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Levulinic acid in organic synthesis

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Abstract. Data concerning the methods of synthesis, chemical transformations and application of levulinic acid are analysed and generalised. The wide synthetic potential of levulinic acid, particularly as a key compound in the synthesis of various heterocyclic systems, saturated and unsaturated ketones and diketones, difficultly accessible acids and other compounds is demonstrated. The accessibility of levulinic acid from hexose-containing wood-processing and agricultural wastes is noted. The bibliography includes 260 references.

I. Introduction

At present, the use of organic synthesis on an industrial scale is so extensive that the problem of limited natural resources, such as petroleum and gas employed in this process comes to the foreground.[1] This generates a need for timely measures aimed at elaboration of alternative strategies of fine organic synthesis on the basis of alternative sources of raw materials. In this context, the synthesis of key compounds from wood processing products holds great promise. The most common cellulose-derived products include glucose, xylose, ethanol, polyhydric alcohols and furfural. Their use in industrial organic synthesis has been documented in numerous publications. Much less attention has been given to such cellulose hydrolysis products as organic acids, first of all, 4-oxopentanoic or levulinic acid (LA). The molecule of LA contains two highly reactive functional groups providing a great number of synthetic transformations. LA has been used to obtain various heterocyclic compounds, saturated and unsaturated ketones and diketones, difficultly accessible acids, alcohols and so on. We have analysed publications devoted to LA and found that despite the great number of these studies, their results have virtually not been generalised. Some reviews on the subject (see Refs 2 and 3) are not sufficiently comprehensive and outdated.

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In our opinion, the synthetic potentialities of LA are far from being exhausted, although the attention of investigators has now switched to starting compounds from other natural sources. Our desire to fill the information gap in this field, on the one hand, and to attract the attention of investigators and practitioners in synthetic chemistry to the high synthetic potentialities of LA manufactured from wood-processing and agricultural wastes on an industrial scale, on the other hand, was the incentive to write this review.

II. Physicochemical characteristics

Under normal conditions, LA is a colourless crystalline compound with a melting point of 37 °C, its boiling point (with decomposition) is 246 °C. The main physical constants for LA are as follows: d_4^{20} 1.140, d_4^{25} 1.1447; n_d^{20} 1.4796, n_d^{25} 1.441; surface tension 39.7 dyne cm^{-1} (25 °C); heat of vaporisation (150 °C) 0.58 kJ mol^{-1} and heat of fusion 79.8 J mol^{-1} (see Ref. 4).

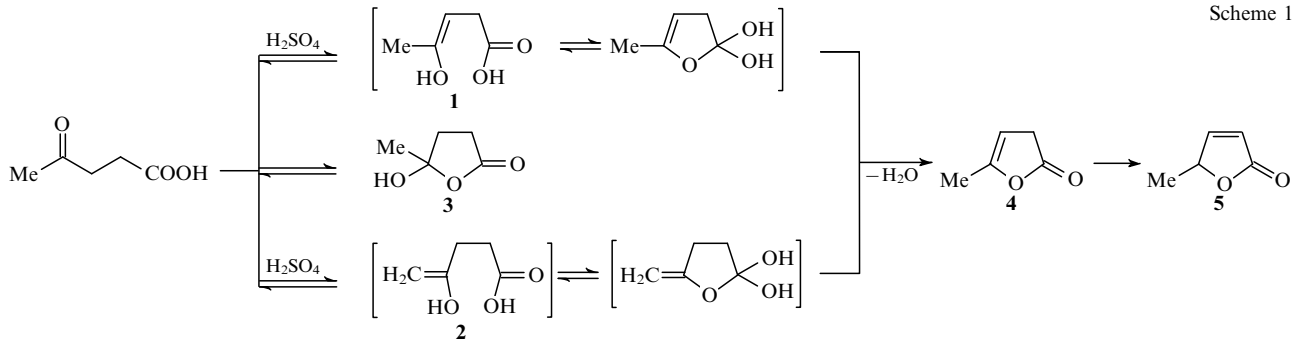
Levulinic acid is readily soluble in water, ethanol, diethyl ether, acetone and many other organic solvents. The temperature dependence of solubility of LA in water has been studied in detail.[5] In water, LA is fairly well dissociated, its pK_a (25 °C) is 4.59, see Ref. 6. In other words, the acidity of LA is comparable with that of the majority of lower alkane carboxylic acids. For comparison of gas-phase acidity of LA with those of other carboxylic acids, see Ref. 7.

The analysis of ^{1}H and ^{13}C NMR spectra of LA allowed a correct assignment of signals,[2] which demonstrated that the protons of the β-methylene group at position 3 are more 'acidic': (δ = 2.71 ppm) than those of the α-methylene group (δ = 2.47 ppm).

The rate of oxygen exchange of LA with water was studied using mass spectrometry. It was found[8] that the exchange of the carbonyl group oxygen occurs 10 times faster than that of the carboxy group. The approximate values of the pseudo-first-order constants in excess of $H_2{}^{18}O$ are $k_{CO} = 7 \times 10^{-3}$ s^{-1} and $k_{COOH} = 5 \times 10^{-4}$ s^{-1}, respectively. As expected, the carbon atom of the carbonyl group of LA is more susceptible to nucleophilic attack than that of the carboxy group.

The first ionisation potential of LA (9.7 eV according to photoelectron spectroscopic data[8]) corresponds to withdrawal of an electron from the orbital for which the main contribution is given by the unshared electron pair of the carbonyl oxygen atom.

Scheme 1



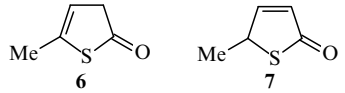
The knowledge of the specific characteristics of the keto–enol equilibrium of LA is substantial for the understanding of mechanisms of its reactions; for the equilibrium constants of LA derivatives see Refs 9 and 10. It was found [10] that the content of the enolic forms of LA, *viz*., 4-hydroxypent-3-enoic (**1**) and 4-hydroxypent-4-enoic acids (**2**), in diethyl ether is as low as 1.9×10^{-2}%. The concentration of the LA enolic forms **1** and **2** in D_2O solutions is negligible, which followed from the absence of deuterium exchange at C(3) and C(4) (^{13}C NMR spectral data). A similar conclusion was made from the analysis of UV spectra of aqueous solutions of LA.[11] Apparently, the ease of intramolecular transfer of the proton from the carboxy group to the carbonyl atom of oxygen is the reason for the predominant formation of 5-hydroxy-γ-valerolactone (**3**) rather than the enolic forms.

On the other hand, in acidic media (D_2O with addition of D_2SO_4) rapid H/D exchange occurred [2] resulting in the formation of $C(3)D_2$, $C(5)D_3$-pentadeuteriolevulinic acid. Thus under conditions of acid catalysis the concentration of the enolic forms **1** and **2** increases substantially. Apparently, the structures **1** and **2** are the intermediates in the cyclisation of LA into the lactones **4** and **5** (Scheme 1).[8]

Thus, the generally accepted viewpoint that LA is at equilibrium with the unsaturated lactones **4** and **5** (see, *e.g*., Ref. 12) is not quite correct, since an appreciable concentration of these lactones is observed only in the presence of strong mineral acids. As expected, removal of water shifts the reaction towards the formation of the cyclic product. Thus the lactone **4** can be easily prepared by boiling LA in the presence of sulfuric or phosphoric acids using a Dean–Stark trap.[13] It should be noted that the lactone **5** is thermodynamically more stable and is formed from the lactone **4** upon heating or treatment of the latter with a base.[14]

Enolisation of the lactone **4** into 2-hydroxy-5-methylfuran is theoretically possible. However, compound **4** does not manifest any enolic properties and its O-alkylation cannot be carried out despite the evolution of 0.3 equiv. of methane in the determination of mobile hydrogen according to the Tserivitinov procedure.[15] The chemical behaviour of furanones is rather specific and its consideration is beyond the scope of this review. Different aspects of furanone chemistry have been described in a comprehensive review.[16]

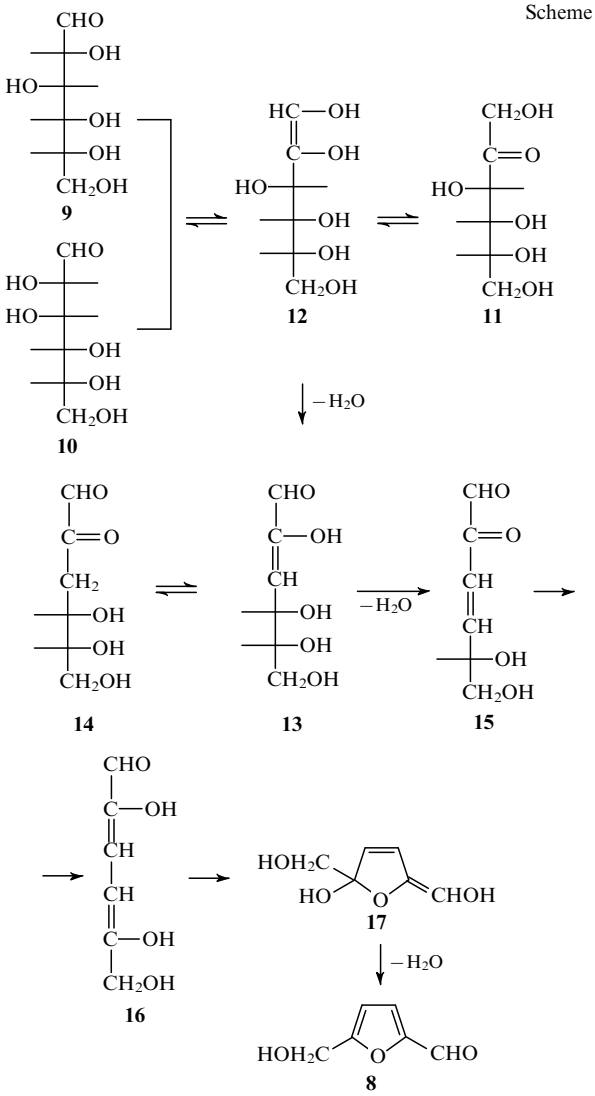
Thio derivatives of LA manifest an even greater trend for intramolecular cyclisation. Thus the reaction of LA with P_2S_5 or H_2S gives only cyclic products, such as the dihydrothiophenones **6** and **7** containing traces of 5-mercapto-5-methyltetrahydrothiophen-2-one.[17,18]



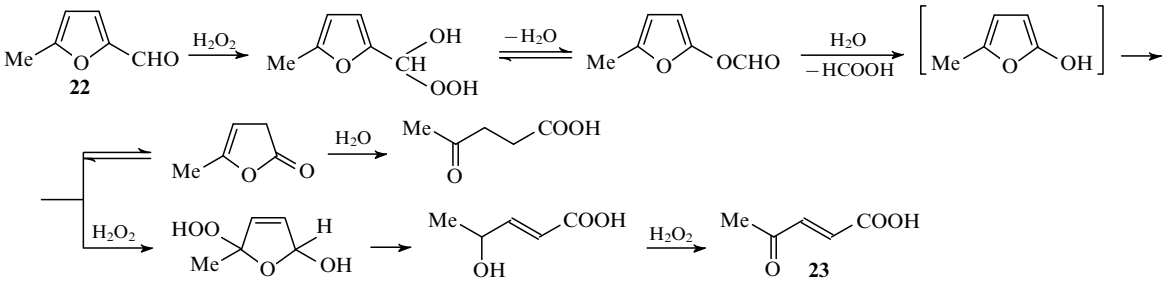
III. Preparation

On an industrial scale, LA is produced from wood-processing and agricultural wastes. The basis of industrial methods for the preparation of LA is transformation of hexoses in acidic media. This is usually considered as a combination of dehydration resulting in the formation of 5-hydroxymethylfurfural (**8**) and its subsequent hydration resulting in LA. The formation of 5-hydroxymethylfurfural **8** occurs through a series of consecutive reactions, which has been established by numerous studies aimed at identification of intermediate products and analysis of pathways of their further transformations (Scheme 2).[19,20] The enediol **12** obtained upon enolisation of D-glucose (**9**), D-mannose (**10**) or D-fructose (**11**) in acidic media is the key compound in the formation of 5-hydroxymethylfurfural **8**. Its dehydration results in compound **13**, which represents the enol form of 3-deoxyhexosulose (**14**). Compound **13** yields 3,4-dideoxyglycosulosene-3 (**15**). The latter is readily converted into the dienediol **16**, which eventually results in 5-hydroxymethylfurfural *via* the intermediate cyclic compound (**17**). Humin compounds are the side products of this reaction.[20]

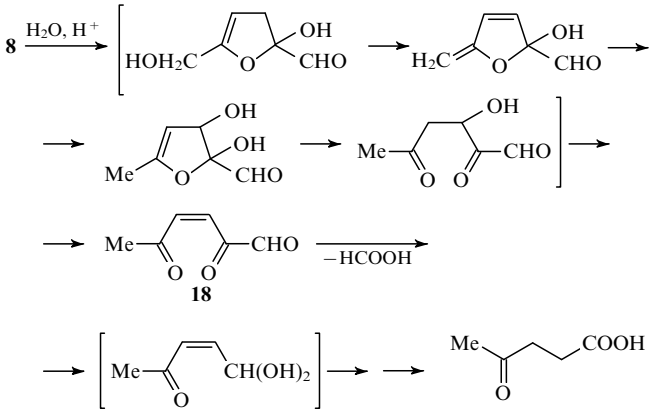
Scheme 2



Scheme 3



The conversion of 5-hydroxymethylfurfural **8** into LA is a result of addition of a molecule of water to the C(2) = C(3) bond of the furan ring.[19, 20] This leads to ring opening with formation of an unstable tricarbonyl intermediate **18**. The latter is decomposed into the final products, *viz*., LA and formic acid.

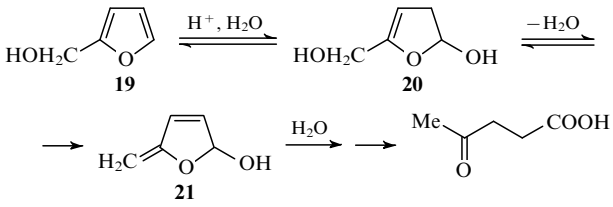


There are several assumptions about the nature of intermediates involved in the conversion of compound **8** into LA. The above scheme has been proposed in a recent study[21] devoted to the analysis of this reaction (the formation of humin compounds is not shown). The sequence of transformations was proposed by Horvat *et al*.[21, 22] on the basis of analysis of ^{13}C NMR spectra of the reaction mixture formed in the hydration of compound **8**.

Acid treatment of plant raw materials containing up to 75% of polysaccharides in the form of cellulose and hemicelluloses results in the hydrolysis of polysaccharides to monosaccharides.[23] The rate of wood pulp hydrolysis depends on the acid concentration, temperature, pressure and particle size.[24] Hydrolysis of cellulose to hexoses at atmospheric pressure is usually performed with strong acids (HCl, H_2SO_4) at 100 °C. The resulting hydrolysate is heated up to 110 °C with 20% HCl and kept at this temperature for 24–28 h. The reaction is accelerated by free halogens, transition metals, anion-exchange resins and other compounds.[2] After termination of the one-pot reaction, the reaction mixture is filtered to separate humin compounds and concentrated. LA is isolated from the mixture by distillation at reduced pressure or extraction with ether, ethyl acetate or ethyl methyl ketone. The yield of LA is about 40% with respect to the hexose content.[2] The reaction performed at 190 °C under pressure gives a considerable gain in time.[25]

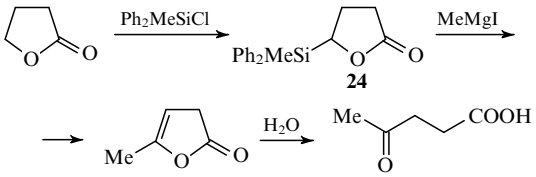
Preparation of LA from hexoses in supercritical reactors (34.5 MPa, 200–385 °C) has been described in many papers over the last decade.[26, 27] In the absence of acidic or basic catalysts, the dehydration reaction is more selective. Currently, degradation of hexoses under hydrothermal conditions[28, 29] or using alcohols in the presence of strong acids at 180–200 °C[30] is being developed. This permits one to reduce the reaction time to several minutes at sufficiently high yields of LA. A search for new efficient catalysts is currently under way. Thus zeolites were found to manifest high catalytic activity in the preparation of LA from glucose and fructose.[31]

Furfuryl alcohol (**19**), another product of wood pulp chemical processing, is an alternative source of LA. Its heating in aqueous organic acids ($K_a = 10^{-6}-10^{-4}$) in the presence of hydrochloric acid affords LA in more than 80% yield. When this reaction is performed in boiling ethyl methyl ketone in the presence of HCl, LA is formed in 90%–93% yield.[33, 34] The hydroxy derivatives **20** and **21** were shown (^{13}C NMR) to be the key intermediates in this reaction.[21, 22]

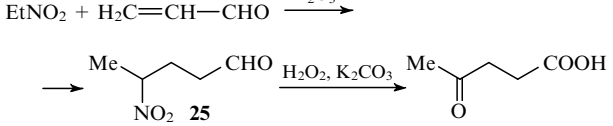


Levulinic acid is also formed upon oxidation of 5-methylfurfural (**22**) with 28% H_2O_2 at 60 °C in the presence of HCOOH. This reaction gives a mixture of levulinic and 4-oxopent-2-enoic (**23**) acids (Scheme 3).[35, 36]

It was shown[37] that LA is formed in high yield in the reaction of 4-(diphenylmethylsilyl)butyrolactone (**24**) with MeMgI.



LA can also be obtained in satisfactory yields[38] upon conjugate addition of nitroethane to acrolein in the presence of Al_2O_3 with subsequent oxidation of 4-nitropentanal (**25**) with an $H_2O_2-K_2CO_3$ system.



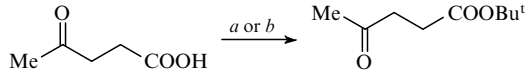
Despite the high yield of LA in the above reactions, they still cannot compete on an industrial scale with the simple and inexpensive procedures used in the preparation of LA from plant raw material.

IV. Reactions involving the carboxy group

Of reactions involving the carboxy group of LA, special mention should be made of esterification which yields useful levulinates. The reaction of LA with primary alcohols, which is a first-order reaction with respect to both reactants,[39] occurs in solutions of LA in respective alcohols even at room temperature.[40] In order to

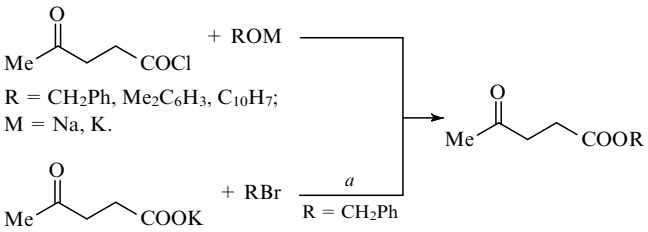
obtain esters in nearly quantitative yields, the reaction is carried out in the presence of typical dehydrating agents, such as sulfuric,[41,42] polyphosphoric[43] or *p*-toluenesulfonic acid.[44,45] The use of anion-exchange resins[46] or 2-halogenopyridinium salts[47] also gives good results. The increase in the size of the hydrocarbon fragment of the primary alcohol does not impede its esterification.[48] Since primary alcohols are easily and selectively acylated under these conditions, LA is used as a protective group in the synthesis of oligonucleotides[49] and oligosaccharides.[50–52] Deprotection can be achieved using sodium borohydride[53] or sulfite anion donors.[54] However, hydrazinolysis is the most efficient method for deprotection.[55,56] Under mild conditions, LA esters quantitatively react with hydrazine and its derivatives, which results in the regeneration of the original alcohol and the formation of the corresponding dihydropyridazinone, as a result of which the acid is completely eliminated from subsequent reaction. The formation of dihydropyridazinones and their reactivities are discussed in Section V.

The synthesis of LA esters with tertiary alcohols in good yields usually involves other reactions than esterification. For example, *tert*-butyl levulinate is obtained by the reaction of LA with dimethylformamide *tert*-butyl acetal[57] or *tert*-butyltrichloroacetimidate.[58]



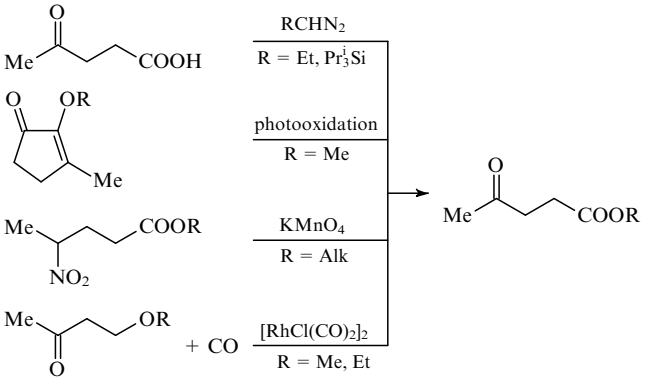
(*a*) $(Bu^tO)_2CHNMe_2$; (*b*) $CCl_3C(=NH)OBu^t$.

Substituted benzyl and aryl esters of LA can be obtained using other classical methods for ester synthesis, *e.g.*, acylation of alcoholates with levulinoyl chloride[2,59–61] or alkylation of LA salts with alkyl halides under conditions of phase-transfer catalysis.[62]



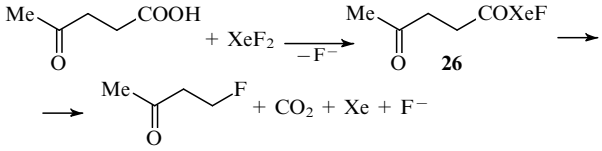
(*a*) KOH, H_2O, $CHCl_3$, Bu_4NBr.

In addition to the methods described above, there are some other ways to obtain LA esters. Levulinates are formed by the reaction of LA with diazomethane derivatives,[63] upon photooxidation of cyclopentenone derivatives,[64] from the corresponding nitro compounds by the Nef reaction[65] or catalytic carbonylation of 4-alkoxybutan-2-one on rhodium catalysts.[66]

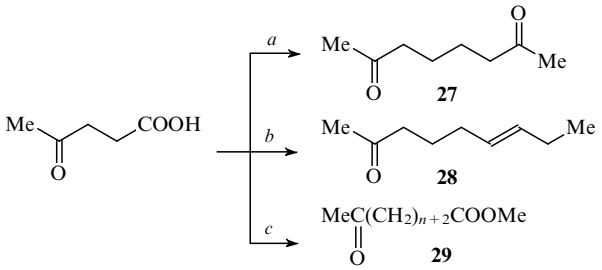


LA thio esters are obtained in high yields by the reaction of thiols with a pyridinium salt of LA formed *in situ* from the free acid and 2-fluoro-1-methylpyridinium tosylate.[67]

Decarboxylation of LA in the gaseous phase occurs with difficulty.[68] Attempts to perform this reaction in a flow of hydrogen over Ni- and Pd-catalysts at 180–330 °C or over zeolites containing group I, II and VIII metals were more successful.[69] Thus heating of the lactone **4** up to 570 °C in the presence of SiO_2 gave up to 80% of ethyl methyl ketone.[70] A method for decarboxylation proposed recently using xenon fluoride was applied successfully to LA. Such fluorodecarboxylation occurs at room temperature[71] *via* intermediate fluoroxenon esters **26**.

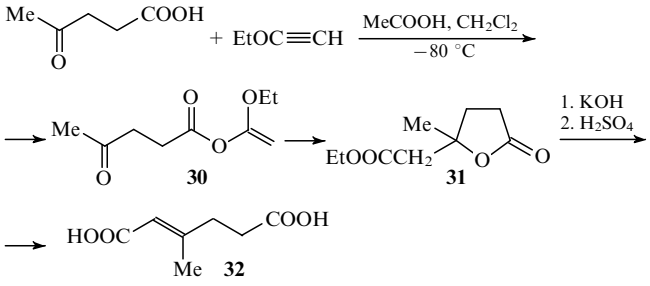


Studies of anodic electrolytic decarboxylation of LA under conditions of the Kolbe reaction have established interesting synthetic possibilities. In methanol, at a potential difference of 80–129 V and 2–3 A in the presence of sodium methoxide, LA was converted into octane-2,7-dione (**27**).[72] Cross-decarboxylation in the presence of other carboxylic acids results in unsaturated ketones **28**[73] and higher aliphatic oxo acid esters **29**.[74,75]



(*a*) MeOH, MeONa; (*b*) Me–⟨ ⟩–COOH; (*c*) $HOOC(CH_2)_nCOOMe$, n = 4, 8, 12.

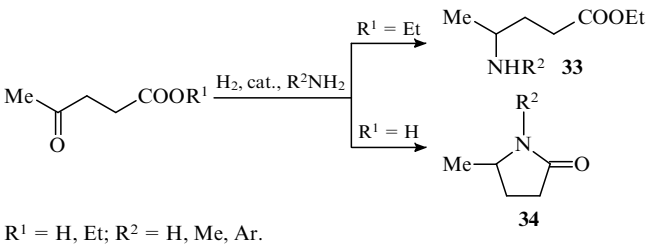
In addition to the above reactions involving the carboxy group of LA, of note is its nucleophilic addition to alkoxyacetylenes.[76] The addition product **30** is unstable and is easily rearranged into the lactone **31** which ultimately yields 3-methylhex-3-enedioic acid (**32**).



V. Reactions involving the carbonyl group

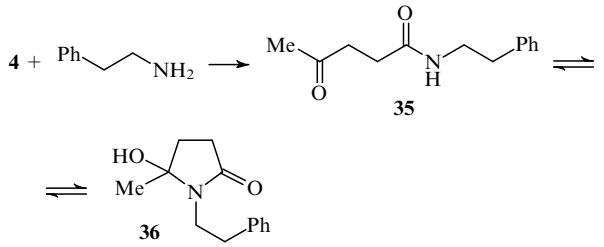
1. Reactions with N-nucleophiles

The presence of two highly reactive functional groups in the LA molecule determines its specific properties. Reactions of LA with nitrogen-containing nucleophiles provide an illustrative example. As a rule, reactions of LA with such nucleophiles are not terminated by their addition to the carbonyl group or the formation of the corresponding amide but result in heterocyclisation. For example, the carbonyl group of LA undergoes the Knoop–Oesterlin reductive amination.[77] This reaction is catalysed by Co, Ni and Pd and gives either the corresponding amino acids **33**,[78] or 5-methyl-2-pyrrolidone derivatives **34** as a result of cyclodehydration, depending on whether the carboxy group of LA is protected or not.[79,80]

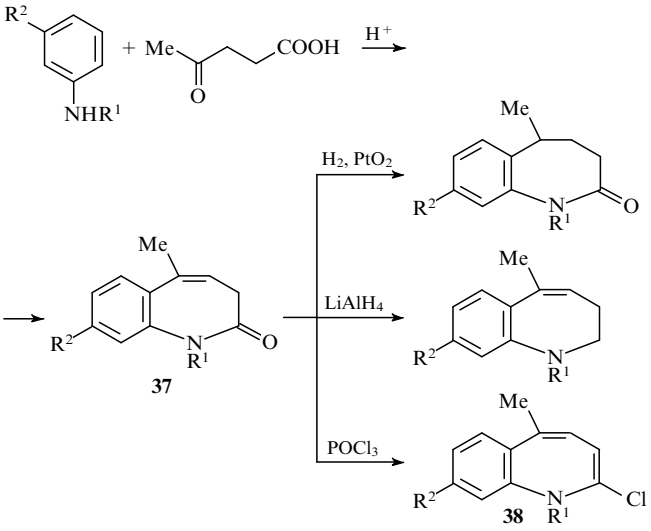


R^1 = H, Et; R^2 = H, Me, Ar.

The amides formed by the reaction of LA with various amines are attractive not only because of their biological activity,[81] but also because of their ability for cyclisation. Thus the amide **35** formed in the reaction of phenethylamine with α-angelicalactone (**4**) is unstable and is at equilibrium with the corresponding pyrrolidone **36** (the **35** : **36** ratio is 1 : 2).[82, 83]

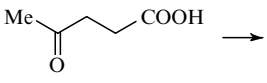


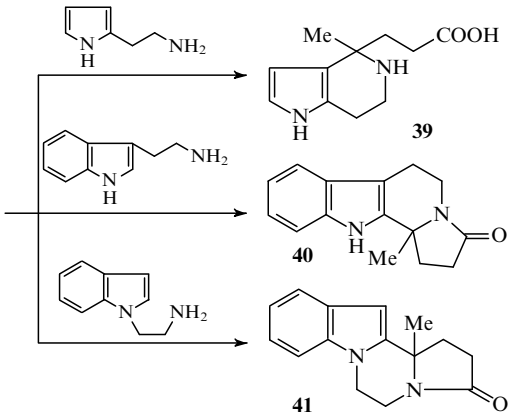
Reactions of anilines with LA or the lactone **4** in acidic media yield reactive benzoazepinone derivatives **37** rather than anilides.[84, 85] The direction of their hydrogenation depends on the nature of the reagent used. Thus hydrogenation with hydrogen over PtO_2 results in saturation of the C(4) = C(5) bond of the azepine ring, whereas treatment of the benzoazepinones **37** with $LiAlH_4$ results in the reduction of the oxo group to the methylene group. Treatment of compound **37** with $POCl_3$ gives the chloro-substituted benzoazepine **38**.



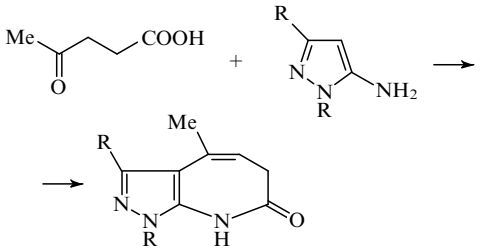
R^2 = H, Me, MeO.

The result of the reaction of LA with pyrrole derivatives containing the 2-aminoethyl group depends on its position in the ring. Thus the reaction of LA with 2-(2-aminoethyl)pyrrole gives the 1*H*-pyrrolo[3,2-*c*]pyridine derivatives **39**.[86] A similar reaction of LA with 3-(2-aminoethyl)indole (tryptamine) or *N*-(2-aminoethyl)indole leads to the formation of fused heterocyclic systems **40** and **41**, respectively.[87, 88]

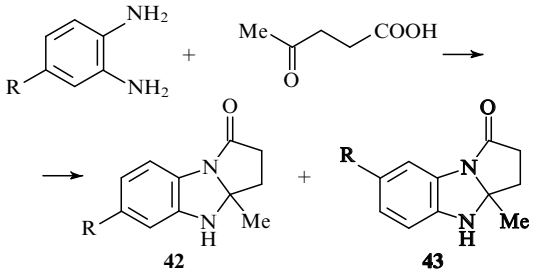




The reaction of LA with 5-aminopyrazoles gives substituted 4-methyl-6*H*-7,8-dihydropyrazole[3,4-*b*]azepin-7-ones.[89]

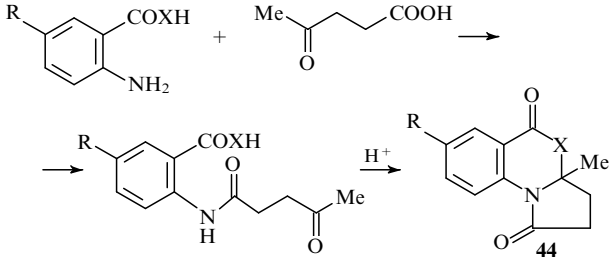


The reaction of LA with *o*-phenylenediamine derivatives results in the formation of the benzoimidazole ring and yields isomeric pyrrolobenzoimidazolones **42** and **43**.[90]



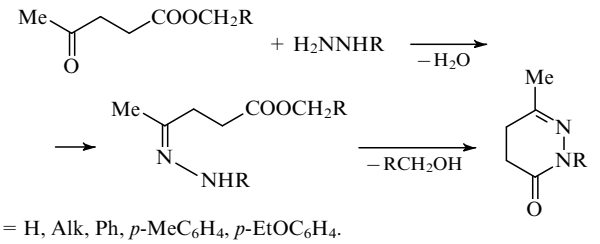
R = Cl, Me.

Substitution of an amide group for an amino group in the aromatic component of this reaction affords other types of heterocyclic derivatives. Thus anthranilic acid and its amides react with LA to give fused heterocyclic systems, *e.g.*, 2,3,3*a*,4-tetrahydropyrrole[1,2-*a*]quinazoline-1,5-diones **44** from anthranilamides.[91, 92]



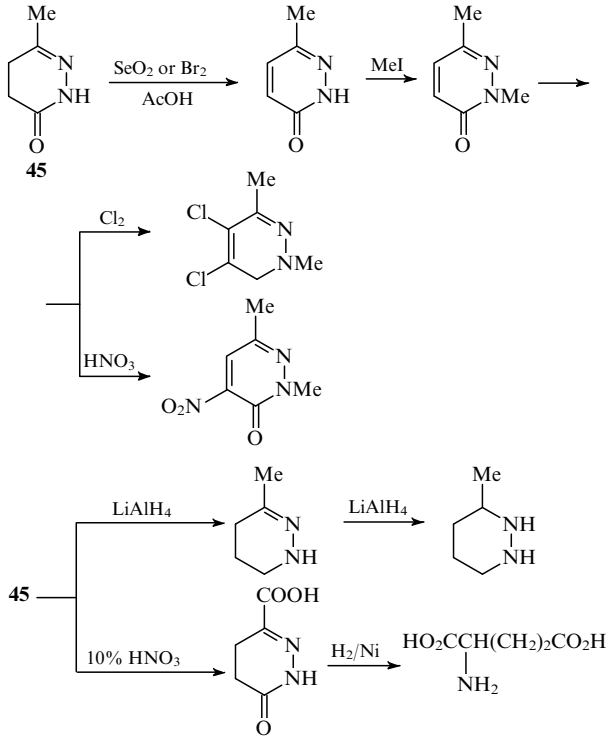
R = H, Cl; X = O, NH, NMe, NPh.

As noted above, LA and its esters readily react with hydrazine and its derivatives to give the corresponding hydrazones. Dihydropyridazinones [93–96] possessing analgesic and diuretic activities are formed from hydrazine and its monosubstituted hydrazones upon cyclodehydration.[97]

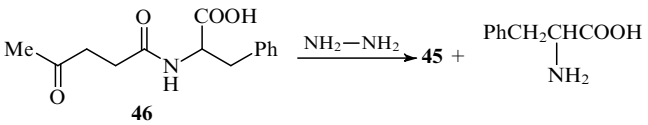


R = H, Alk, Ph, *p*-MeC_6H_4, *p*-$EtOC_6H_4$.

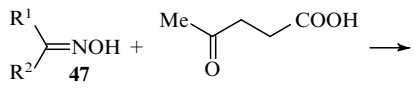
Dihydropyridazinones are highly reactive compounds and can be used in organic synthesis. Using compound **45** as an example, it was demonstrated that dihydropyridazinones are easily oxidised with bromine or SeO_2 to the corresponding pyridazinones [93, 94] and reduced with $LiAlH_4$ first to tetrahydropyridazines [95] and then to hexahydro derivatives.[98] Pyridazinones undergo alkylation, nitration and chlorination.[99] Compound **45** was also used to obtain glutamic acid *via* the intermediate pyridazinone-3-carboxylic acid.[100]

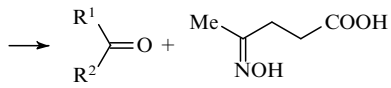


The formation of the dihydropyridazinone ring upon treatment of levulinamide with hydrazine illustrates the possibility of nonenzymic hydrolysis of the peptide bond. This is exemplified by reaction of *N*-levulinoyl-L-phenylalanine (**46**) with hydrazine.[101]



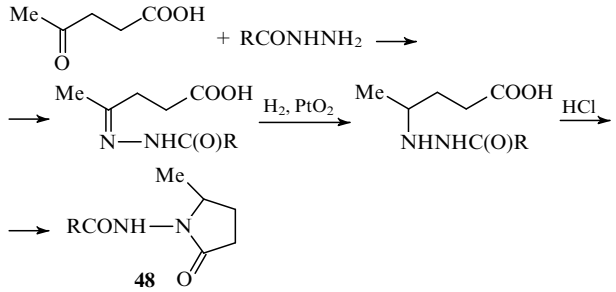
LA reacts very easily with 2,4-dinitrophenylhydrazine. This circumstance was used in the development of a semi-quantitative colorimetric procedure for determination of hydrazones. This method is based on the ability of LA to serve as an acceptor of 2,4-dinitrophenylhydrazine and to regenerate the ketone from the corresponding hydrazone as a result of the exchange reaction.[102] It was noted also that treatment of the oximes **47** with LA recovers carbonyl derivatives.[103]





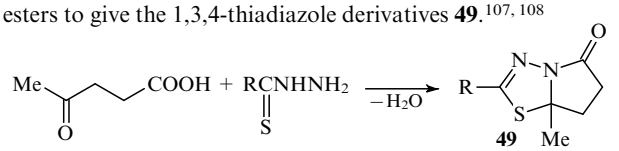
R^1 = Me, R^2 = Ph; R^1 = Ph, R^2 = H; $R^1 = R^2$ = Ph.

LA hydrazones manifest noticeable antibacterial activity.[104–106] They also serve as a source of *N*-subsituted pyrrolidones. The reaction between LA and hydrazides of nicotinic or isonicotinic acids demonstrates an approach to the synthesis of *N*-acyl pyrrolidones **48**.[107]

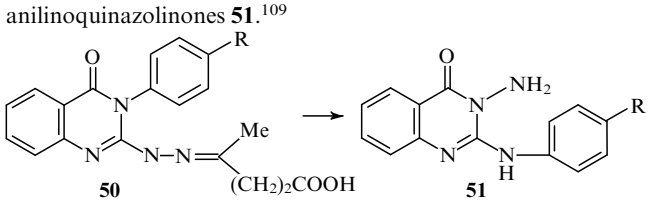


R = 3-pyridyl, 4-pyridyl.

Unlike acylhydrazines, their thio analogues react with LA or its esters to give the 1,3,4-thiadiazole derivatives **49**.[107, 108]

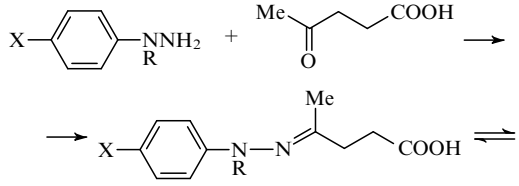


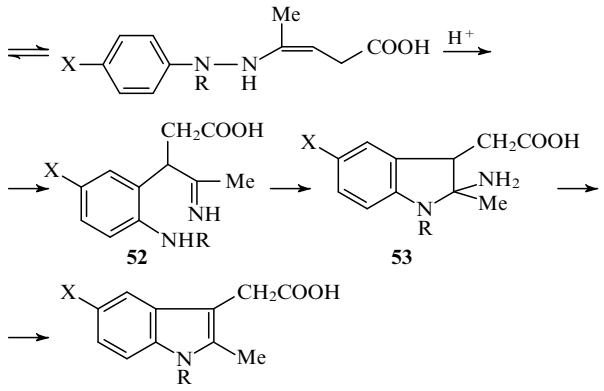
The hydrazones **50** prepared from LA and 3-aryl-2-hydrazinoquinazolinones are thermally unstable and undergo the Dimroth rearrangement at melting temperature with simultaneous cleavage of the imine bond, eventually resulting in 3-amino-2-anilinoquinazolinones **51**.[109]



The role of LA arylhydrazones in the Fischer indole synthesis has been studied in most detail, since this reaction gives an access to not only heteroauxin analogues manifesting growth-regulating activity [110] but also to a broad range of antiinflammatory drugs, such as indometacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-ylacetic acid].[111] Halogen-, alkyl- and alkoxy-substituted arylhydrazines,[112, 113] 1-naphthylhydrazine [114] and various *N*-acyl-*N*-arylhydrazines enter into this reaction.[115–120] Sodium arylhydrazinesulfonate can be used instead of phenylhydrazine hydrochloride which is unstable on storage.[121, 122]

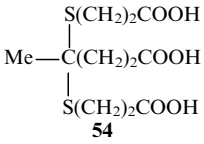
The mechanism of this reaction was studied with LA as an example. It was found that hydrazone rearrangement, which is probably similar to the Claisen rearrangement of allyl phenyl ethers, is the key stage. The key intermediate of the imine type, *viz*., compound **52**, which gives the intermediate **53** upon heterocyclisation, was studied by ^{13}C NMR spectroscopy.[123]





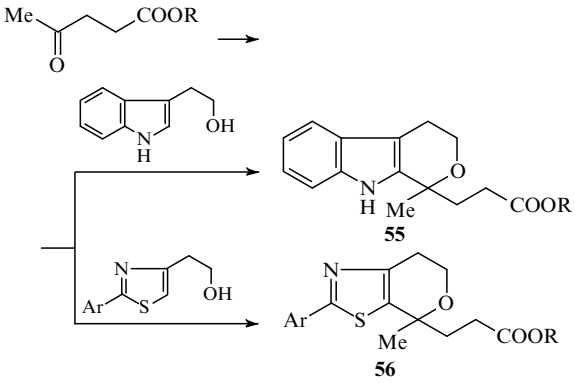
2. Reactions with O- and S-nucleophiles

Under conditions of acid catalysis, LA esters react easily with alcohols and thiols to give the corresponding dialkylacetals and dialkyldithioacetals in more than 90% yields.[124] Special mention should be made of compound **54** formed in the reaction of LA with 3-mercaptopropionic acid, which can selectively extract some metal cations.[125]



54

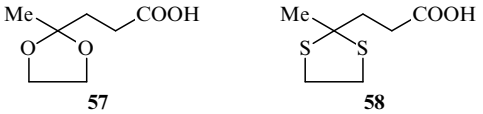
The reaction of LA with thiazolyl- and indolylethanols gives the fused tetrahydropyrans **55** and **56**.[126, 127]



55

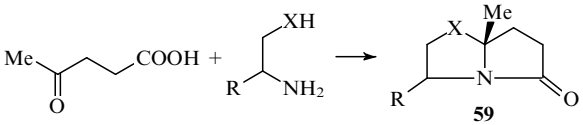
56

The reaction of LA or its esters with 1,2-diols or dithiols gives dioxolanes and dithiolanes.[128, 129] As is known, the formation of such structures is often used to protect the carbonyl group. This approach is also used in multistage syntheses involving LA. Thus the 1,2-dioxolane (**57**) and 1,3-dioxolane (**58**) derivatives of LA were used to protect its carbonyl group in the syntheses of a natural pheromone,[130] *Z*-jasmone and dihydrojasmone.[131–133]



57 **58**

The presence of an amino group in the α-position with respect to the hydroxy or the mercapto group in amino alcohols or amino thiols makes it possible to carry out heterocyclisation on their reactions with LA [134, 135] to give the bicyclic lactams **59**.

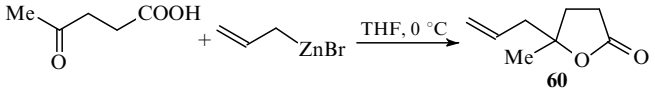


59

R = COOH, $CHMe_2$; X = O, S.

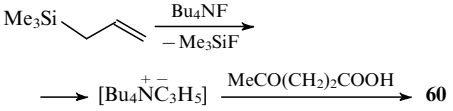
3. Reactions with organoelement compounds

The carbonyl group is capable of nucleophilic addition of organometallic compounds. However, this reaction is often complicated due to involvement of the carboxy group. γ-Valerolactone derivatives [136–140] are formed instead of the expected hydroxy acid derivatives even in reactions of organometallic derivatives of group I and II elements with levulinates with the protected carboxy group. Thus the reaction of LA with allylzinc bromide gives 5-allyl-γ-valerolactone (**60**) in 80% yield.[139]



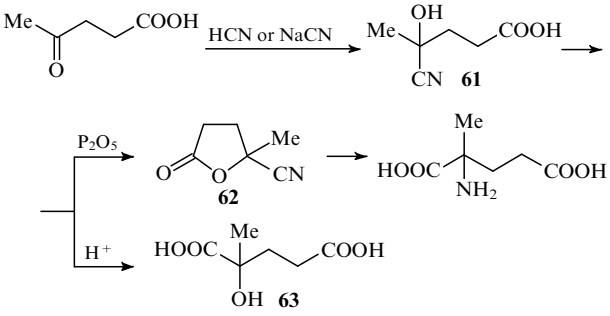
60

The allyl carbanion formed *in situ* as a result of hydrolysis and scission of the Si–C bond in allyltrimethylsilane under the action of tetrabutylammonium fluoride adds to LA to give the γ-valerolactone **60** following hydrolysis of the intermediate product.[141]



Nevertheless, allylation of LA and its esters to the corresponding derivatives of 4-hydroxyvaleric acid can be achieved with allyl bromide in the presence of metallic Zn, Sn and Al [142, 143] as well as alkyl complexes of transition metals.[144] The pseudo-Barbier reaction involving ethyl levulinate and alkyl halides in the presence of samarium cyclopentadienyl complexes is also possible.[145]

The reaction of LA with metal cyanides and hydrocyanic acid gives the cyanohydrin **61**.[146] The latter yields 5-cyano-γ-valerolactone (**62**) under the action of dehydrating reagents; its hydrolysis gives 2-hydroxy-2-methylglutaric acid (**63**). The lactone **62** can also be converted into 2-methylglutamic acid.[147]

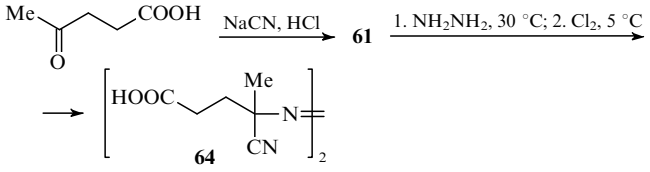


61

62

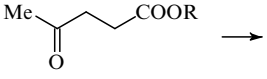
63

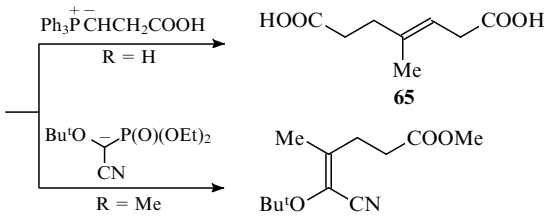
The reaction of the cyanohydrin **61** with hydrazine followed by oxidation gave the azo compound **64**, which is an initiator of radical reactions.[148, 149]



64

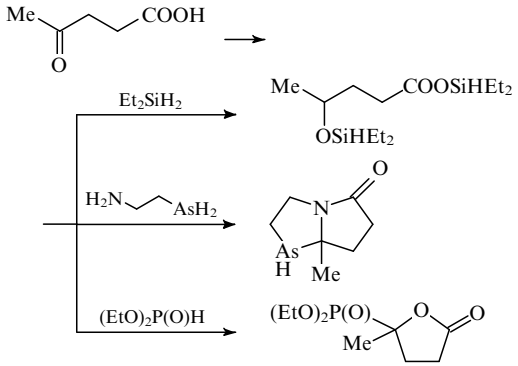
The carbonyl group of LA or its esters reacts with phosphorus-substituted carbanions [150, 151] in the Wittig and Horner–Emmons reactions to give compounds **65** and **66**.



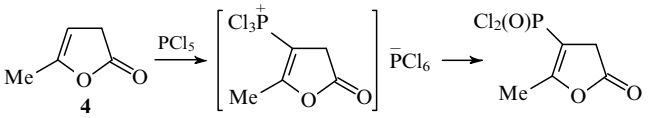


R = H, Me.

Hydrides of group IV and V elements also easily add to the carbonyl group of LA. Hydrosilylation in the presence of rhodium complexes with chiral ligands occurs as enantioselective reduction.[152, 153] However, unlike diethylsilane, which gives a stable silylation product,[154] hydride derivatives of arsenic and phosphorus yield unstable addition products that easily undergo intramolecular cyclisation.[155, 156]

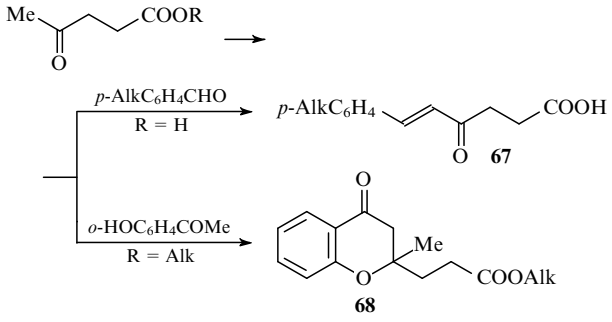


The result of the reaction of halides of group V elements with LA depends on the nature of the halide. As would be expected, bismuth and antimony halides yield predominantly acyl derivatives,[157, 158] whereas the reaction with $MeNbCl_4$ results in the chlorination of the carbonyl group of LA.[159] The same result is observed in the interaction of LA with phosphorus pentachloride.[160] However, the reaction of PCl_5 with α-angelicalactone (**4**) leads to phosphorylation of the multiple bond.[161]



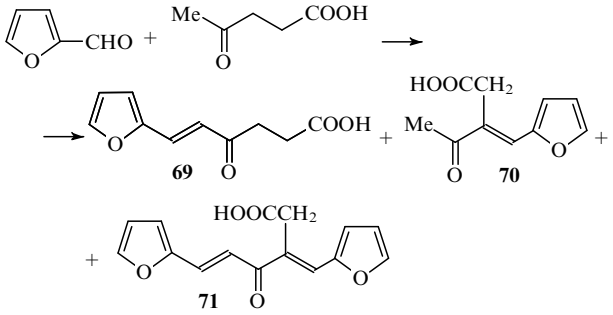
4. Condensation reactions

Aldol condensation of LA with aromatic and heterocyclic aldehydes under conditions of the Claisen reaction gives α,β-unsaturated carbonyl compounds and their derivatives. Benzaldehyde and its analogues easily enter into the condensation reaction to give 6-aryl-4-oxohex-5-enoic acid (**67**),[162–164] while the reaction of LA esters with 2-hydroxyacetophenone yields the 2-substituted chromone **68**.[165–167] It is believed [168] that this reaction proceeds *via* the lactone intermediate by the Stobbe condensation.

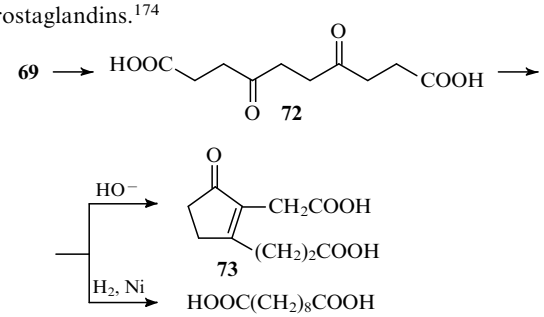


Since the unsaturated acids **67** thus formed are γ-oxo acids, they retain ability to form pyridazinones on reaction with hydrazine. Pyridazinones can undergo bromination and yield pyridazines.[169]

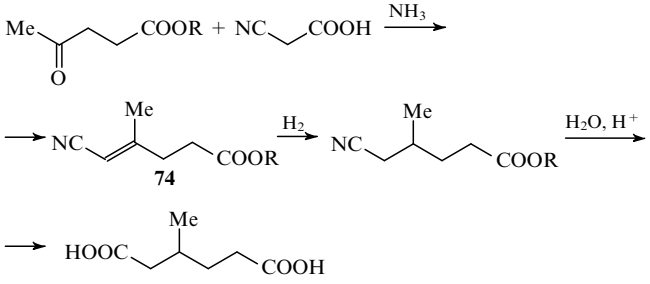
Condensation of LA with furfural offered even broader possibilities for the synthesis.[170–175] This reaction can yield diverse furancarboxylic acids. 5-Furfurylidenelevulinic acid (**69**) is the main reaction product at room temperature. However, at a temperature above 50 °C, the proportion of 3-furfurylidene- (**70**) and 3,5-difurfurylidenelevulinic acids (**71**) increases.[173]



Acid treatment of the acid **69**, *i.e.*, the main reaction product, gives dilevulinic acid **72**; its reduction on a Raney nickel catalyst yields sebacic acid,[171] and its cyclisation results in the dicarboxylic acid **73**, which served as the starting compound in the synthesis of prostaglandins.[174]

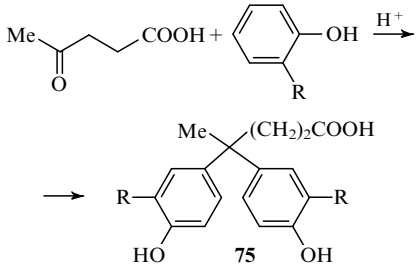


Condensation of LA or its esters with cyanoacetic acid under conditions of the Knoevenagel reaction yields the nitriles **74**. The latter were used to obtain 3-methyladipic acid by reduction of the double bond and acid hydrolysis.[176]



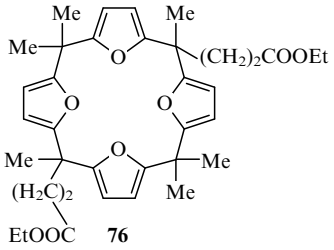
R = H, Me, Et, CH_2Ph.

Like aldehydes and ketones, LA undergoes acid-catalysed condensation with phenols and naphthols to give the 4,4-diaryl-substituted valeric acids **75**.[177–180]

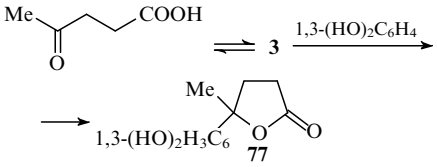


R = H, Me.

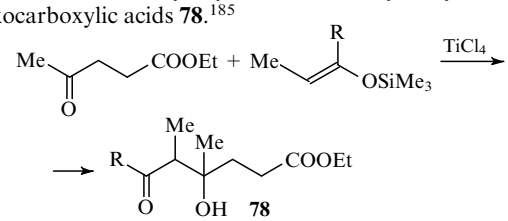
Furan and its derivatives react analogously.[181–183] Conjugate condensation of furan with acetone and LA or its esters makes it possible to obtain macrocycles of the type **76**, which can selectively extract metal ions similarly to crown ethers.



The reaction of LA with resorcinol occurs in a different way and gives the arylated γ-valerolactone **77**.[184]



In the reaction of LA esters with enol silyl ethers in the presence of equivalent quantities of $TiCl_4$, cross-aldol condensation occurs smoothly to yield esters of 4-hydroxy- 4,5-dimethyl-6-oxocarboxylic acids **78**.[185]



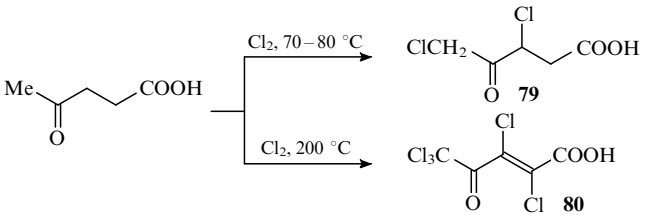
R = Alk.

A similar reaction takes place in the condensation of LA with chlorodifluoromethyl ketones.[186]

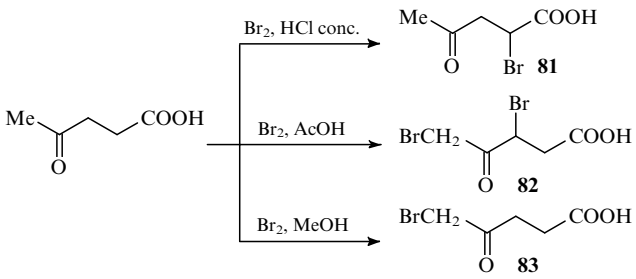
VI. Reactions involving the methyl and the methylene groups

The carbonyl and the carboxy groups of LA activate the neighbouring carbon atoms. Therefore, LA undergoes easy chlorination and bromination. These reactions yield organic halides which represent valuable 'building blocks'.

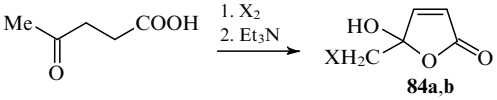
Chlorination of LA with chlorine at moderate temperatures results in 3,5-dichlorolevulinic acid (**79**).[187] With a rise in temperature or in the presence of Lewis acids, more profound chlorination takes place to give 2,3,5,5,5-pentachloro-4-oxopentenoic acid (**80**),[188–191] which can be used as defoliant.



The result of bromination of LA strongly depends on the medium in which the reaction is performed. By varying the solvent, one can obtain different bromo derivatives of LA with sufficiently high selectivity. Thus bromination in the presence of concentrated HCl gives predominantly 2-bromolevulinic acid (**81**),[191] whereas in acetic acid 3,5-dibromo-derivative **82** is obtained.[192] In methanol, the reaction results in regioselective bromination of LA at the methyl group to give 5-bromolevulinic acid (**83**).[193]

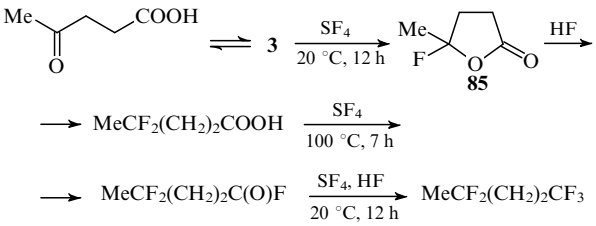


Combination of halogenation and dehydrohalogenation of LA affords halogen-containing hydroxyfuranones **84a**,**b**.[194, 195]



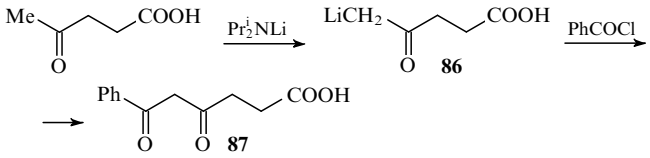
X = Cl (**a**), Br (**b**).

Sulfur tetrafluoride[196–198] and its derivatives[199] are the most effective fluorinating agents for LA. However, this does not involve the methyl and the methylene groups. It was shown that the lactone **3**, which is always present in a solution of LA, is the first to undergo fluorination. The latter is converted into 1,1,1,4,4-pentafluoropentane through the intermediate **85**.



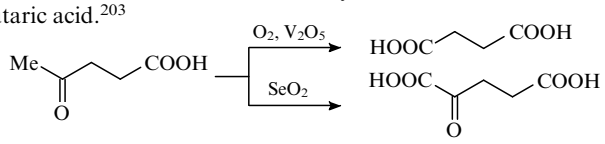
Ethyl levulinate undergoes fluorination only at the carbon atom of the carbonyl group under these conditions.[200]

The methyl group of LA is active in the metallation reaction. Thus treatment of LA with lithium diisopropylamide gives the organolithium compound **86** which, in turn, yields 6-phenyl-4,6-dioxohexanoic acid (**87**) in the reaction with benzoyl chloride.[201]

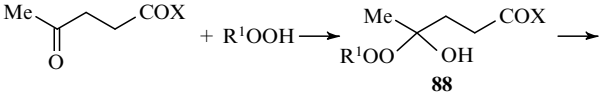


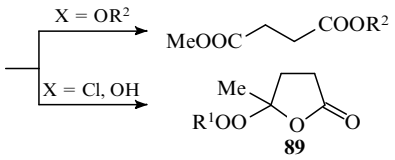
VII. Oxidation and reduction reactions

The result of oxidation of LA strongly depends on the type of the oxidant. High-temperature oxidation of LA with oxygen over V_2O_5 gives succinic acid[202] and oxidation of LA with selenium dioxide under conditions of the Riley reaction results in 2-oxoglutaric acid.[203]



Oxidation of LA and its derivatives with peroxy compounds in the Baeyer–Williger reaction has been studied.[204–207] The first step of this reaction yields hydroxyperoxyvaleric acid derivatives **88**, which rapidly cyclise to peroxyvalero-γ-lactones **89**. If the carboxy group is protected, succinates are formed.



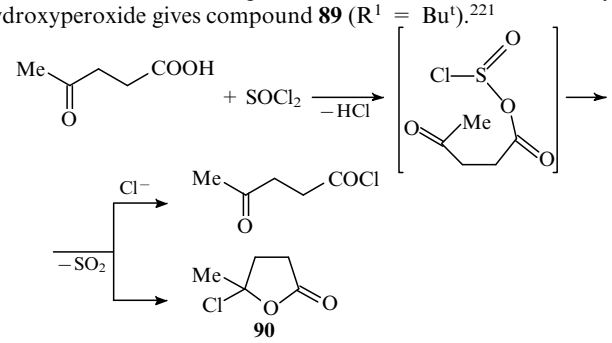


89

Reduction of LA can be carried out by various methods. First, mention should be made of catalytic hydrogenation of LA and its esters on Raney nickel. The free acid is quantitatively converted into γ-valerolactone,[208] while its esters are reduced to 4-hydroxyvaleroates.[209] Analogous products are obtained upon hydrogenation of LA and its esters on a copper–chromium catalyst (CuO, 80%; Cr_2O_3, 20%).[210] Modification of hydrogenation catalysts with optically active substances (L-alanine, L-phenylalanine, L-glutamic acid, D-tartaric acid) allowed one to accomplish asymmetric synthesis of γ-valerolactone from LA.[211–213]

Under conditions of reductive cyclisation, LA and its esters serve as starting compounds in the synthesis of different saturated lactones, *e.g.*, 5-substituted butyrolactones.[214–216] Thus the optically active γ-valerolactone is obtained in good yield by reduction of LA with silanes in the presence of rhodium catalysts with chiral ligands.[217]

The reaction of LA with $SOCl_2$ gives the saturated lactone **90** in addition to levulinoyl chloride. This reaction is believed to occur according to the mechanism depicted in the scheme given below.[218] The yield of compound **90** can reach 100%.[219] Apparently, the formation of 5-methoxy-γ-valerolactone in the reaction of LA with methyl chloroformate occurs in a similar way.[220] The halogen atom in compound **90** is rather mobile. Thus the reaction of the lactone **90** with equimolar amount of 90% *tert*-butyl hydroxyperoxide gives compound **89** (R^1 = Bu^t).[221]



90

The reaction of LA with sodium dithionite in boiling aqueous dioxane also gives γ-valerolactone. It is believed[222] that this reaction occurs through the formation of α-hydroxysulfinates. For catalytic hydrogenation of the oxo group of LA catalysed by ruthenium and rhodium complexes see Refs 223 and 224.

More profound reduction of LA derivatives to diol or valeric acid is also possible. Thus reduction of LA with lithium aluminium hydride gives racemic pentane-1,4-diol,[225] while electrochemical reduction of LA under conditions of catholyte recirculation and membrane separation of anolyte gives valeric acid.[226] Bakers yeast reduce LA esters to 4-hydroxyvalerates in good yields and then to (*R*)-γ-valerolactone and (*S*)-pentane-1,4-diol.[227]

VIII. Conclusion

Thus, easy access to LA from natural renewable raw materials makes this acid a readily available starting compound for the synthesis of 1,4-dicarbonyl systems the synthetic approaches to which are limited.[228]

On the one hand, LA enter into miscellaneous reactions of nucleophilic addition of N-, O-, S- and C-centred nucleophiles at the oxo group; on the other hand, it undergoes classical transformations characteristic of carboxylic acids. Moreover, LA as a typical representative of γ-oxo carboxylic acids reacts with involvement of both functional groups at once. This permits the synthesis of various types of heterocyclic compounds on the basis of LA, *e.g.*, pyrrolidone, benzoazepinone, indole and chromone derivatives.

It is noteworthy that the presence of an electron-acceptor carbonyl group in the LA molecule strongly increases the acidity of the protons at C(3). Their mobility favours the alkylation and halogenation of the LA molecule as well as its lactonisation.

Owing to the accessibility of LA, the methods for synthesis of various compounds based on it efficiently compete with alternative synthetic approaches.

In addition, both LA and its derivatives possess various useful properties which significantly expand the range of their ever increasing synthetic applications. Thus levulinic acid is used to control plant growth.[229] Being an inhibitor of choline photolysis,[230] LA can inhibit or stimulate chlorophyll synthesis.[231] It is used as a modifying additive to resins based on furfuryl alcohol,[232] modifies the surface of aminoaerosils,[233] confers radiation-protective properties to polymers[234] and is used for scheelite flotation.[235] Its esters and salts are used in the food industry[236–240] as preservatives, stabilising and flavouring agents as well as in the manufacture of cosmetics[241–246] and in medicinal practice.[247–250] LA esters as additives increase thermal stability of poly(vinyl chloride)[251] and improve the characteristics of motor fuels,[252] while glycol esters are perfect plasticisers.[41, 61, 253] Compounds synthesised from LA are used as corrosion inhibitors,[254] initiators of radical polymerisation,[148, 149, 255–257] cross-linking reagents[258] and components of liquid crystals.[259, 260]

There is no doubt that LA may be used as one of the components in the elaboration of an alternative source of raw materials in organic synthesis.

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