).[47]



Scheme 18

Reactions with N-nucleophiles. An important direction for the medical chemistry is the reaction of triacetic acid lactone with primary amines, which is accompanied by the opening of pyrone ring and the formation of more stable pyridones **52** and **53** (Scheme 19).[49] Since molecule **1** contains three electrophilic centers, the amine attack can occur not only at the most obvious C^2 and C^6 positions, but also at the C^4 atom. 4-Hydroxy-2-pyridones **52** are usually formed in reactions with one equivalent of amine, while an excess of amine results in 4-amino-2-pyridones **53**, which can also be obtained from compounds **52**. Although the ring opening reactions proceed *via* various open-chain intermediates, only carbamoylated amino enones **54**,[49(c),(d)] which are the result of attack at the C^2 and C^6 atoms by the amine molecule, have currently been isolated (see Scheme 19).

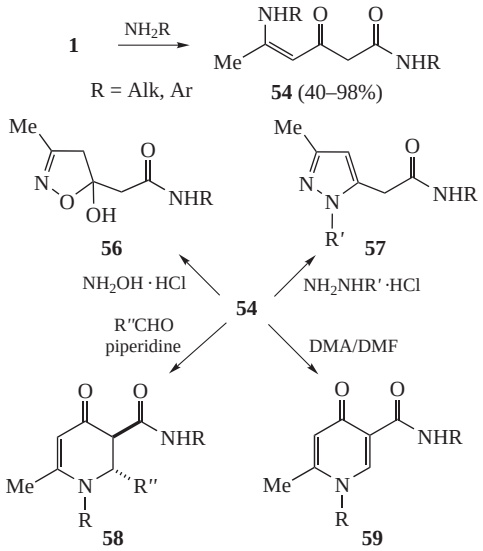
It has been recently demonstrated[50] that lactone **1** reacts due to its tautomers **1a**,**b** (see Scheme 1) with primary amines at the C^4 atom at room temperature in water to afford 4-amino-2-pyrones **55** as kinetically controlled products, while thermodynamically more stable 4-hydroxy-2-pyridones **52** are formed upon boiling, as was shown for ethyl derivative **52a** as the example (see Scheme 19). In our opinion, it cannot be excluded that compounds **55** are salts of lactone **1** with amines. Note that the reactions of triacetic acid lactone with amines are of great practical interest,



Scheme 19

since they open an access to 4-hydroxy- and 4-amino-2-pyridones, the base structures in the design of wide range of biologically active compounds, *e.g.*, glucokinase activators.[51]

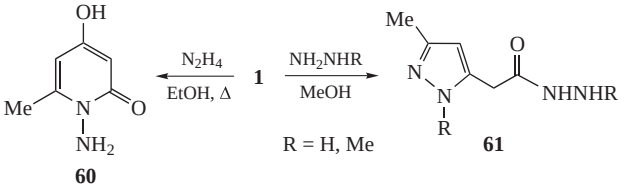
We have recently developed a preparative method for obtaining carbamoylated amino enones **54** *via* the reaction of lactone **1** with amines in boiling EtOH or without a solvent (Scheme 20).[52] Compounds **54** are the polyfunctional and highly reactive building blocks for the synthesis of 5- and 6-membered heterocycles **56**–**59** under mild conditions, which cannot be prepared directly from lactone **1**.[52,53]



Scheme 20

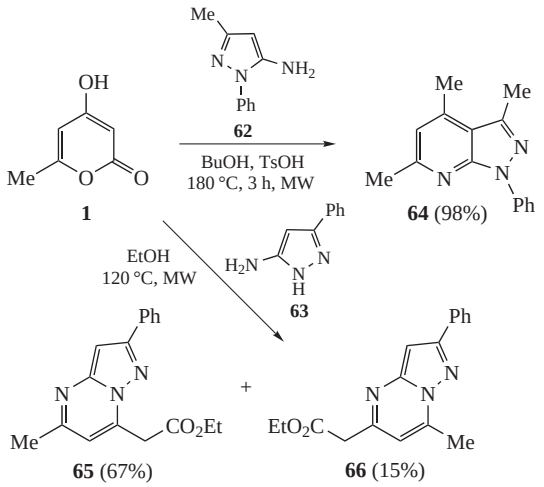
In some works,[54] the structures of *N*-amino-2-pyridone **60** and pyrazole-5-hydrazides **61** were proposed without their complete confirmation for the products of interaction of lactone **1** with hydrazine hydrate and methyl hydrazine, which were isolated in almost quantitative yields (Scheme 21).

5-Aminopyrazoles **62** and **63**, substituted and unsubstituted at the ring nitrogen atom, respectively, react with lactone **1** under rather harsh conditions (microwave irradiation, 120–180 °C). *N*-Phenyl substituted aminopyrazole **62** reacts as 1,3-C,N-dinucleophile in butanol in the presence of TsOH, and lactone **1** acts as acetylacetone equivalent giving pyrazolo[3,4-*b*]pyridine



Scheme 21

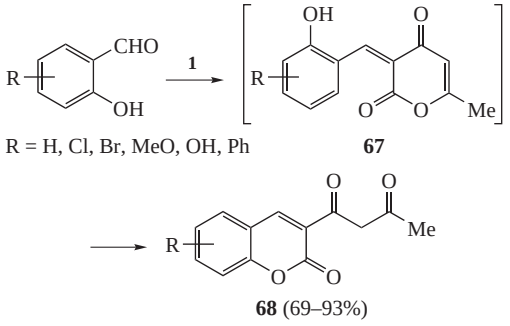
64.[55] Meantime, N-unsubstituted aminopyrazole **63** acts as a 1,3-N,N-dinucleophile, and the pyrone ring of lactone **1** is opened with the simultaneous esterification of the carboxyl group and the formation of regioisomeric pyrazolo[1,5-*a*]pyrimidines **65** and **66** (Scheme 22).[56] The reaction with 3-amino-1-phenylpyrazolin-5-one proceeds ambiguously and leads to the mixture of products.[8,57]



Scheme 22

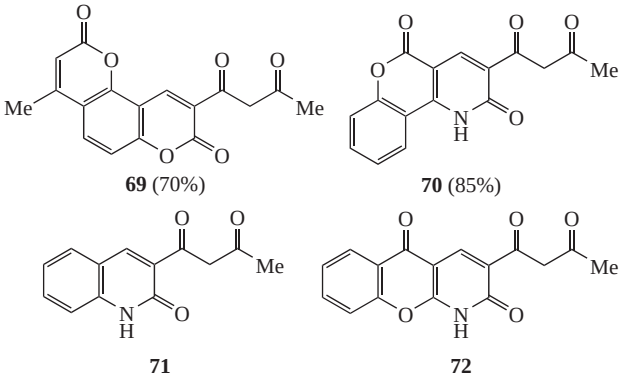
Reactions with ambiphiles. The transformations of lactone **1** upon treatment with ambiphiles, whose molecules contain both electrophilic and nucleophilic centers, will be considered in this chapter. Since the reactions of this type are related at the final step to intramolecular transformations, they do not require harsh conditions and proceed in high yields.

It is known that lactone **1** reacts with aldehydes to give the products of bisaddition,[4] however, its reaction with salicylic aldehydes, which can be considered as the 1,4-ambiphiles proceeds in a different way and leads to coumarins **68** containing a β-dicarbonyl moiety at 3-position.[58] It is obvious that the reaction starts from the Knoevenagel condensation followed by the intramolecular opening of pyrone ring of intermediate **67** upon the attack by the OH group of salicylic aldehyde. The reaction is tolerant to the nature of substituents at the aromatic ring and provides high yields regardless of used conditions (Al_2O_3/KF;[58(*a*)] $AcONH_4$/EtOH;[58(*b*)] piperidine/EtOH/MW;[58(*c*),(*d*)] ethanol/EPZ-10[58(*e*)]) (Scheme 23).

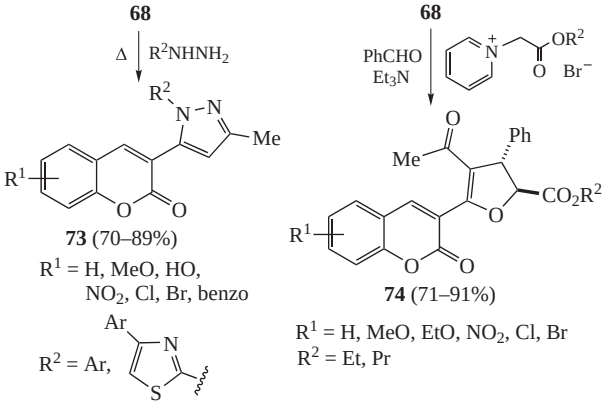


Scheme 23

Compounds **69**–**72** bearing an acetoacetyl substituent were obtained in a similar manner *via* the reaction of lactone **1** with 8-formyl-7-hydroxy-4-methylcoumarin,[59] 4-amino-3-formylcoumarin,[60] 2-aminobenzaldehyde *N*-phenylimine,[4] and 2-amino-3-formylchromone,[61] respectively.



Since compounds **68**–**72** are the 1,3-diketones, this structural feature allows one to synthesize from them a wide variety of 3-hetaryl-substituted coumarins and quinolones, including fused derivatives. These reactions are especially widespread in the mode of three- and four-component transformations. Thus, the reaction of lactone **1** and salicylic aldehydes with arylhydrazines in the presence of meglumine upon boiling in aqueous alcohol[62] or with thiazolylhydrazines in the presence of piperidine[63] affords 3-pyrazolylcoumarins **73** *via* the step of formation of 3-acetoacetylcoumarins **68** (Scheme 24). Microwave irradiation of a four-component mixture of lactone **1**, salicylic aldehyde, benzaldehyde, and pyridinium ylide in the presence of Et_3N leads to dihydrofuranyl coumarins **74**.[64]

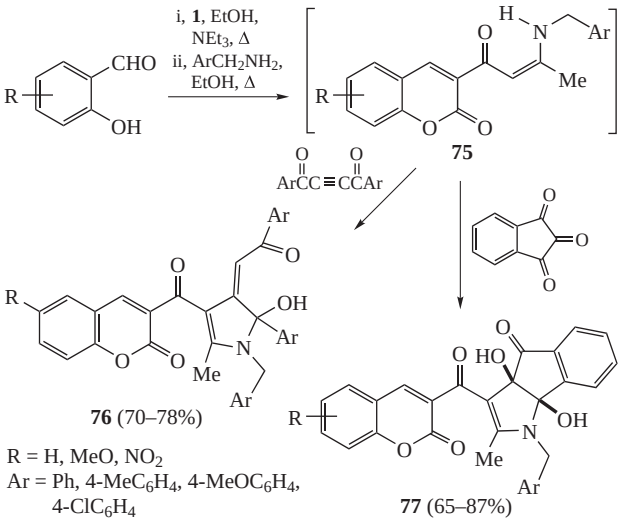


Scheme 24

Some works[65] report on the reaction of initially generated coumarin **68** with benzylamines and on the transformation of amino enone intermediate **75** upon the treatment with diaroylacetylenes and ninhydrin into products **76** and **77**, respectively (Scheme 25).

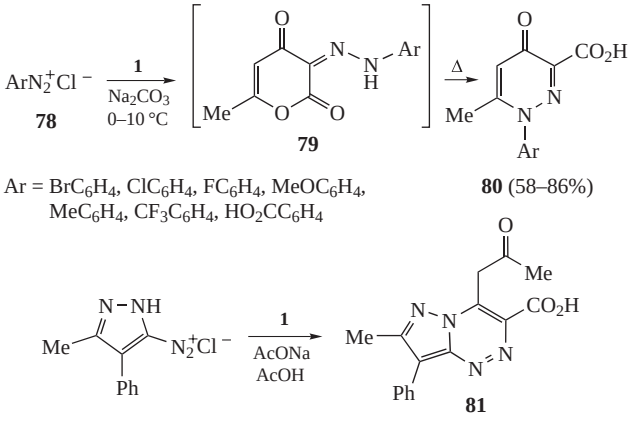
If a mixture of lactone **1** and salicylic aldehyde was boiled in acetic acid for 15 h in the presence of ammonium acetate, the intramolecular cyclization of amino enone would occur with the consequent oxidation of intermediate product with air oxygen into chromeno[4,3-*b*]pyridine-4,5-dione in low yields (23–33%).[58(*b*)]

The reaction of aryldiazonium salts **78** with lactone **1** proceeds at the C^3 position to form hydrazones **79**, whose pyrone ring is opened upon heating and cyclizes due to the internal N-nucleophile and electrophilic C^6 atom into 1-arylpyridazin-4-one-3-carboxylic acids **80** substituted at the benzene ring and exhibiting antibacterial activity (Scheme 26).[66] Another example, where



Scheme 25

lactone **1** acts as triacetic acid, was reported,[67] however in this case, the role of internal nucleophile is played by the pyrazole nitrogen, which attacks the C^4 atom of pyrone giving pyrazolotriazine **81** (see Scheme 26).

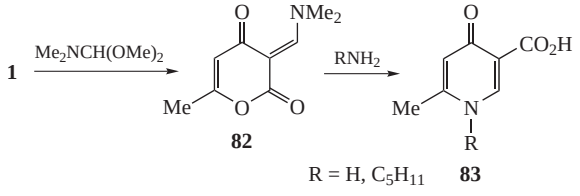


Scheme 26

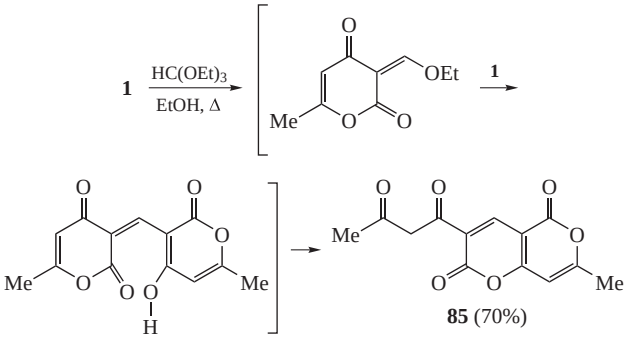
Reactions with electrophiles and nucleophiles. While the previous examples included the opening of lactone **1** ring upon treatment with ambiphiles whose electrophilic and nucleophilic centers belong to the same molecule, this chapter is aimed at the reactions involving two reactants: one of them exerts an electrophilic character and the other possesses a nucleophilic character.

The reaction of lactone **1** with dimethylformamide dimethylacetal leads to the enamination at position C^3 forming pyrandione **82**, whose treatment with ammonia or amylamine as the external nucleophile allows one to obtain pyridone-3-carboxylic acids **83**, which are the convenient platform for a design of biologically active compounds (Scheme 27).[68]

The treatment of lactone **1** with ethyl orthoformate in refluxed ethanol for 4 h furnished 4-methyl-3-(3-oxobutanoyl)-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione **85**, which was formed from the intermediate methylidene dimer **84** during the nucleophilic opening



Scheme 27



Scheme 28

of one of the pyrone rings caused by the attack of enol hydroxyl (Scheme 28).[69] Transformations of this product resulted from the treatment with aromatic amines were also reported.[70]

Many multicomponent reactions of lactone **1** covered in the review[6] proceed *via* the similar route: the formation of a 3-methylidene derivative, the Michael reaction, and the pyrone ring opening due to an attack with the internal nucleophile.

Conclusions

Major recent trends in the development of chemistry of triacetic acid lactone have been analyzed. Due to its structural features, the molecule of this lactone can react with either electrophiles or nucleophiles and these reactions can proceed with both the preservation and opening of pyrone ring. In addition to its great synthetic meaning, the triacetic acid lactone may be an alternative source in the transition from carbohydrates towards biologically active compounds and food chemistry products, *e.g.*, sorbic acid, which is currently produced from crotonaldehyde and ketene.

Due to the natural origin and diverse chemical properties, the triacetic acid lactone became widely employed in the synthesis of complex natural and medicinal molecules.[12(*d*),71] However, this mini-review format does not allow us to comprehensively cover those works and some examples of inter- and intramolecular cycloaddition reactions.[72]

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