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Organoelement derivatives of 2-pyrone and their applications in organic synthesis

V N Kalinin, O S Shilova

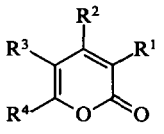
Contents

I. Introduction
II. The synthesis and properties of organoelement σ-derivatives of 2-pyrone
III. η^4-Iron tricarbonyl complexes of 2-pyrones

Abstract. The methods of synthesis and properties of organometallic (Li, Cu) and organoelement (Si, N, S) σ-derivatives and η^4-iron tricarbonyl complexes of 2-pyrone are considered. The Diels-Alder reactions of the organoelement derivatives of 2-pyrone with dienophiles take place stereoselectively and under mild conditions, which opens new pathways to the specific synthesis of polyfunctional cyclohexenes and cyclohexadienes. The bibliography includes 40 references.

I. Introduction

2-Pyrone systems **1** [1] form part of the composition of steroid,[2-4] nor- and dinor-diterpenoid[5-9] and many monocyclic[10] natural products with a broad spectrum of physiological activity.



1

Thus steroid bufadienolides exhibit cardiotonic and antineoblastic[3] properties while certain nor- and dinor-diterpenoid of 2-pyrones are insecticides[9] and cytotoxic agents.[5-7]

The use of 2-pyrones as dienes in Diels-Alder reactions with acetylenic[11,12] or olefinic dienophiles[13] gives rise to extensive possibilities for the stereoselective synthesis of cyclohexene and cyclohexadiene derivatives. Derivatives of 2-pyrone and the methods of their synthesis are therefore of great interest for organic chemists engaged in synthesis.

The chemistry of 2-pyrones has been reviewed,[1,14] but organoelement derivatives of 2-pyrones have been little studied. Two types of organoelement derivatives of 2-pyrones are known: Li, Cu, Si, N, S compounds with a σ-bond between the element and the carbon atom of the pyrone ring and η^4-iron tricarbonyl complexes of 2-pyrones.

The present review is an attempt at a systematic treatment of the available literature data on organoelement compounds of 2-pyrones, the methods of their synthesis, their reactivities, and the prospects for their use in organic synthesis.

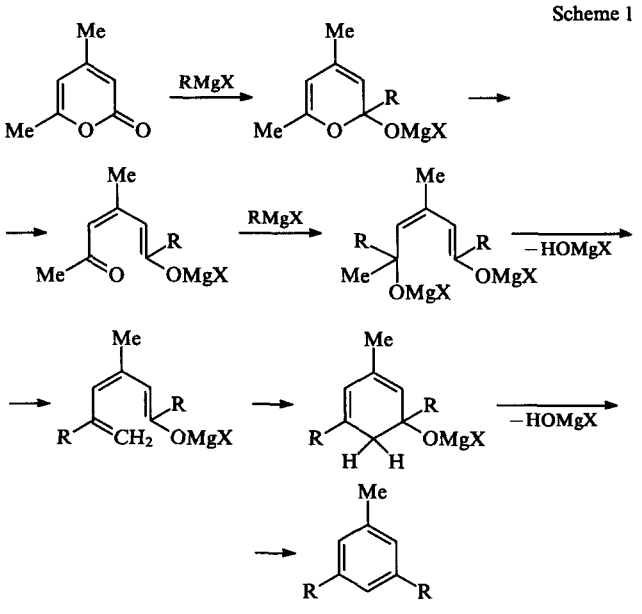
V N Kalinin, O S Shilova Laboratory of Fine Organic Synthesis, Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 85, Tel. (7-095) 135 92 51

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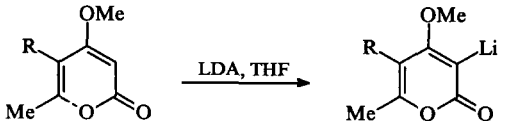
II. The synthesis and properties of organoelement σ-derivatives of 2-pyrone

The synthesis of organolithium derivatives of 2-pyrone is associated with certain difficulties since the pyrone ring is extremely sensitive to nucleophiles. The nucleophile attacks the carbonyl carbon atom of 2-pyrone,[15-19] which leads to the opening of the pyrone ring and its recyclisation to a ring of a nonpyrone type, for example a benzene ring (Scheme 1).[16]

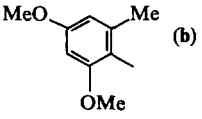
Scheme 1



However, it has been found that lithium can be substituted in the 3-position of 4-methoxy-2-pyrones **2** under mild conditions on treatment with lithium diisopropylamide (LDA) with formation of organolithium derivatives **3**.[17]



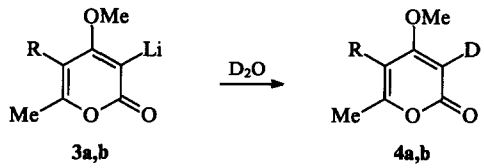
2a,b **3a,b**

R = H (**a**),  (**b**)

The authors suggest that the simultaneous presence of 4-methoxy- and 2-oxo-groups in compounds **2** can influence both the mode of the lithium substitution reaction and the stability of the carbanion formed.

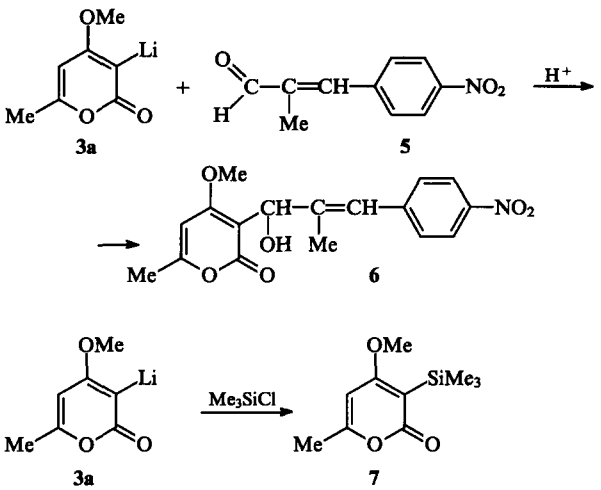
The lithio-derivative **3a** has also been obtained in 70% yield from compound **2a** by treatment with n-butyllithium.[18]

Lithium-substituted pyrones **3a, b** interact with heavy water to form the 3-deuterio-derivatives **4a, b**.[17]



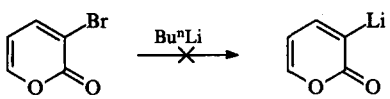
3a,b **4a,b**

The lithio-derivative **3a** interacts with 2-methyl-3-(4-nitrophenyl)-prop-2-enal **5**, affording the secondary alcohol **6**,[18] and also with chlorotrimethylsilane to form 4-methoxy-6-methyl-3-trimethylsilylpyrone **7**.[17] 4-Methoxy-6-phenyl-2-pyrone can also be lithium-substituted in the 3-position but the yield of products obtained from it has not been stated.[17]

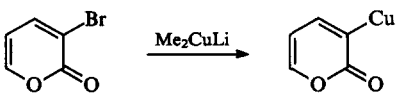


3a **5** **6** **3a** **7**

The attempt to obtain 3-lithio-2-pyrone without other substituents in the pyrone ring, by treating 3-bromo-2-pyrone with n-butyllithium, was unsuccessful.[19]

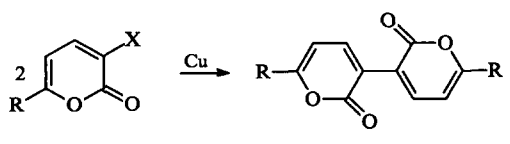


In 1985 Posner et al.[19] obtained for the first time 3-cuprio-pyrone **8** by the reaction of 3-bromopyrone with lithium dimethylcuprate.



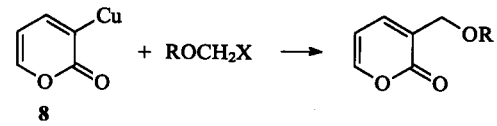
8

Previously Sokolovskaya and Moldovanova[20] synthesised a series of bispyrones by the Ullmann reaction, which proceeds via the intermediate formation of organocopper compounds.[21]



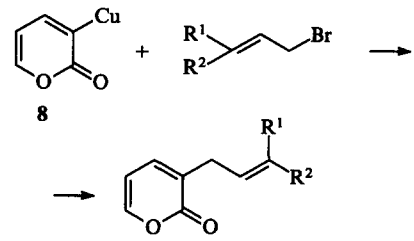
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$C_{10}H_7$; X = Br, I.

3-Cuprio-2-pyrone **8** reacts under mild conditions with chlorobenzyl and bromomethyl ethers[19] and with allyl bromides.[19,22]

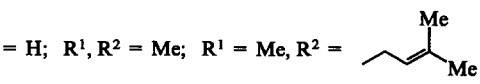


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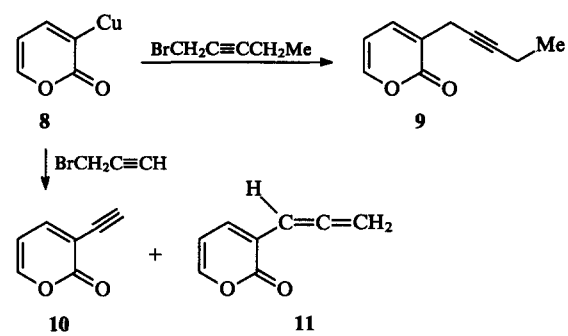
R = Me, X = Br; R = $PhCH_2$, X = Cl.



8

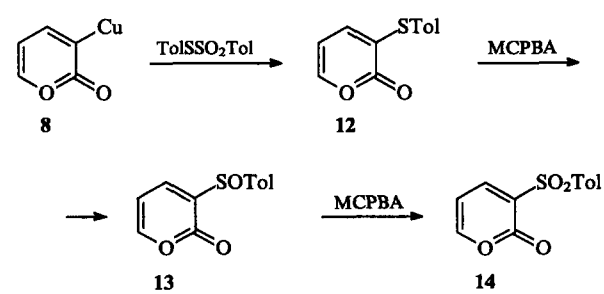


3-Cuprio-2-pyrone reacts with 1-bromopent-2-yne to form 3-(pent-2-yn-1-yl)pyrone **9** while its reaction with propargyl bromide affords a mixture of 3-propargylpyrone **10** and 3-allenylpyrone **11** in proportions of 3:1, but it does not react with alkyl, benzyl, and benzoyl halides and is thus an appreciably less nucleophilic agent than the majority of the organocopper compounds described previously.[19]



8 **9** **10** **11**

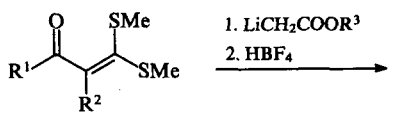
3-Cuprio-2-pyrone **8** reacts with $TolSSO_2Tol$ (Tol = 4-MeC_6H_4) to form 3-tolylthiopyrone **12**, which can be oxidised with *m*-chloroperbenzoic acid (MCPBA) to 3-tolylsulfinylpyrone **13** and 3-tolylsulfonylpyrone **14** respectively.[19]



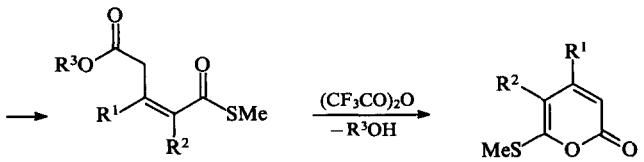
8 **12** **13** **14**

Another method of synthesis of organosulfur derivatives of pyrone involves the cyclisation of the thioesters of unsaturated dicarboxylic acids.[23-25]

Dieter and Fishpaugh[24] observed that α-oxoketene dimethyl thioacetals **15** react with *tert*-butyl or isopropyl lithioacetates to form the monothioesters of pent-2-ene-1,5-dioic acids **16**, which cyclise to substituted 6-methylthiopyrones **17** on treatment with trifluoroacetic anhydride.



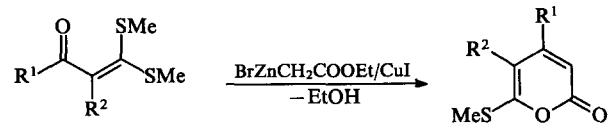
15

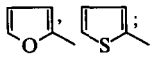


16 17

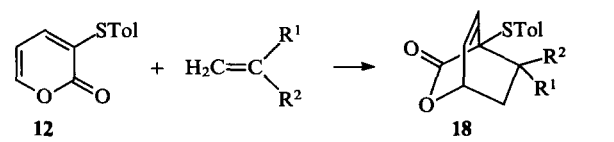
R^1, R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$; R^1 = Et, R^2 = Me;
R^3 = Bu^t, Pr^i.

Bromozinc acetates in the presence of univalent copper may be used instead of lithioacetates.[23]



R^1 = Me, Ph, Tol, α-$C_{10}H_7$, ;
R^2 = H, Me

A review by Posner is devoted to the reactivity of organosulfur derivatives of 2-pyrones.[26] The introduction of the electron-donating 4-tolylthio- and electron-accepting toluene-4-sulfinyl and toluene-4-sulfonyl substituents alters sharply the reactivity of 2-pyrones towards dienes. Thus, whereas 2-pyrones without organosulfur groups react with dienes at 100–200 °C, 3-(4-tolylthio)-2-pyrone **12** interacts with electron-deficient dienes (for example, with nitroethylene and acrolein) even at 85–90 °C. Mild reaction conditions make it possible to isolate the intermediate bicyclic lactones **18**, which lose CO_2 at high temperature.[27] The reactions of tolylthiopyrone **12** with nitroethylene, acrolein, 2-methylpropenal, and but-3-en-2-one take place stereoselectively (the ratio of *endo*- and *exo*-isomers is 98 : 2).[27]



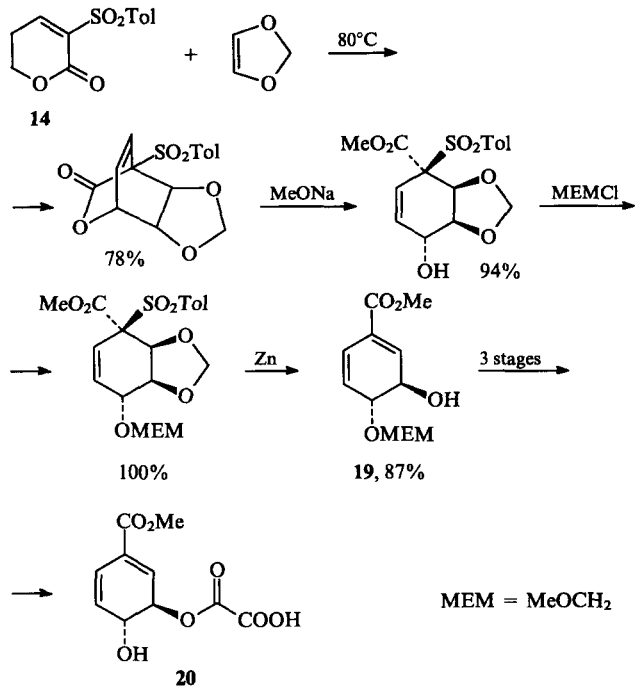
12 18

R^1 = H, Me; R^2 = NO_2, CHO, COMe

Stereoselectivity is much lower in the reactions of compound **12** with acrylonitrile, methylacrylate, methylmethacrylate, and benzyl acrylate, but the *endo*-isomer is still the main product of the reaction.[27]

The introduction of electron-accepting sulfinyl and especially sulfonyl substituents into the pyrone ring greatly facilitates the reaction of the pyrone with electron-donating alkenes such as vinyl ethers and dioxoles.[28] As in the case of 3-(4-tolylthio)-2-pyrone **12**, in the reactions of 3-(toluene-4-sulfonyl)-2-pyrone **14** with dienes it is possible to isolate bicyclic intermediates. These reactions also proceed stereoselectively, which fact has been used successfully in the synthesis of the cyclic compounds **19**. The scheme constitutes a convenient method of synthesis of the cyclic compound **19**, which is a precursor of chorismic acid **20**.[26] Chorismic acid is in its turn a key intermediate in the shikimate biosynthetic pathway which bacteria and lower plants use to convert carbohydrates into aromatic compounds.[29,30]

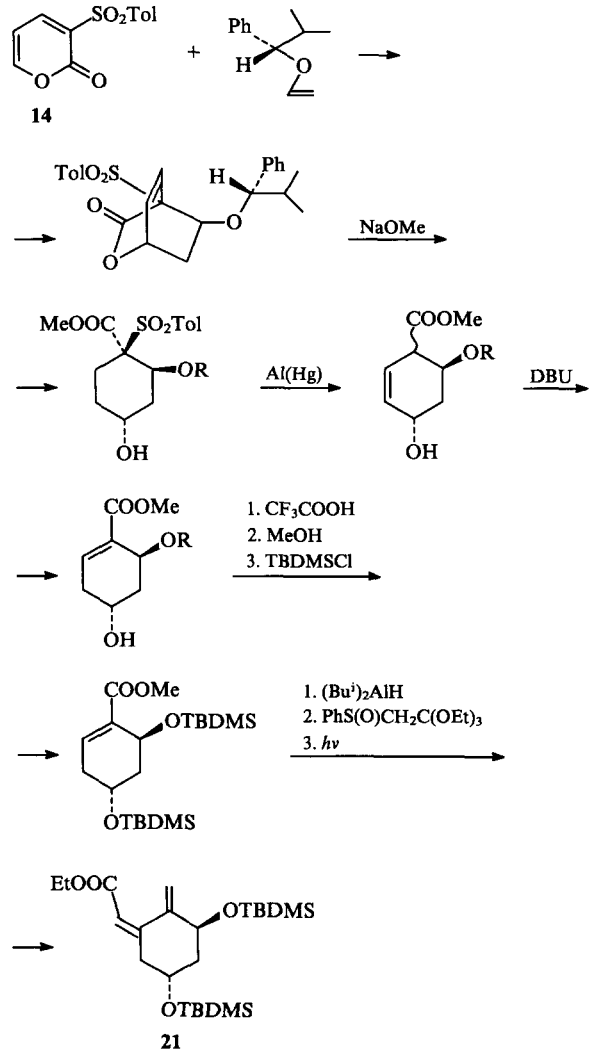
The toluenesulfonylpyrone **14** has also been used in the synthesis of the A ring of hydroxyvitamin D_3 **21**.[26]



14 78% 94% 100% 19, 87%

MEM = $MeOCH_2$

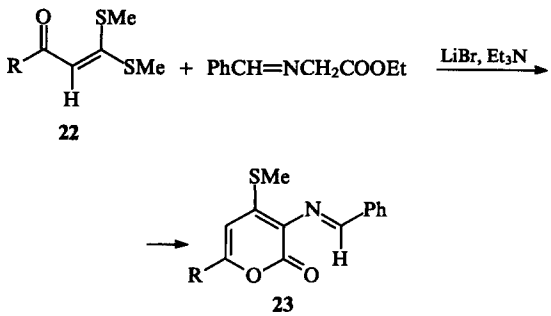
20



21

TBDMS = Bu^tSoMe_2;
DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

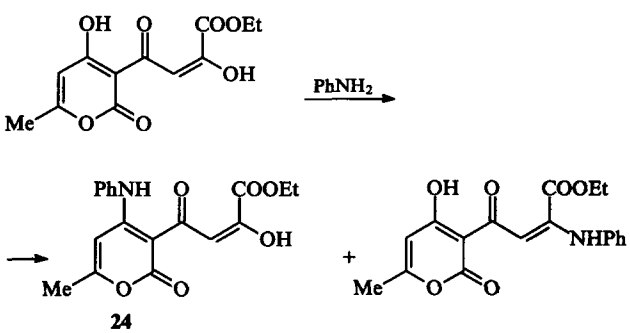
The reaction of the bis(methyl thioacetal) **22** with benzylideneaminoacetate leading to pyrones containing thio- and imino-substituents (compound **23**) is interesting.[31]



22 **23**

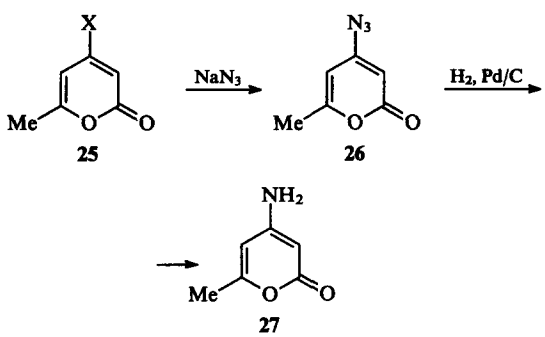
R = Alk, Ar

Ammonia and amines are known to open the pyrone ring with formation of acyclic products, which then recyclise to benzene derivatives or pyridones.[32,33] However, phenylaminopyrone **24** was obtained in the reaction of substituted 4-hydroxypyrone with aniline.[34]



24

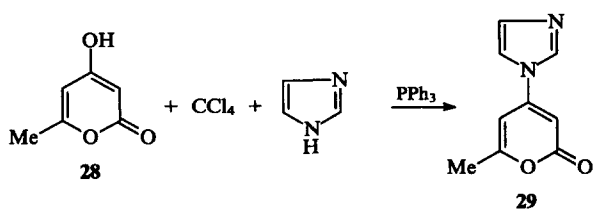
The pyrone **27**, containing a primary amino-group, was synthesised by the exchange of the halogen in 4-halo-6-methylpyrones **25** for the azido-group and the subsequent reduction of the 4-azidopyrone **26** with hydrogen over a palladium catalyst.[35]



25 **26** **27**

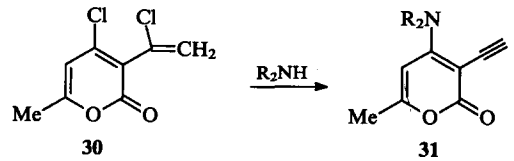
X = Cl, Br

When an attempt was made to obtain 4-chloro-6-methylpyrone by substituting the OH group in the pyrone **28** for chlorine on refluxing with CCl_4, imidazole, and triphenylphosphine, only 4-(1-imidazolyl)-6-methylpyrone **29** was isolated.[35]



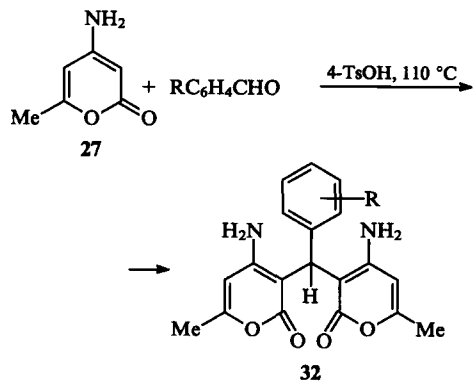
28 **29**

There are literature data showing that the reaction of 4-chloro-3-(1-chlorovinyl)-6-methylpyrone **30** with secondary alkylamines leads to 4-dialkylamino-3-ethynyl-6-methylpyrones **31**.[36]



30 **31**

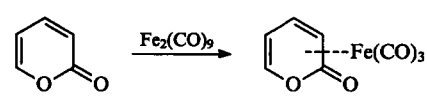
In the presence of toluene-4-sulfonic acid, 4-amino-6-methyl-2-pyrone **27** reacts with aldehydes at the 3-position in the pyrone ring to form bis(4-aminopyron-3-yl)methanes **32**.[34]



27 **32**

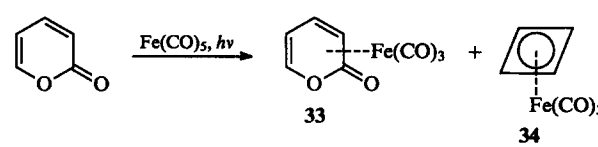
III. η^4-Iron tricarbonyl complexes of 2-pyrones

The diene system of the pyrone ring can form complexes with transition metal atoms. Thus the first organometallic derivative of 2-pyrone — the η^4-diene complex **33** — was obtained in 1967 by heating 2-pyrone and diiron nonacarbonyl in heptane.[37]



33

Irradiation of the pyrone and iron pentacarbonyl with UV light leads to the formation of a mixture of complex **33** and cyclobutadieneiron tricarbonyl **34**. (The overall yield of the products **33** and **34** is 10%–15%.)

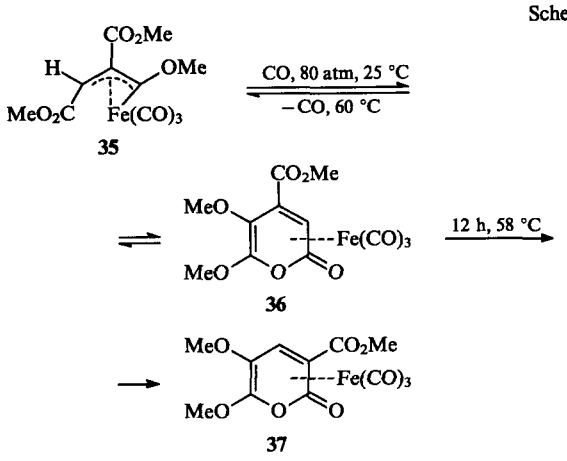


33 **34**

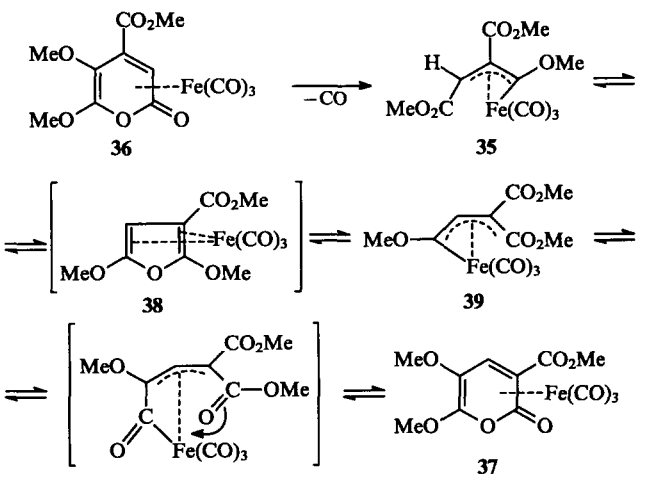
The authors confirmed the structure of the pyroneiron tricarbonyl complex by IR and ^1H NMR spectroscopic data. The product **33** is the only η^4-diene complex of pyrone obtained by the interaction of the latter with a metal carbonyl. In the remaining cases, the η^4-pyrone ligands were formed as a result of the cocyclisation of ligands having a simpler structure in the coordination sphere of the transition metal.

Mitsudo et al.[38] described the synthesis of the η^4-pyrone ligand by carbonylating the σ,π-allyliron tricarbonyl derivative **35** under pressure (Scheme 2). On heating in dichloroethene, the η^4-pyrone complex **36** is converted into the isomeric product **37** in 21% yield. The structures of compounds **36** and **37** were established by X-ray diffraction. On heating to 60 °C, complex **36** is decarbonylated and reconverted into the initial σ,π-allyl derivative **35**.

Scheme 2

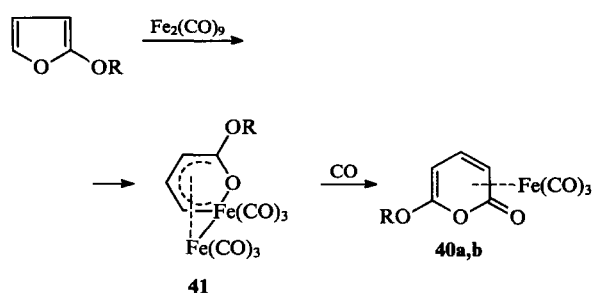


Scheme 3



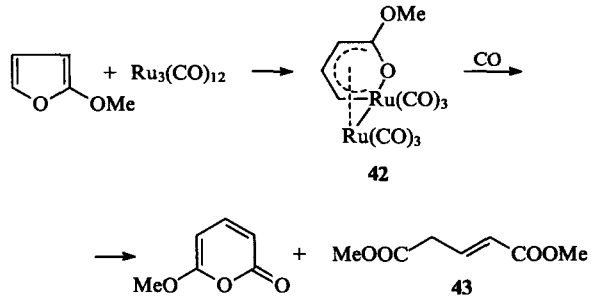
Bearing in mind that on heating under CO pressure complex **36** does not isomerise to complex **37** Mitsudo et al.[38] proposed the mechanism of the rearrangement presented in Scheme 3. In the initial stage, the η^4-pyrone complex **36** is decarbonylated to the σ,π-allyl derivative **35**, which rearranges to the σ,π-allyl derivative **39** via the intermediate formation of the fairly unstable 2,5-dimethoxyfuran complex **38**. The derivative **39** is probably carbonylated and is then converted into complex **37**. If account is taken of the fact that complex **37** is formed on carbonylation of compound **35** under pressure, then the authors' hypothesis that compound **39** is carbonylated in solution in the absence of pressure appears doubtful, but is nevertheless probable since the rearrangement product **37** is obtained in a low yield.

Mitsudo et al.[38] mention the formation of the 6-methoxypyroneiron tricarbonyl complex in the reaction of 2-methoxyfuran and diiron nonacarbonyl, which evidently proceeds via the insertion of CO in the furan ring.

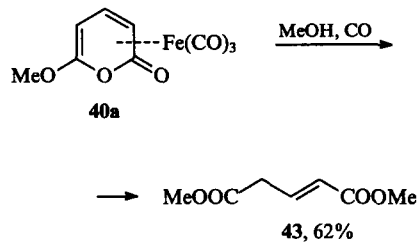


R = Me (**a**), Bu^t (**b**).

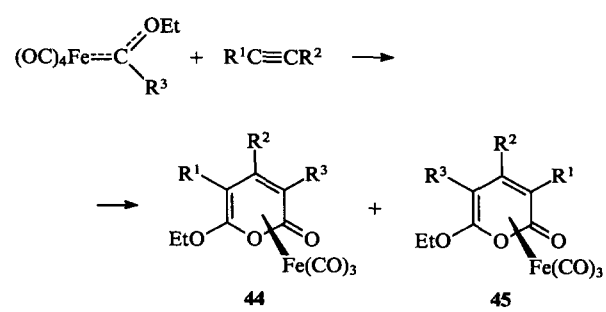
In a later study, Mitsudo et al.[39] showed that 2-alkoxyfurans interact with diiron nonacarbonyl to form η^4-(6-alkoxypyrone)iron tricarbonyl complexes **40**. It is postulated that complexes **41**, containing a metallacycle and an iron-iron bond, are formed initially. Their carbonylation leads to compounds **40**. In contrast to diiron nonacarbonyl, triruthenium dodecacarbonyl reacts with 2-methoxyfuran at 120 °C, affording only the ruthenacyclic compound **42**. Under more severe conditions (150 °C) and under CO pressure, appreciable amounts of 6-methoxypyrone and dimethyl glutaconate **43** were obtained together with compound **42**.[39]



The mechanism of the formation of compound **43** is not entirely clear, but the authors[39] suggest that it is obtained by the reaction of 6-methoxypyrone with the methanol formed as a result of the decomposition of 2-methoxyfuran. In order to confirm their hypothesis, the authors carried out the reaction of the pyroneiron tricarbonyl derivative **40a** with methanol under CO pressure and obtained dimethyl glutaconate **43**.[39]

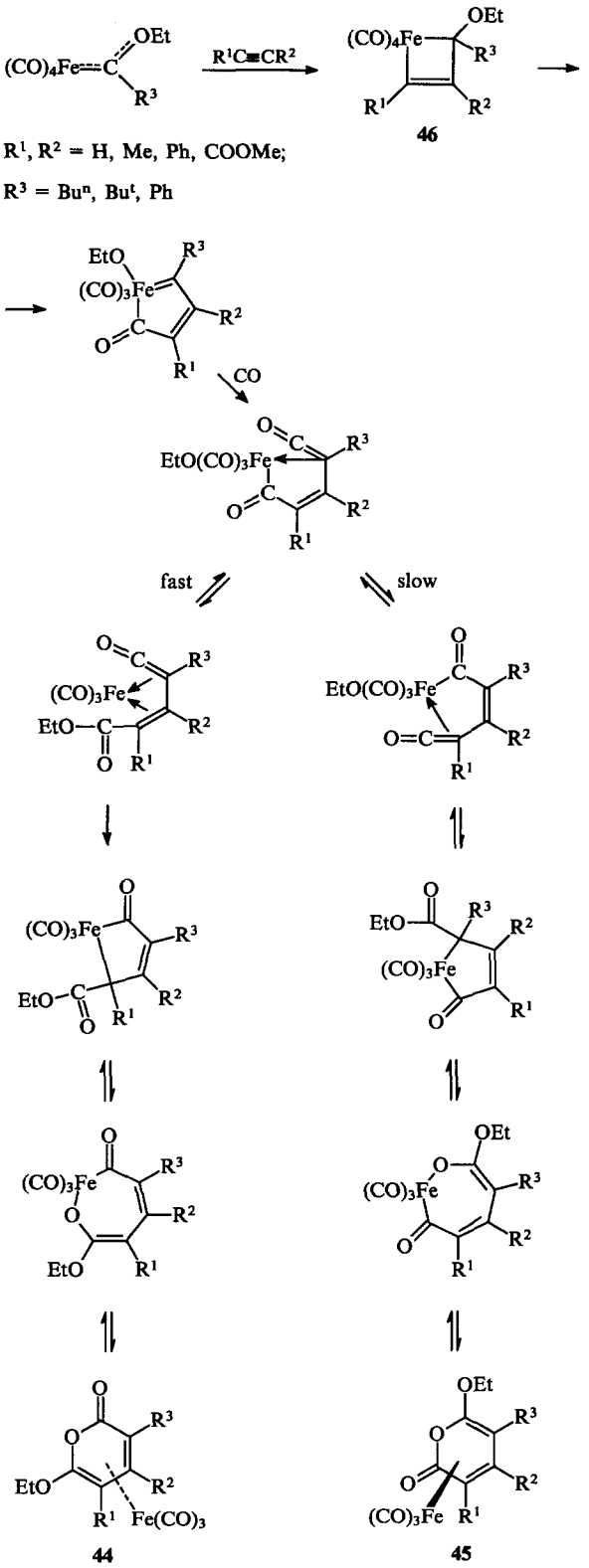


The η^4-pyroneiron tricarbonyl complexes **44** and **45** were obtained by the reaction of the carbene complexes of iron with acetylenes under CO pressure.[40] The pyrone ligand is formed in this case from the carbene ligand, two CO molecules, and an acetylene molecule. η^4-Pyrone complexes were isolated in high yields, the isomer **44** predominating. The authors proposed the following scheme for the formation of the pyrone complexes (Scheme 4), although they believe that the reaction mechanism has not been established exactly. However, rapid chromatography of the reaction mixture on silica gel led to the isolation of the product **46**, to which a metallacyclobutene structure may be assigned on the basis of ^{13}C NMR spectroscopic data. The product **46** is unstable and decomposes readily with formation of the pyroneiron tricarbonyl complex **44** and other compounds.[40]



R^1, R^2 = H, Me, Ph, COOMe; R^3 = Bu^n, Bu^t, Ph

Scheme 4



The reactions involving the formation of the η^4-pyrone ligand from the allyl fragment and a CO molecule[38] and also from an acetylene molecule and the carbene and carbonyl ligands in the coordination sphere of the iron atom[40] have no analogies in the organic chemistry of 2-pyrones. Presumably the use of transition metals will significantly expand the scope of the synthesis of 2-pyrones and their derivatives.

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