Chemistry of 2-Acylcycloalkane-1,3-diones

Dmitry B. Rubinov,* Irene L. Rubinova, and Aphanasy A. Akhrem

Institute of Bioorganic Chemistry, Belarussian Academy of Sciences, ul. Zhodinskaya 5/2, Minsk, CIS 220141, Belarus

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I. Introduction

The β-tricarbonyl polyfunctional group, the main structural feature of 2-acylcycloalkane-1,3-diones (cyclic β-triketones), forms part of the skeleton of many biologically active natural products with both simple and rather complex structures. Components of plant extracts, for example, from *Eucalyptus*, *Humulus lupulus*, and *Hypericum* ssp., various fungal metabolites and antibiotics (chelocardin, dutomicin, usnic acid), filicines—constituents of ferns, pheromones, and the kairomones of some *Lepidoptera* species, as well as many others, are cyclic β-triketones. Many of these biologically active compounds are used in traditional and modern medicine. They exhibit antibiotic, antibacterial, antihelmintic, antimalarial, antidiabetic, anticancer, and other useful therapeutic properties. Since their detection from natural sources more than 100 years ago, 2-acylcycloalkane-1,3-diones have been extensively studied.

Details of chemical structure and biological activity as well as the syntheses of naturally occurring 2-acylcycloalkane-1,3-diones have been summarized in earlier reviews[1,2] as well as in a more recent review.[3] Some heterocyclic natural compounds such as 3-acylated tetramic[4] and tetronic[5] acids also include the β-tricarbonyl group as a part of their structures.

The chemistry of 2-acylcycloalkane-1,3-diones has acquired increased applied importance due to the creation and wide application of a number of modern plant growth regulators based on 2-acylcyclohexane-1,3-dione derivatives. Among these are the well-known herbicides kusagard, nabu, grasp, and cycloxydim, developed by the efforts of the largest chemical companies such as Nippon Soda, ICI, BASF, and Stauffer Chemical Co. They exhibit high selectivity against gramineous and herbaceous weeds contaminating cereal crops at grams per hectare doses. Due to their close structural relationship to related natural products, both 2-acylcyclohexane-1,3-dione herbicides and their metabolites have a low toxicity, a low persistence in the environment, and no cancerogenic, mutagenic, or other undesirable properties. Therefore the patenting of cyclohexane graminicide data was so extensive in the 1980s that a large amount of information on cyclic β-triketones was included in hundreds of patents, but they claimed few rather universal methods of synthesis and herbicidal activities of numerous cyclic β-triketone derivatives.[6]

Although many publications dwell on the chemical transformations of this class of compounds, surprisingly, there is no review that deals with the development of the cyclic β-triketone chemistry. Some reviews, dealing with the use of cyclohexane-1,3-diones and some cyclic β-triketones, for example, 2-formylcyclohexane-1,3-diones, in heterocycle synthesis have been published.[7] The development of new, effective synthetic routes to this class of natural products, as well as the discovery of new biologically active substances, is limited due to the lack of a systematic analysis of synthetic pathways to β-tricarbonyl compounds and their derivatives.

This review aims at filling this gap by systemizing the experimental data on cyclic β-triketone chemistry. Aspects of 2-acylcyclopentane-1,3-dione and 2-acylcyclohexane-1,3-dione synthesis as well as their regioselective chemical transformations will be reviewed. The potential use of various cyclic β-triketone derivatives as block synthones of natural products and analogues of biologically active hetero- and carbocycles is considered. Focus will be on the synthetic methodology rather than on scarce mechanistic or stereochemical details. Starting with the easily available 2-acylcycloalkane-1,3-diones and uti-

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Dmitry B. Rubinov, born in Minsk, received his B.S. degree from the Belarussian State University in 1981. Since 1983 he has carried out research on the cyclohexane β-triketone derivatives in the Institute of Bioorganic Chemistry of the Belarussian Academy of Sciences. Synthesis and study of a large number of herbicidal and fungicidal 2-acylcyclohexane-1,3-dione derivatives led to the award of his Ph.D. in 1989. He acquired his postdoctoral experience under the guidance of Academician A. A. Akhrem. Currently he is engaged in the development of synthetic approaches to various heterocycles based on cyclohexane β-triketones. His area of scientific interests: chemistry of natural and biologically active compounds, synthetic methods of a modern organic chemistry.

Irene L. Rubinova graduated from the Belarussian State University in 1976 and currently works in the Institute of Bioorganic Chemistry under the supervision of academician A. A. Akhrem. She participated in the elaboration of approaches to prostanoids from steroids and cyclopentenes. Since 1987 she has engaged in the research of 2-acylcyclohexane-1,3-diones and their derivatives. Her main interests include the chemistry of natural compounds and their biologically active analogues and also modern organic synthesis.

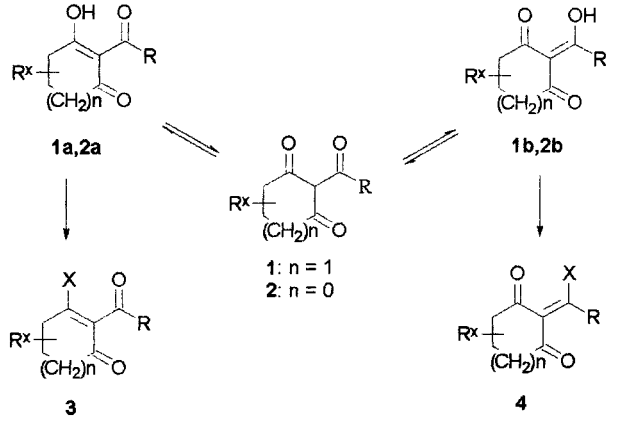
lizing the results of a systematic analysis of known synthetic methods should lead to an expansion of the synthetic scope of new bioactive compounds based on β-triketones and their hetero analogues.

II. Enolization of the β-Tricarbonyl Group and Classification of 2-Acylcycloalkane-1,3-dione Derivatives

All cyclic β-triketone derivatives can be conveniently classified according to the mode of enolization of the β-tricarbonyl group. This is due to the fact that the polycarbonyl system of these compounds (**1, 2**) permits two different modes of enolization.[8] The first is enolization into the ring with the formation of the enol forms **1a** and **2a**. For unsymmetrical β-tri-

Aphanasy A. Akhrem, professor, academician of the Belarussian Academy of Sciences (1970), was the founder (1974) and is the present honorary director of the Institute of Bioorganic Chemistry. His main publications include monographs and articles on organic and bioorganic chemistry in the field of steroid chemistry (general synthesis from polyfunctional blocks, chemical transformations and rearrangements), prostanoid synthesis, and research of enzymes and neuropeptides. Investigation of 2-acylcycloalkane-1,3-diones was initiated by him toward the end of the 1960s in the Moscow Institute of Organic Chemistry and was then continued in the Institute of Bioorganic Chemistry in Minsk.

Scheme 1



R = alkyl, alkenyl, alkynyl, aryl...
Rx = (un)subst.alkyl, aryl, heterocyclyl...
X = alkoxy, alkoxycarbonyl, (un)subst.amino, alkylthia...

ketones, where the cyclic carbonyl groups have different attached substituents, additional regioisomeric forms must be considered. The second enolization occurs into the side chain with the formation of the enol forms **1b** and **2b**. β-Triketones are usually completely enolized and have an acidity close to that of aliphatic acids.[9] The two types of enols give rise to two forms of the corresponding regioisomeric vinylogous derivatives, namely, *endo*-cyclic (**3**) and *exo*-cyclic (**4**) (Scheme 1). Both types of derivatives are the subject of intense research interest due to the large number of products with diverse biological activities. Thus, for example, based on cyclohexane alkoxyimines of type **4** (n = 1, X = HNOR*, where R* = C_2−C_3−alkyl, alkenyl) the herbicides kusagard, nabu, grasp, cycloxydim, and others have been developed.

The cross-conjugated dicarbonyl system (CCDS), which forms the structure of enol derivatives **3** and **4**, determines in many respects the spectral and chemical properties of all these substances. Due to

inductive and mesomeric effects, as well as to the formation of an intramolecular H-bond with one of the keto groups, the X-substituent in the β-position of CCDS is capable of determining the electron density distribution of this system. Thus, both the chemical and synthetic potential of 2-acylcycloalkane-1,3-dione derivatives are significantly changed and expanded compared to α,β-enones or β-dicarbonyl compounds.

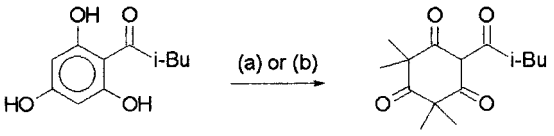
III. Synthesis of Cyclic β-Triketones: O–C Isomerization—General 2-Acylcycloalkane-1,3-dione Synthesis

Up to the mid-1970s, synthetic schemes based on destroying the aromatic character of 2-acylphlorophenols by exhaustive alkylation were used for the synthesis of the most widespread naturally occurring 2-acylcyclohexane-1,3-diones, namely, those containing polyalkylated and 5-oxygenated rings. Such techniques aimed at the preparation of specific substances and had no general utility. For example, leptospermone (**6**) was obtained by the 4-fold methylation of 3-methyl-1-(2,4,6-trihydroxyphenyl)butane-1-one (**5**) by extended refluxing of an alkaline methanolic or aqueous solution with an excess of MeI (Scheme 2).[10] This process was preceded by the Friedel–Crafts acylation of phloroglucine. References for related reactions are found in the literature reviews.[1–3]

Cyclopentane β-triketones were obtained from the appropriate 2-acylcyclohexane-1,3-diones through ring constriction. Alkaline hydrolysis of bromides (**7**)[11] or ketols (**8**)[12] caused their transformation into hulupone analogues (**10**). Similar rearrangements took place when lupulones (**9**) were oxidized by oxygen in the presence of sodium sulfite or by sodium persulfate[13] (Scheme 3).

By the end of the 1970s, a more general approach to the synthesis of both cyclohexane and cyclopentane β-triketones had been developed.[14,15] According to this method cycloalkane-1,3-diones (**11, 12**) are converted

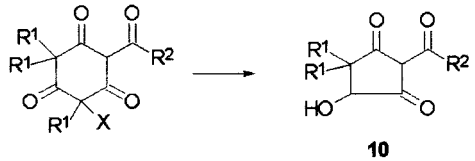
Scheme 2[a]



5 **6**

[a] (a) MeI, aq KOH, sealed tube, 70 °C, 3 days (32%); (b) MeI, MeONa, boiling MeOH, 3 h (65%).

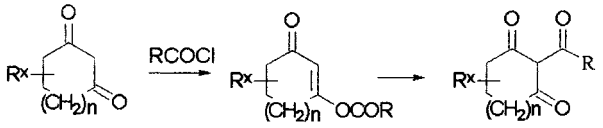
Scheme 3



10

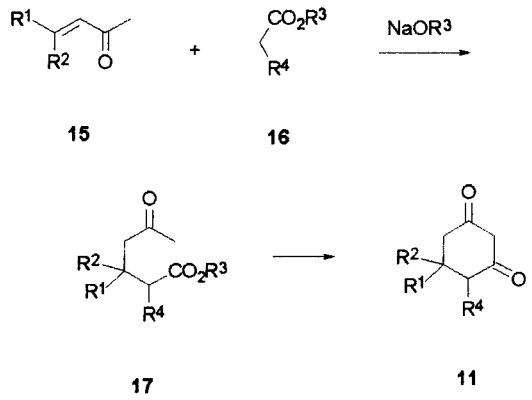
7: R^1 = Me, R^2 = C_1-C_4-alkyl, X = Br
8: R^1 = Me, R^2 = C_1-C_4-alkyl, X = OH
9: R^1 = $CH_2CH{=}CMe_2$, R^2 = C_1-C_4-alkyl, X = H

Scheme 4



11: n = 1 **12**: n = 0 **13**: n = 1 **14**: n = 0 **1**: n = 1 **2**: n = 0

Scheme 5



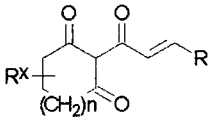
15-17: R^1 = H, alkyl; R^2 = alkyl, alkenyl, aryl...; R^3 = Me, Et; R^4 = CO_2R^3, cyano, aryl...

into mono-*O*-enol acyl derivatives (**13, 14**) by the action of acyl chlorides and pyridine. The resulting enol esters (**13, 14**) underwent O–C isomerization to give the target β-triketones (**1, 2**) in the presence of Lewis acids ($AlCl_3$, $ZnCl_2$) (Scheme 4).

Because the method appeared suitable for large-scale industrial synthesis, the development of such an approach has been reflected in many patents. It has been shown that the reaction of cyclohexane-1,3-diones (**11**) with acyl chlorides can proceed either using phase-transfer catalysis in the presence of a tertiary amine in an inert organic solvent or through the interaction of β-diketone sodium salts with acyl chlorides or carboxylic anhydrides.[16] Various catalysts such as zinc chloride,[17] tin tetrachloride,[18] methanesulfonic acid,[19] imidazole,[20] and 4-(dimethylamino)pyridine (DMAP)[21] have proven useful for the isomerization of 3-acyloxy-2-cyclohexen-1-ones (**13**) into β-triketones (**1**). The latter appears to be the most effective and convenient catalyst at the stage of the O–C isomerization of aliphatic enol acylates.

Cyclohexane-1,3-diones (**11**) usually have been obtained by the alkaline condensation of mesityl oxide and related substances (**15**) with esters of the type (**16**), bearing active methylene groups, such as malonic acid diesters or acetoacetates, through intramolecular cyclization of the Michael adduct (**17**) according to the classical synthetic scheme for dimedone (5,5-dimethylcyclohexane-1,3-dione) (Scheme 5).[22] Through judicial choice of α,β-enones (**15**) and activated methylene components (**16**), this approach allows the preparation of a number of cyclohexane-1,3-diones with various 4- and 5-substituents. None of the catalysts mentioned above are suitable for the synthesis of 2-aroylcyclohexane-1,3-diones. To prepare such triketones an isomerization procedure in the presence of a cyanide ion source has been

Chart 1



18: n = 1; R^x = H, 5-Me, 5,5-Me$_2$;
R = 2-furyl, Ph, 4,5-(OCH$_2$O)C$_6$H$_3$,
4,5-(MeO)$_2$-C$_6$H$_3$, 4-(CO$_2$H)C$_6$H$_4$

19: n = 0; R^x = H; R = 2-furyl, 4-(CO$_2$H)Ph

20: n = 0,1; R^x = H, 5-Me, 5,5-Me$_2$;
R = NMe$_2$, NEt$_2$

developed.[23] This method is also pertinent for the synthesis of β-triketones with nonaromatic side chains.

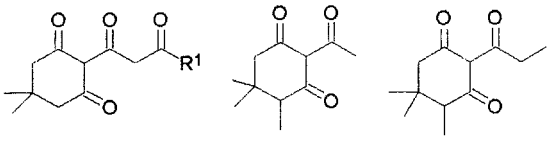
Despite the many publications on the synthesis of 2-acylcycloalkane-1,3-diones and patents claiming hundreds of cyclic β-triketones prepared by this method,[6,14−21,23] the actual mechanism of the O−C isomerization, in particular whether it proceeds via an intermolecular or intramolecular process, is still not clearly established. It is more than likely that it is similar to the mechanism of the Klaisen−Haase rearrangement,[24] which is used for obtaining acyclic β-di- and β-tricarbonyl compounds from the corresponding enol esters of ketones or β-diketones in the presence of basic or acidic catalysts. It is believed that this rearrangement is intermolecular in the presence of basic catalysts,[24a] but intramolecular in the presence of Lewis acids.[24c] Some authors[25] proposed that the acid-catalyzed O−C isomerization of acyloxy vinyl ketones is a variant of the Fries rearrangement. To clarify this problem a cross-isomerization experiment of a pair of enol esters (**13**) with different ring structures and side chains using either acidic ($AlCl_3$, $ZnCl_2$) or basic (NaOAc, K_2CO_3, DMAP) catalysts has been performed.[26] In all cases, irrespective of the nature of the catalyst, a mixture of all four possible triketones in roughly equal ratios was obtained. This points to an intermolecular process.

Certain opportunities for cyclic β-triketone modification and a new β-triketone synthesis are afforded by reaction with aryl aldehydes or activated amides, as well as by acylation and alkylation in the presence of a strong base. The aldol condensation of 2-acetylcyclohexane-1,3-diones (**1**)[27] and 2-acetylcyclopentane-1,3-diones (**2**)[28] (R = Me) with aromatic aldehydes is regioselective. It takes place mainly at the α-carbon of the acetyl group and gives rise to the formation of new β-triketones with the double bond in the side chain (**18, 19**) (Chart 1).

β-Triketones (**1, 2**) readily react with *N*,*N*-dialkylacetamide dialkyl acetals also at the α-position, yielding β-[(dialkylamino)acryloyl]cyclohexane-1,3-diones (**20**).[29] α′-Acylation of the dimedone disodium salt by the action of either ethyl formate or ethyl oxalate in toluene (50 °C, 5 h) results in tetracarbonyl products (**21**) in reasonable yields (Chart 2).[30]

It has been shown that the selectivity of the 2-acetyldimedone alkylation with excess methyl iodide depends on the reaction conditions (solvent, temperature, base strength). Mono-α-alkylated triketone (**22**) has been synthesized by alkylation at

Chart 2



21: R^1 = H, CO$_2$Et **22** **23**

−78 °C in the presence of 3.2 equiv of LDA. Alkylation at 0−4 °C afforded mostly α,α′-dialkylated derivative (**23**).[31]

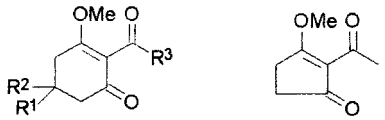
IV. Enol Ethers and Esters of 2-Acylcycloalkane-1,3-diones

A. Synthesis of Enol Ethers

The majority of synthetic methods used for the preparation of cyclic and acyclic β-diketone enol ethers are inapplicable for the synthesis of cyclic β-triketone enol ethers. O-Alkylation of the silver salts of 2-acylcycloalkane-1,3-diones (**1, 2**) by methyl iodide was the most general method for the synthesis of methyl ethers (**24, 25**)[32] (Chart 3) until the highly efficient alkylation of 2-acylcyclohexane-1,3-dione (**1**) sodium salts by dimethyl sulfate in acetone was developed.[33] Starting with unsymmetrical β-triketones, regiomeric methyl ethers (**26, 27**) were obtained in ratios of 4:1 to 7:1, with overall yields of about 90%.

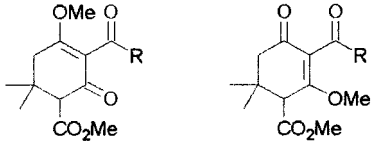
The reaction of cyclohexane β-triketones (**1**) with diazomethane, generated from *N*-methyl-*N*-nitrosourea, has been investigated in detail as a possible source of enol methylates (**24**).[34] In all cases a complex mixture of products is formed. The composition depends on the method for diazomethane generation and on the size and structure of the ring as well as on the reaction conditions as a whole. Target ethers of type **24** have not been obtained with the exception of 2-acetylsincarpine acid derivatives (**28**) (Chart 4).[34a] The main products are furans (**29, 30**) obtained by the nucleophilic attack at the acyl carbonyl followed by cyclization. In addition, 2-acetonyldimedone (**31**) has been isolated as a result of the interaction of 2-acetyldimedone and diazo-

Chart 3



24: R^1, R^2 = H, Me, Ph;
R^3 = Me, Pr, Ph

25



26 **27**

R = Me, Pr, $C_{11}H_{23}$

Chart 4

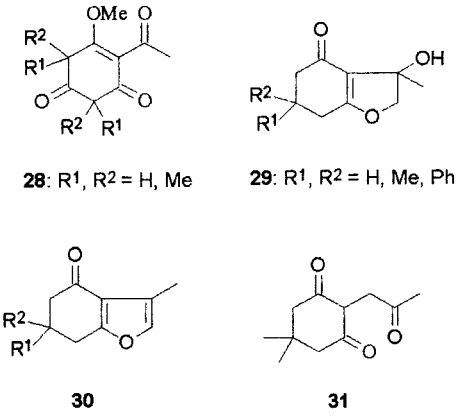
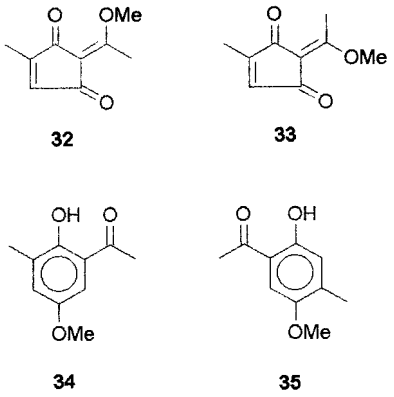


Chart 5



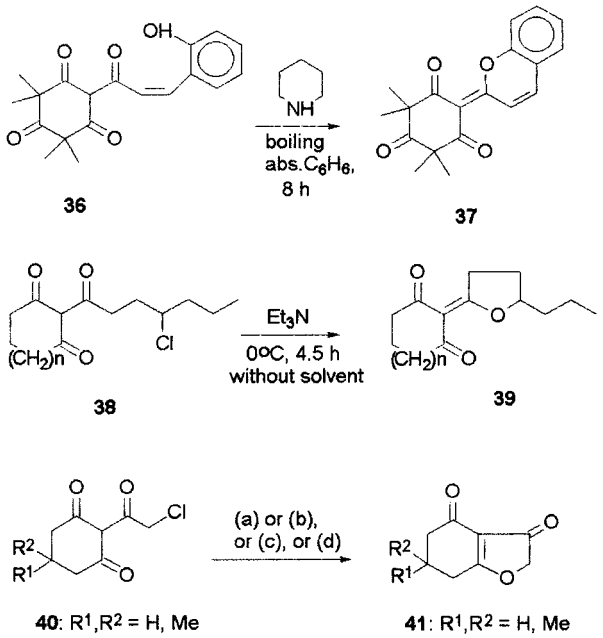
methane.[34c] Cyclopentane β-triketones (**2**) react with an excess of diazomethane to form a mixture of *Z*- and *E*-enol ethers at the side chain carbonyl group (**32, 33**) as well as the isomeric 2-acetyl-1,4-dihydroquinone monomethylates (**34, 35**) (Chart 5).[35] The treatment of 2-acetylcyclopentane-1,3-dione with an ethereal solution of diazomethane, in a manner similar to the alkylation with methyl iodide, gives rise to the *endo*-cyclic enol ether (**25**) (Chart 3).[34b,36] Some intramolecular cyclohexane β-triketone enol ethers, such as the naturally occurring sincarpine (**37**)[37] and oudenone (**39**)[28a,38] as well as benzofuran derivatives (**41**),[39] have been obtained via the intramolecular nucleophilic heterocyclization of appropriately substituted β-triketones (**36, 38, 40**, respectively) (Scheme 6).

B. Chemical Properties of Enol Ethers

Vinylogous replacement by different nucleophiles is a characteristic reaction for all cyclic β-triketone enol derivatives. The interaction between enol ethers and some N-containing nucleophiles represents a preparative method of vinylogous amide synthesis and will be considered below in detail.

Enol ethers (**24**−**27**) can be easily hydrolyzed under either basic or acidic conditions to give the corresponding 2-acylcycloalkane-1,3-diones (**1, 2**).[32,33] The alkylation of enol ethers (**24**) by methyl iodide in the presence of sodium hydride affords 2-methylated derivatives (**42**), which lose the acyl group during the course of the hydrolysis to give the final products (**43**) (Scheme 7).[32c]

Scheme 6[a]



[a] (a) NaOAc, Me_2CO, heating; (b) AcOAg, AcOH, heating; (c) $NaNO_2$, MeOH, rt; (d) MeONa, MeOH, rt.

Treatment of methyl ethers (**24**) with cyanide ion yields diketonitriles (**44**), which are predominantly present in the ketodienol form (**45**).[40] The isoxazoles (**46**) are easily prepared by the reaction of cyclohexane β-triketone enol ethers (**24**) and azide ion.[40,41] Unstable benzo[*c*]furan derivatives (**47**) are formed in the related addition of diazomethane to ethers (**24**).[42] In the latter work[42] enol ethers (**24**) are shown to be easily transformed into 2-acetylresorcinols (**48**) in the presence of palladium and hydrogen acceptors. 2-Acylcyclohexane-1,3-diones (**1**) themselves can also be aromatized in the presence of dehydrogenating agents or catalysts.[43] Catalytic hydrogenation of 2-acetyldimedone methyl ether (**24**) results in ring carbonyl group reduction leading to the diketone (**49**) (Scheme 7).[32c−d]

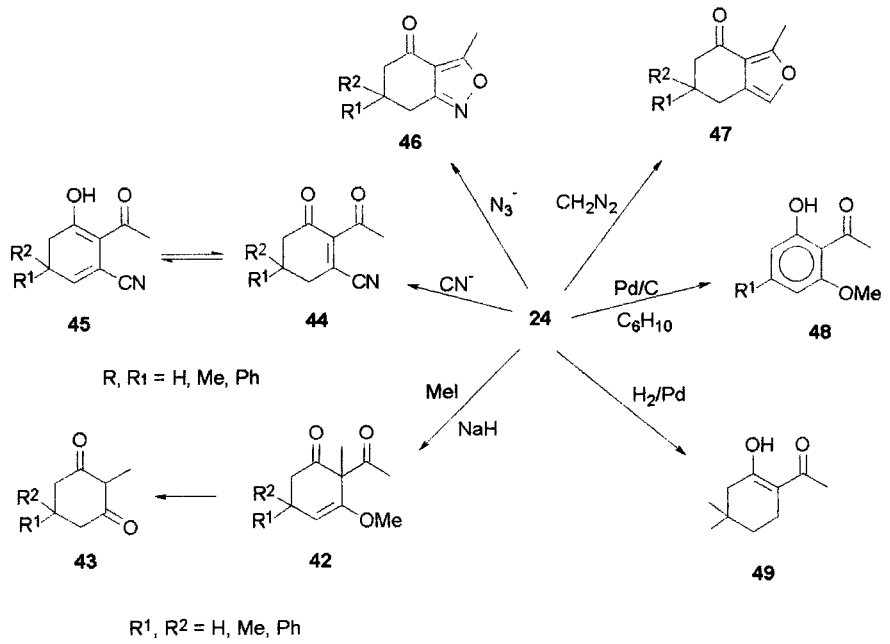
Ionic hydrogenation of enol methylates,[44] as well as of β-triketones,[44,45] represents a useful procedure for acyl carbonyl group reduction, giving 2-alkyl-substituted enol methylates (**50**) in high yields in the case of methyl ethers (**26**) (Scheme 8).

Methyl enol ethers are used as protective groups for the triacylmethane group in oxidation processes. This is documented by the regioselective 4-hydroxylation of the ether (**26**) by lead tetraacetate, *tert*-butylhypochlorite−silver acetate, or *m*-chloroperoxybenzoic acid, leading to compound **51** and useful for the synthesis of the widely occurring natural 4-hydroxylated β-triketones (Scheme 8).[46]

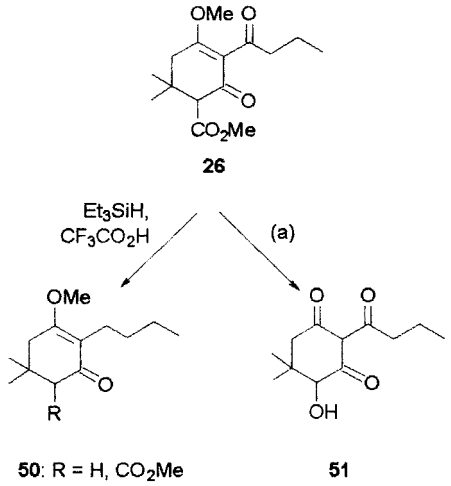
C. Enol Esters, Silyl Enol Ethers, and Thiaenol Ethers

Enol esters of cyclohexane β-triketones are often used for the preparation of more active herbicidal compounds.[47] However, there are few papers on the synthesis and chemical properties of such 2-acylcycloalkane-1,3-dione enolacylates in the scientific literature. To obtain the O-acylated enol derivatives of

Scheme 7

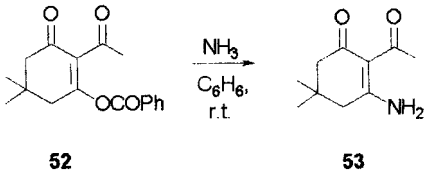


Scheme 8[a]



[a] (a) 1. $Pb(OAc)_4$ or *t*-BuOCl−AcOAg−AcOH or NaH, Me_3SiCl−mCPBA, 2. NaOH, MeOH−H_2O [−CO_2].

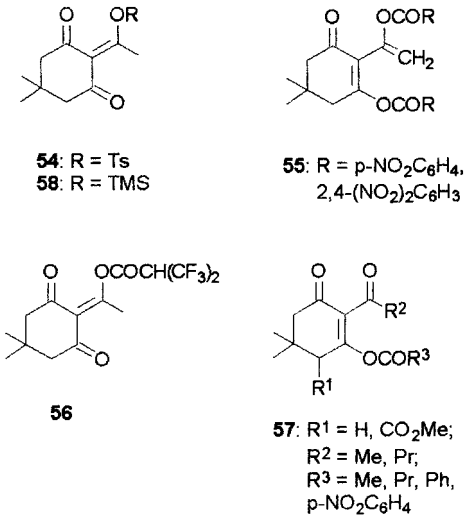
Scheme 9



cyclic *β*-triketones, the reactions of their silver salts with acetyl chloride, benzoyl chloride, and ethyl chloroformate under various conditions have been investigated.[32d] The only enol benzoate (**52**) to date has been prepared in this way in low yield from benzoyl chloride and 2-acetyldimedone (**1**) (R = Me, R^x = 5,5-Me_2). The structure of the ester (**52**) has been indirectly proven by its transformation into enamino diketone (**53**) on reaction with ammonia (Scheme 9).

Similar to acyl chlorides, sulfur chlorides react with the 2-acetyldimedone silver salt, giving a complex

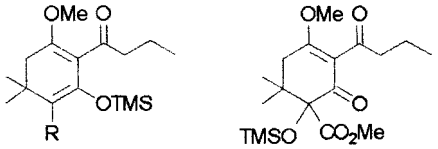
Chart 6



mixture of products. In the case of *p*-toluenesulfonyl chloride the only obtainable product is the tosylate (**54**) (Chart 6). The formation of enol dibenzoates (**55**) has been detected in the acylation of 2-acetyldimedone with *p*-nitrobenzoyl or 2,4-dinitrobenzoyl chlorides in the presence of pyridine or triethylamine. However, the related monoenol esters have not been obtained. Mono-*O*-ester (**56**) has been described as a result of the interaction between 2-acetyldimedone and bis(trifluoromethyl)ketene.[48]

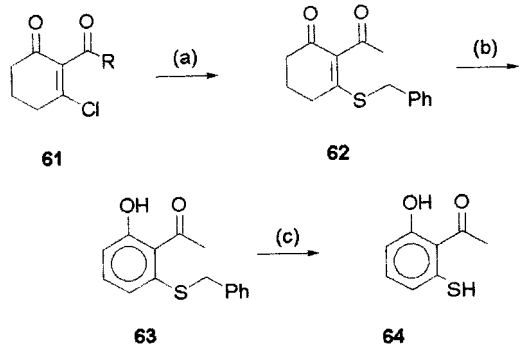
It has been shown[49] that the acylation of the sodium salts of cyclohexane *β*-triketones (**1**) (R = Me, Pr; R^x = 5,5-Me_2, 4-CO_2Me) by acetyl, benzoyl, and *p*-nitrobenzoyl chlorides in acetone proceeds smoothly and leads to the formation of monoesters (**57**) in yields of 50−90%. In contrast to the amination described in Scheme 9, the chemical behavior of enol acylates (**57**) toward pyrrolidine, benzylamine, and propylamine is shown to be distinct from other enol derivatives such as methyl ethers and vinylogous chlorides. They react with amines not via a vinylo-

Chart 7



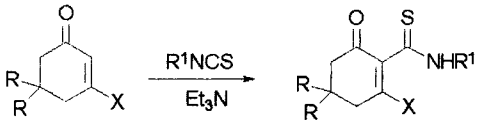
59: R = H, CO_2Me **60**

Scheme 10[a]



[a] (a) $PhCH_2SH$, Et_3N; (b) NBS; (c) $AlCl_3$.

Scheme 11



11: X = OH
65: X = NH_2, NHPh

66

11, 65-66: R,R = H,H; H,Me; H, Ph; Me, Me; R^1 = Ph, p-ClC_6H_4, p-$NO_2C_6H_4$

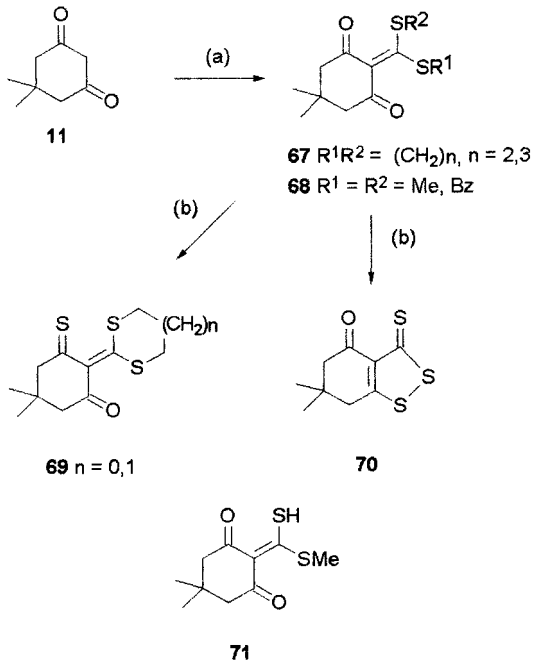
gous replacement, but at the acyl carbonyl in a manner similar to the β-triketones (see below, Section VI.A).[49]

Information on the synthesis and chemical properties of cyclic β-triketone silyl derivatives is very scarce. *Exo*-cyclic silyl enol ether (**58**) (Chart 6) has been described as a product of the reaction between 2-acetyldimedone and bis(trimethylsilyl)amine.[50] The formation of the *endo*-cyclic silyl ether (**59**) has been observed in the reaction of the enol methylate (**26**) with trimethylchlorosilane in the presence of sodium hydride (Chart 7). In the course of the 4-hydroxylation of this ether **59** by *m*-choroperoxybenzoic acid, the appearance of ether **60** has been confirmed.[46]

Information on sulfur-containing derivatives of cyclohexane β-triketones is more plentiful. The diketovinyl chloride (**61**) has been shown to react with benzylmercaptane in the presence of triethylamine yielding the vinylogous thioether (**62**). This in turn can be aromatized by the action of *N*-bromosuccinimide yielding the ketophenol (**63**), which then is converted into the thiophenol (**64**) on treatment with aluminum chloride (Scheme 10).[51]

Thioanilides (**66**) have been obtained by the condensation of isothiocyanates with β-diketones (**11**) (R^x = H, 5-Me, 5-Ph, 5,5-Me_2) and enamino diketones (**65**) (Scheme 11).[52]

Scheme 12[a]



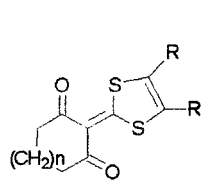
[a] (a) NaH, CS_2, alkyl halide or α,ω-dihaloalkene; (b) Lawesson's reagent.

The sodium salt of dimedone (**11**) (R^x = 5,5-Me_2) reacts with both carbon disulfide and alkyl (or aryl-substituted alkyl) halides or terminal alkyl dihalides in DMF to give diacylketene thioacetals (**67**−**68**) (Scheme 12). Cyclic dithioacetals (**67**) can be thionated to give thia derivatives (**69**) with Lawesson's reagent and other dithiadiphosphetane disulfides.[53] Under these conditions acyclic dithioacetals (**68**) readily undergo dealkylation (dearylation) followed by intramolecular condensation to give the 1,2-dithiol-3-thione (**70**). The reaction of the dimethyl derivative (**68**) with P_4S_{10}−Et_3N in acetonitrile at −30 °C has permitted isolation of the primary dealkylation product: dimedonedithiocarboxylate (**71**). Condensation of cyclohexane-1,3-dione or cyclopentane-1,3-dione with 1,3-dithiols represents a pathway to the dithiafulvalenes (**72**) (Chart 8).[54] Related compounds (**73, 74**) with various N-containing substituents in the thiafulvalene ring have been synthesized by the consecutive reaction of cyclohexane-1,3-diones with carbon disulfide in DMS−KOH followed by reaction with the appropriate amines. These products have proven to be liver-protective agents.[55]

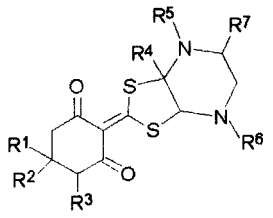
Transformations of the ketene dithioacetal (**67**) (*n* = 2) into the diaminoacetal (**75**) and then into the dithia derivative (**76**) have been realized by reactions with *N*,*N*′-dibenzylethylenediamine and Lawesson's reagent.[56] Compounds **67** and **68** have been used for the synthesis of condensed aromatic systems such as **77** via a cycloaromatization reaction (Scheme 13).[57]

To prepare compounds **78** and **79**, bearing a sulfur-containing substituent in the ring, methyl enol ethers of 2-acylcyclohexane-1,3-diones (**26**) (R = Pr) have been treated with either a methanolic solution of sodium hydrosulfide or an excess of ethylmercaptane in the presence of catalytic amounts of triethylamine (Scheme 14). Alternatively, thia triketones (**78**) have

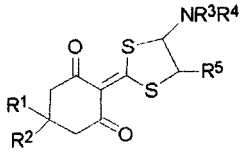
Chart 8



72: R,R = H,H; condens. Ph; n =0,1

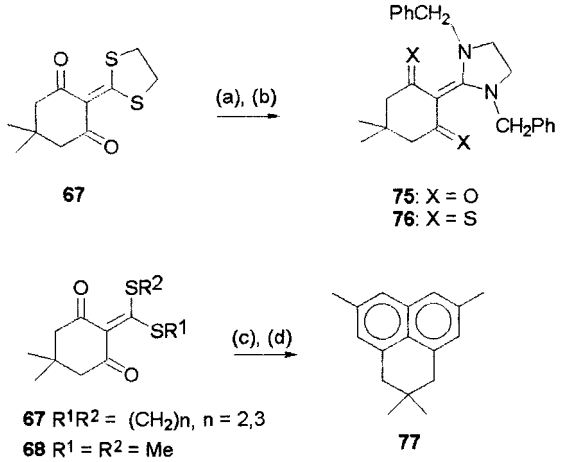


73: R^1,R^4,R^7 = H, alkyl; R^2 = alkyl, alkenyl, cycloalkyl, aryl, heterocycle... R^3 = H, alkyl, alkoxycarbonyl; R^5,R^6 = H, alkyl, alkylcarbonyl



74: R^1 = H, alkyl, aryl, heteroaryl; R^2 = H, alkyl; R^3,R^4 = alkyl; R^3R^4N = O- or N-cont. heterocycle; R^5 = R^3R^4N, HO, R^6COO, R^6 = alkyl, alkoxy, aryl, heteroaryl

Scheme 13[a]



67 R^1R^2 = $(CH_2)n$, n = 2,3; **68** R^1 = R^2 = Me

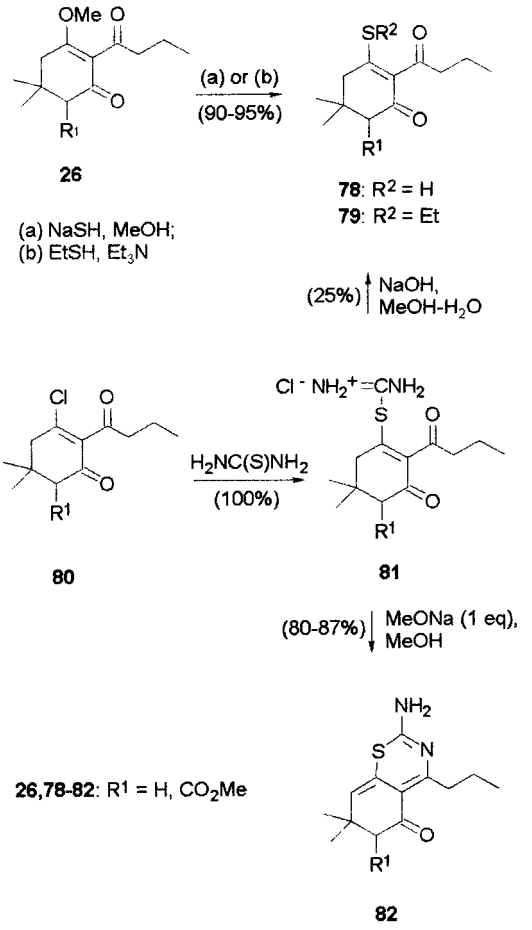
75: X = O; **76**: X = S

77

[a] (a) $(CH_2NHCH_2Ph)_2$; (b) Lawesson's reagent; (c) methallyl Grignard reagent; (d) $BF_3{\cdot}Et_2O$.

been obtained by the reaction of β-chloro enones (**80**) with thiourea followed by alkaline hydrolysis of the intermediate thiuronium salts (**81**). Careful treatment of salts such as **81** with 1 equiv of base followed by refluxing in anhydrous methanol provides a way to benzothiazinones (**82**), which can also be formed by the direct interaction of enol methyl ethers (**26**) with thiourea.[58] In this work some of the chemical properties of thia triketones (**78**) have been studied. They have been shown to react with primary (ammonia, propylamine, benzylamine) and secondary (pyrrolidine) amines at the enthiol group, yielding the corresponding enamines of the type **83** (Scheme 15). They also react with ethyl- or allyloxyamines at the acyl carbonyl to give thiaimino ketones (**84**). There is some evidence for herbicidal activity of cyclohexane β-triketone thia derivatives (**78, 79, 84**);[59] therefore,

Scheme 14



26

(a) NaSH, MeOH; (b) EtSH, Et_3N

78: R^2 = H; **79**: R^2 = Et

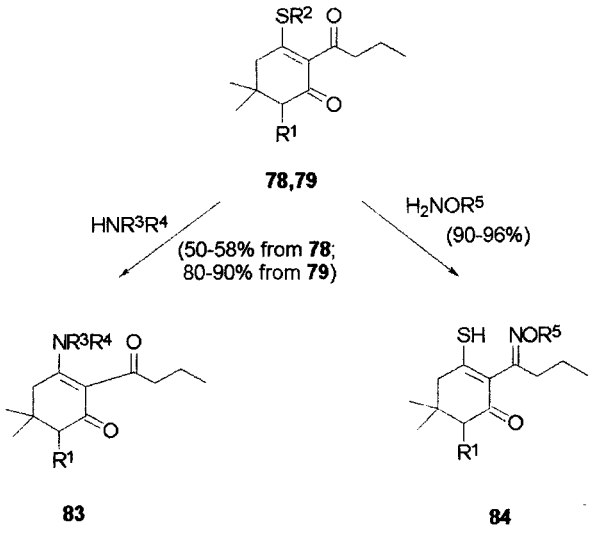
80

81

26,78-82: R^1 = H, CO_2Me

82

Scheme 15



78,79

83

84

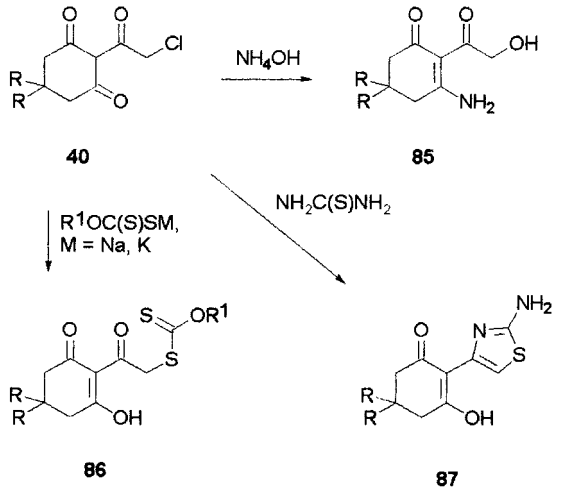
78-79, 83-84: R^1 = H, CO_2Me; R^2 = H, Et; R^3,R^4 = H,H; H, Pr; H, CH_2Ph; $(CH_2)_4$; R^5 = Et, $CH_2CH{=}CH_2$

such products might have a promising future as potential agrochemicals.

V. Chloro Derivatives of 2-Acylcycloalkane-1,3-diones

Chloro derivatives with the structures **38** and **40**, shown in Scheme 6, bearing a halogen in the side

Scheme 16



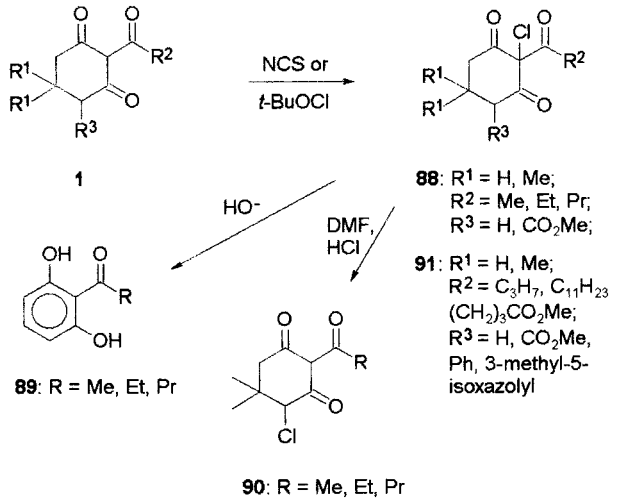
40,85-87: R = H, Me; **86**: R^1 = Me, Et, i-Pr

chain, are synthesized in a manner similar to β-triketones through the acylation of β-diketones with appropriate chlorine-substituted acyl chlorides.[39b] Through the nucleophilic substitution of the halogen atom, it is possible to modify the side chain of the β-triketones. As mentioned above (Scheme 6), 2-chloroacetylcyclohexane-1,3-diones (**40**) have been converted into 3,4-dioxo-2,3,4,5,6,7-hexahydrobenzo[*b*]-furans (**41**) by the action of various nucleophiles (NaOAc, AgOAc, $NaNO_2$, NaOMe) which acted as basic deprotonating agents and did not interact with the carbonyl group. The same result has been achieved by the action of excess ammonia, but under prolonged reaction times they have been transformed into enamino alcohols (**85**) (Scheme 16).[39b] Chloro derivatives (**40**) have been shown to react with sodium or potassium *O*-alkyldithiocarbonate, forming S-substituted compounds (**86**),[39b] and with thiourea to yield 2-aminothiazoles (**87**) (Scheme 16).[60]

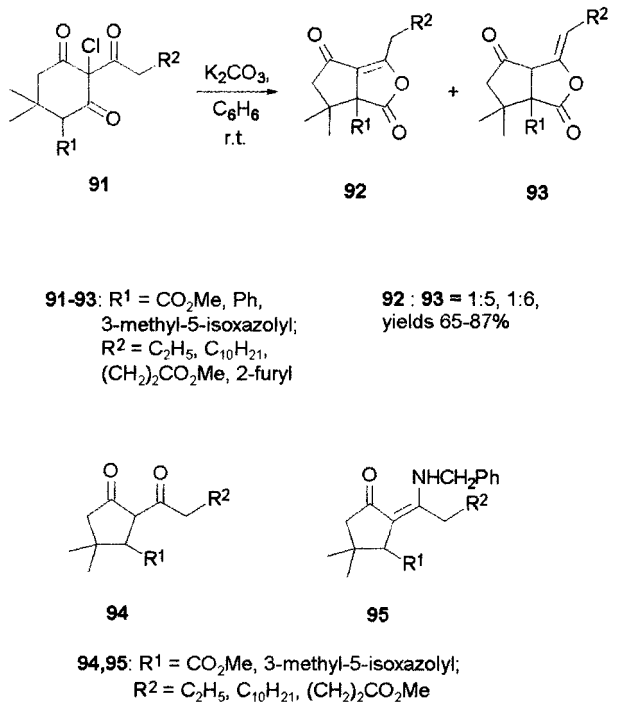
Chlorine can be introduced into the ring of 2-acylcyclohexane-1,3-diones. 2-Acetylcyclohexane-1,3-diones (**1**) (R = Me, R^x = H, 5-Me, 5,5-Me_2) have been chlorinated at the α-position by the action of *N*-chlorosuccinimide.[61] Depending on the presence of the C_5-substituent, 2-chloro triketones (**88**) (Scheme 17) obtained by this way can be aromatized to give resorcinol (**89**) under mild alkaline conditions. Rearrangement to 4-chloro derivatives (**90**) by heating in dimethylformamide containing dry hydrogen chloride also occurs. A more effective procedure, yielding the final 2-chlorinated cyclohexane β-triketones (**90**) in quantitative yield, consists of the treatment of the initial β-triketones with *tert*-butyl hypochlorite in chloroform.[62]

4-Substituted 2-chloro triketones (**91**) have been found to undergo a Favorsky-type rearrangement with ring constriction under the action of potassium carbonate in benzene.[63] The main products of this reaction are the condensed cyclopenta[*c*]furanones (**92, 93**). They have been easily converted into the 2,3,4-substituted cyclopentanones (**94, 95**), which may prove useful as convenient intermediates for the

Scheme 17



Scheme 18

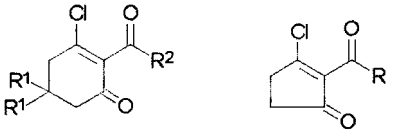


synthesis of the naturally occurring cyclopentanoid bioregulators and their analogues (Scheme 18).

In contrast to the cyclic β-diketones, their 2-acyl derivatives, the β-triketones, fail to form β-chloro enones either under treatment with phosphorus chlorides or by other methods.[40,64] 2-Acetyl- and 2-benzoylcyclohexane-1,3-diones of type **1** have been shown to react with oxalyl chloride, forming β-chloro enones (**96**).[41,65] For cyclopentane β-triketones this reaction proceeds less smoothly, although the desired chlorovinyl diketones (**97**) have been synthesized by the action of excess oxalyl chloride in chloroform (Chart 9).[66]

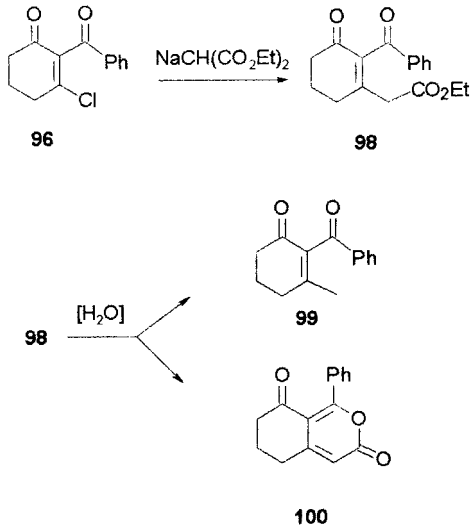
The chemical properties of chlorovinyl diketones (**96, 97**) resemble these of enol ethers (**24**−**27**). They are easily hydrolyzed under either acidic or basic conditions to the starting β-triketones and react with cyanide and azide ions in a manner similar to enol ethers, giving the same products (**44**−**46**) in the

Chart 9

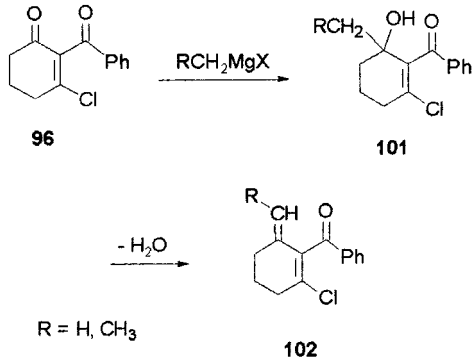


96: R1, R2 = H, Me, Ph **97**: R = C_6H_{13}, C_7H_1

Scheme 19



Scheme 20



corresponding reactions.[41,42] The 1,4-addition of diethyl malonate to 2-benzoyl-3-chlorocyclohex-2-en-1-one (**96**) has been reported.[68] The final product of this reaction (**98**) can be either hydrolyzed, followed by decarboxylation to 3-methyl diketone (**99**), or cyclized to give the lactone (**100**) (Scheme 19).

The 1,2-addition of metalloorganic compounds to the 2-benzoyl-substituted **96** takes place at the *endo*-cyclic carbonyl yielding either carbinols (**101**) or dehydration products (**102**) (Scheme 20).[65b] Chlorovinyl diketones (**96**) can be reduced regioselectively by the appropriate reducing agents. Under the action of sodium borohydride they have been transformed into chlorovinyl diols (**103**), which in turn have been reduced to diols (**104**) by sodium in liquid ammonia (Scheme 21).[69] Reduction by zinc activated by silver acetate provides a method for the conversion of chlorides (**96**) to diones (**105**),[70] which easily isomerize into keto dienols (**106**) (Scheme 21).[71]

The ionic hydrogenation of β-chloro enones (**96**) in trifluoroacetic acid in the presence of triethylsilane or ethyldimethylsilane is a preparative procedure for

Scheme 21

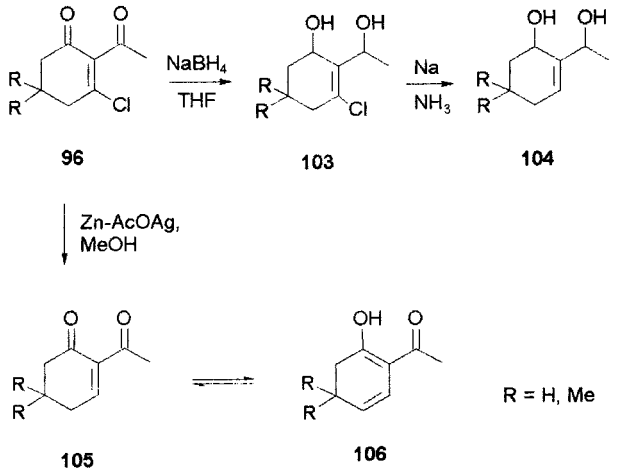
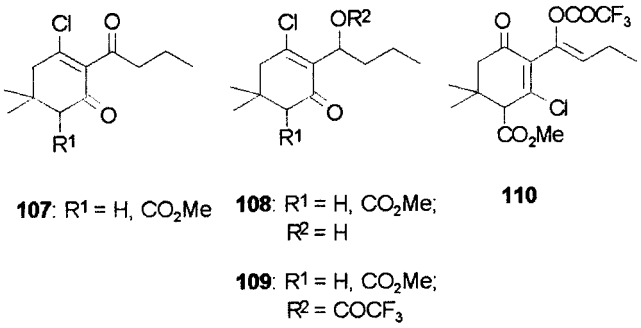


Chart 10



the regioselective reduction of the acyl carbonyl to a hydroxy group. In the case of 2-butanoyl-3-chloro-5,5-dimethylcyclohex-2-en-1-ones (**107**) (Chart 10), the final products obtained have been either keto alcohols (**108**) or trifluoroacetates (**109**), depending on the reaction time. The regioisomeric 4-methoxycarbonyl chlorovinyl diketone (**107**) does not undergo reduction under these conditions but instead is esterified with formation of the enol trifluoroacetate (**110**).[44]

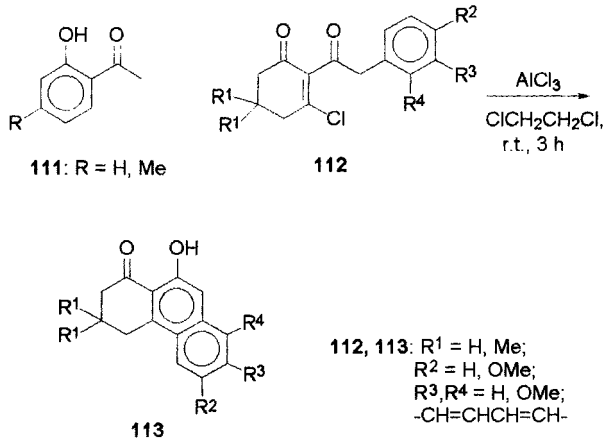
Similar to enol methyl ethers, β-chloro enones (**96**) can be easily aromatized to give ketophenols (**111**) with loss of chlorine.[42] Since diketovinyl chlorides are acyl chloride analogues, they can participate in Friedel−Crafts reactions. Thus, the intramolecular acylation of the aryl group in chloro derivatives (**112**) has been used for the synthesis of phenanthrenones and chrysenones (**113**) (Scheme 22).[72] The interaction of diketovinyl chlorides with nitrogen-containing nucleophiles is considered in detail in the next section.

VI. Vinylogous Amides of 2-Acylcycloalkane-1,3-diones

A. Preparation of *Exo*-Cyclic Vinylogous Amides

The main route to *exo*-cyclic vinylogous amides of type **4** is the direct amination of 2-acylcycloalkane-1,3-diones (**1, 2**) by amines. This reaction is well-documented for both cyclohexane and cyclopentane β-triketones. It should be noted that there is no clear explanation for the observed regioselectivity. Existing in the enol form, cyclic β-triketones represent rather

Scheme 22



Scheme 23

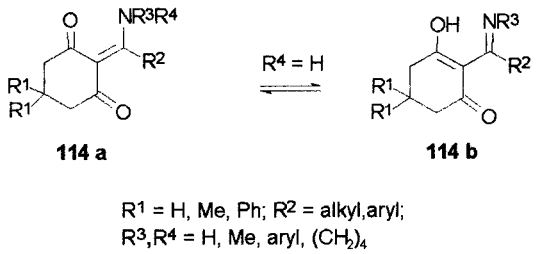
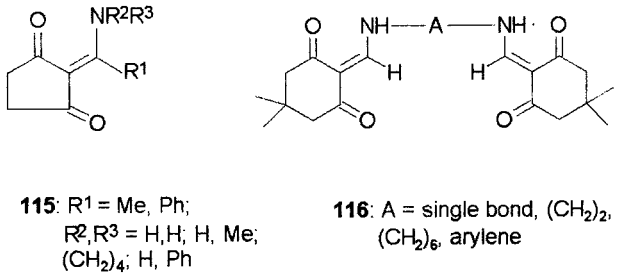


Chart 11



strong vinylogous acids which easily react with ammonia and primary amines in boiling methanol or benzene to give enamino diketones **114** (Scheme 23)[73] and **115** (Chart 11).[67,74] Symmetric diamines (ethylenediamine, hexamethylenediamine, *p*-phenylenediamine, benzidine) can bind two molecules of *β*-triketones at the side-chain carbonyls to give derivatives of the type **116** (Chart 11).[75] It has been reported that 2-isobutyrylcylohexane-1,3-dione does not react at all with aniline. This is perhaps due to steric hindrance.[76] The predominant tautomeric form (**114a**) (Scheme 23) has been established by means of spectral analysis[67,73d,77] and molecular mechanics calculations.[78] Secondary amines usually produce ammonia salts with *β*-triketones. It has been shown that some 2-acetylcyclohexane-1,3-dione pyrrolidinium salts can be transformed into enamino diketones (**114**) (R^3,R^4 = $(CH_2)_4$) in refluxing benzene.[67,79]

2-Acylcyclohexane-1,3-diones (**1**) readily react at the *exo*-cyclic keto group with various bifunctional nitrogen-containing nucleophiles such as hydrazine, alkylhydrazines, arylhydrazines, hydroxylamine, and hydrazides to form unstable hydrazones, oximes, and hydrazides, respectively.[73a,c,80] These products are useful building blocks for the construction of the various heterocyclic systems discussed below. 2-Acyl-

Scheme 24

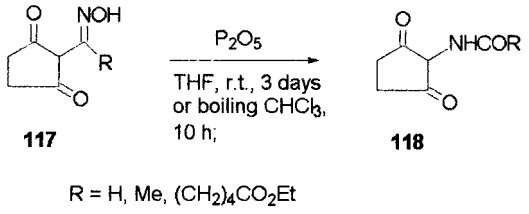
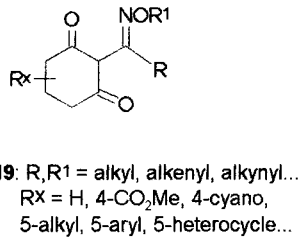
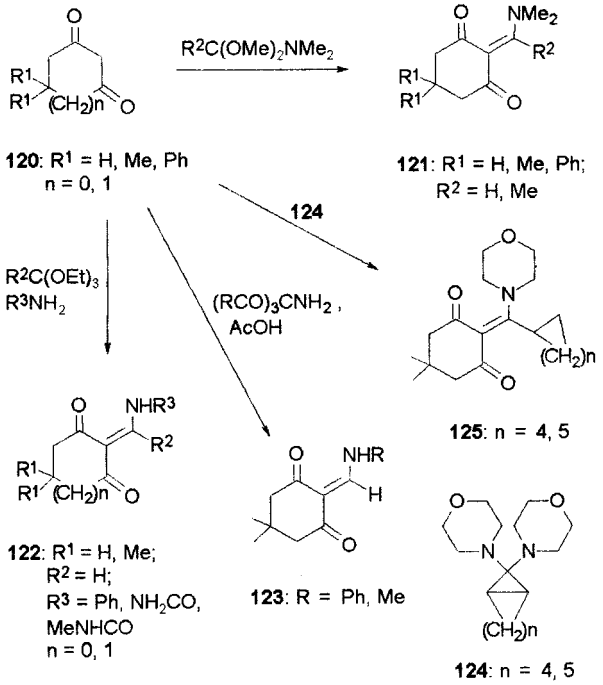


Chart 12



Scheme 25

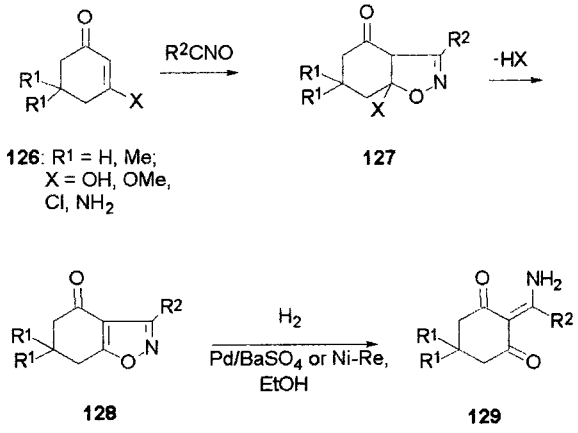


cyclopentane-1,3-diones on treatment with hydroxylamine are converted into stable oximes (**117**). In contrast to their cyclohexane analogues, cyclopentane oximes (**117**) fail to undergo spontaneous cyclization to isoxazoles. They can be either isolated in pure form or transformed into the amides (**118**) via a Beckmann rearrangement (Scheme 24).[81]

The reaction of cyclohexane *β*-triketones with O-substituted hydroxylamines at the acyl carbonyl group represents a key step in the industrial procedure for the synthesis of herbicidally active substances (**119**) (Chart 12).[6]

Condensation of cyclohexane-1,3-diones (**120**) with amide acetals in DMF represents another approach to the synthesis of dimethylamino derivatives (**121**) (Scheme 25). However, this reaction gives preparatively useful yields only in the case of an acetyl chain. A longer side chain decreases the yield of the target product because of competitive O-acylation.[82] A similar reaction takes place when cyclohexane and cy-

Scheme 26



clopentane β-diketones are treated with either orthoformate or orthoacetate in the presence of arylamine or urea derivatives, yielding compounds of the type **122**.[79a,83] The synthesis of 2-acylamino derivatives (**123**) is a result of the reaction of dimedone with tris-(acylmethane)s.[84] Morpholine enamino diketones (**125**) have been prepared from dimedone by condensation with cyclic aminals (**124**), followed by thermolysis and protonation of the cyclopropane ring.[85]

Another approach to making *exo*-enamino diketones is based on the reductive transformation of condensed 4,5,6,7-tetrahydrobenz[*d*]isoxazoles (**128**), which are easily prepared by 1,3-dipolar addition of nitrile oxides to either cyclic β-diketones or their enol derivatives (**126**) (Scheme 26). The reaction proceeds regioselectively with the exclusive formation of the cycloadducts (**127**), which are spontaneously transformed into isoxazoles (**128**) via elimination of HX. Conjugation of the carbonyl group activates the isoxazole ring allowing an easy cleavage of the N−O bond in a mild catalytic hydrogenation in the presence of a palladium catalyst to give the target enamine (**129**) in quantitative yield.[86]

B. Preparation of *Endo*-Cyclic Vinylogous Amides

Methyl enol ethers of cyclic β-triketones and diketovinyl chlorides differ from β-triketones in their reaction with N-containing nucleophiles. They do not react at the acyl carbonyl, but rather at the trigonal center of the cross-conjugated dicarbonyl system with the replacement of either the methoxy group or the chlorine atom, respectively. Due to increased reactivity, amination of these enol derivatives (**130**) by ammonia or primary and secondary amines is possible at ambient temperature and results in the formation of enamino diketones (**131**) in high yields (Scheme 27).[41,65b,66,87]

A more convenient procedure, however, is to use the enol methylates. A large number of herbicidal and fungicidal enamino derivatives (**132**) have been prepared in quantitative yields according to this scheme by the action of amines, as well as ethyloxyamine or

Scheme 27

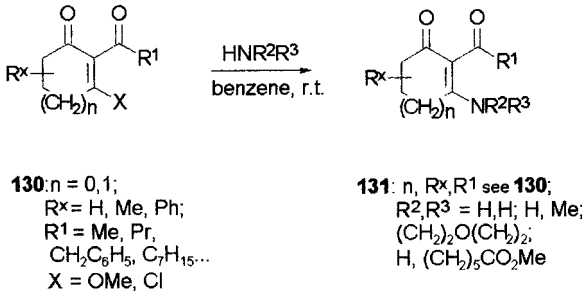
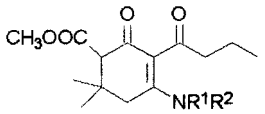
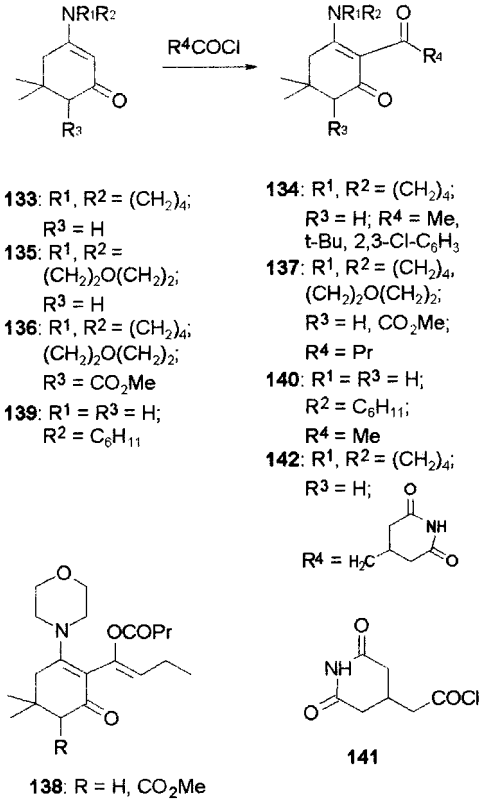


Chart 13



132: R^1,R^2 = H, H; H, C_1-C_6-alkyl, H, Ph; H, $CH_2C_6H_5$; Et, Et; H, OEt; $(CH_2)_2O(CH_2)_2$; H, $OCH_2CH{=}CH_2$

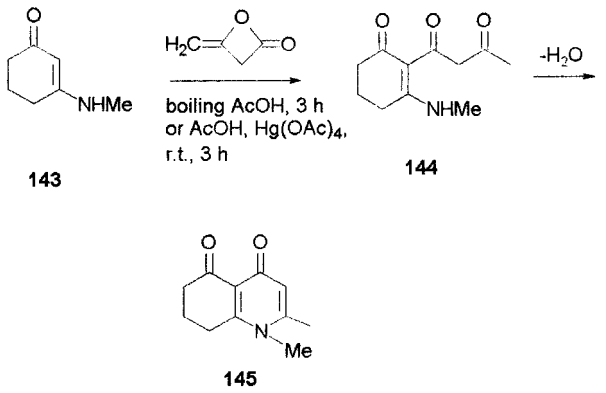
Scheme 28



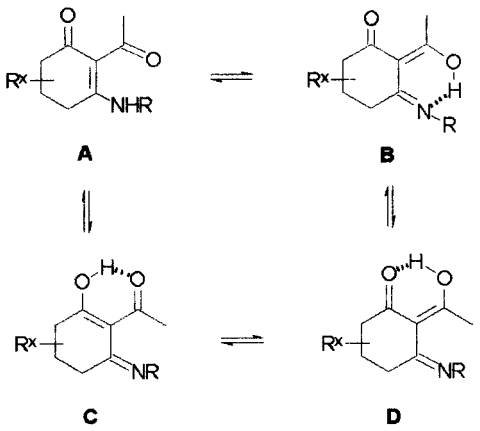
allyloxyamine on appropriate methyl enol ethers (**130**) (Chart 13).[88]

A useful variant of the synthetic approach to *endo*-vinylogous amides is the α-acylation of enamino ketones (**133**) (Scheme 28). However, detailed research of this reaction has shown that N-monoalkylated and N,N-dialkylated enamino ketones are converted preferably into the *N*- or *O*-acylates.[89] It has been established[90] that the pyrrolidine derivative (**133**), lacking an α-proton, is acylated by acetic anhydride or acyl chlorides in the presence of tri-

Scheme 29



Scheme 30



ethylamine to yield 35−59% of enamino diketones (**134**). The morpholine enamino ketone (**135**) does not react under these conditions.

An effective procedure for the α-acylation of the derivatives **133** and **135** and their 4-methoxycarbonyl-substituted analogues **136** by butanoyl chloride in the presence of pyridine, giving rise to up to 70% of the target compounds **137**, has been described (Scheme 28).[91] In the case of the morpholine enamines (**135, 136**), the corresponding enol acylates (**138**) have been isolated together with α-acylated products. The known transamination of enamino diketones (**134, 137**) provides a tool for an exchange of the tertiary amino groups for unsubstituted, primary, and secondary amines. Essentially it expands an area for the synthetic employment of such acylations.[91,92] Refluxing the enamino ketone (**139**) which contains a secondary amino group, in acetic anhydride, also yields the α-acylation product (**140**) in 60% yield.[93] Acylation of enamino ketone (**133**) by acyl chloride (**141**) has been used for the preparation of compound **142**, which is related to the glutarimide antibiotics.[94]

Interaction of 3-methylaminocyclohex-2-en-1-one (**143**) with diketene in acetic acid or acetic anhydride in the presence of mercury acetate results in the formation of the unstable enamino triketone (**144**), which is further spontaneously converted into pyridone (**145**) (Scheme 29).[95]

Endo-enamino diketones containing a primary or secondary nitrogen atom differ from their tertiary analogues in their ability to exist in four tautomeric forms **A**−**D** (Scheme 30). Based on IR[96] and NMR[97] spectral data, it has been determined that the preferred tautomeric form is the enamino diketone **A**, which is similar to enamino derivatives (**114**).

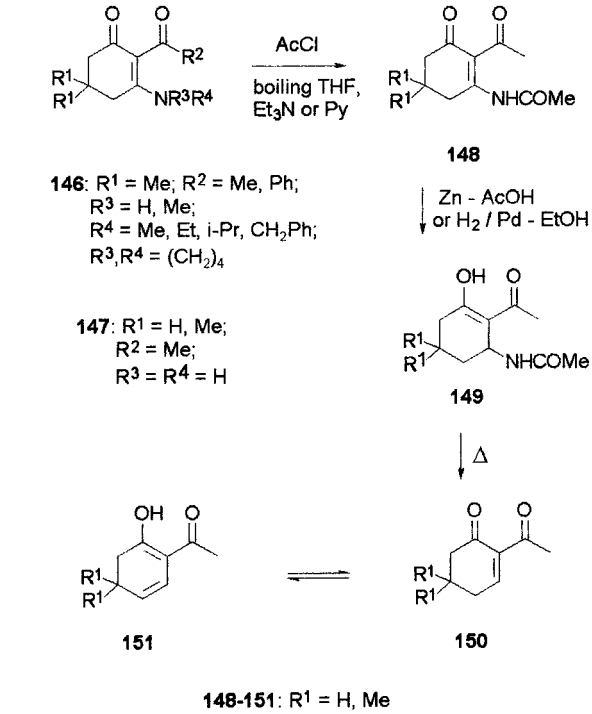
C. Chemical Properties of Vinylogous Amides

Vinylogous amides of types **114**, **115**, **131** can be hydrolyzed under harsher conditions than enol derivatives such as methyl ethers and chlorovinyl diketones. Compounds such as **131**, where the enamino group is in an *endo*-cyclic position, are especially stable to hydrolysis.[79c,87]

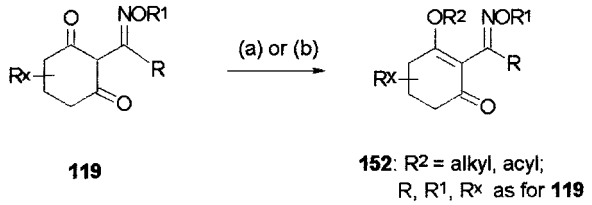
The transamination equilibrium of enamino diketones (**134, 137**) has already been mentioned.[91,92] This same reaction permits the exchange of *exo*-cyclic primary, secondary, and tertiary amino groups.[98] This possibility forms the basis of the application of the available 2-dimethylaminomethylidenedimedone (**114**) ($R^1 = R^3 = Me$, $R^4 = Me$, $R^2 = H$) (Scheme 23) as a protecting group in the synthesis of branched peptides on a solid support[98a] as well as a starting material for the preparation of the antiviral enamino diketones substituted at the nitrogen atom by various hydroxyl-containing groups.[98b]

Endo-enamino diketones (**146**) undergo photochemical dealkylation of secondary and tertiary amino groups, yielding the corresponding primary and secondary amino-substituted compounds.[99] Acylation and alkylation of compounds such as **147**, bearing a primary amino group, usually result in the formation of N-acylated or N-alkylated products. Tertiary amino derivatives give rise to quaternary ammonia salts in similar reactions. Drastic acylation conditions have yielded 40−60% of amides (**148**), which can be reduced easily by zinc in acetic acid or by catalytic hydrogenation to yield diketoamides (**149**). Subsequent pyrolysis yields endiones (**150**) in the ketodienol form (**151**) (Scheme 31).[71a,100]

Scheme 31

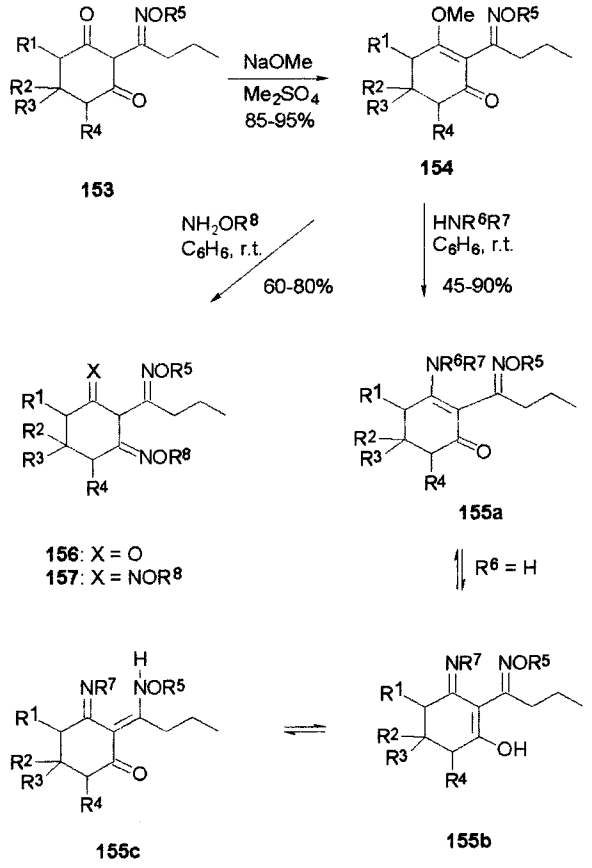


Scheme 32[a]



[a] (a) Et_2SO_4, aq NaOH, $Bu_3N^+EtBr^-$, rt, 5 h; (b) BzCl, Na, Me_2CO, rt, 0.5 h.

Scheme 33



153-157: R^1, R^4 = H, CO_2Me; R^2, R^3 = H, H; Me, Me; H, $CH_2CH(SEt)Me$; R^5, R^8 = Et, $CH_2CH{=}CH_2$; R^6,R^7 = H, H; H, Me; H, Pr; H, sec-Bu; H, C_6H_{13}; H, Ph; Me, Me; $(CH_2)_4$

The effective O-alkylation of oximes (**119**) (R^1 = H) by alkyl sulfates or alkyl halides in the presence of bases has been used as an alternative procedure for the preparation of the above-mentioned herbicides (Chart 12). Besides alkoximes (**119**), dialkylated enol ethers (**152**) have been obtained as byproducts in this reaction.[101] Alkoximines (**119**) can be readily converted into O-alkylated and O-acylated herbicidal derivatives (**152**) (Scheme 32).[102]

The sodium salts of allyl oximes (**153**) have been successfully methylated using dimethyl sulfate in acetone. The resulting methyl enol ethers (**154**) have been transformed into enaminoimines (**155**) by the action of 3−5 equiv of ammonia, or primary or secondary amines,[103] and into bis- (**156**) and tris-(alkoxyimino) derivatives (**157**) through the interaction of **154** and **155** with an excess of the appropriate

Scheme 34

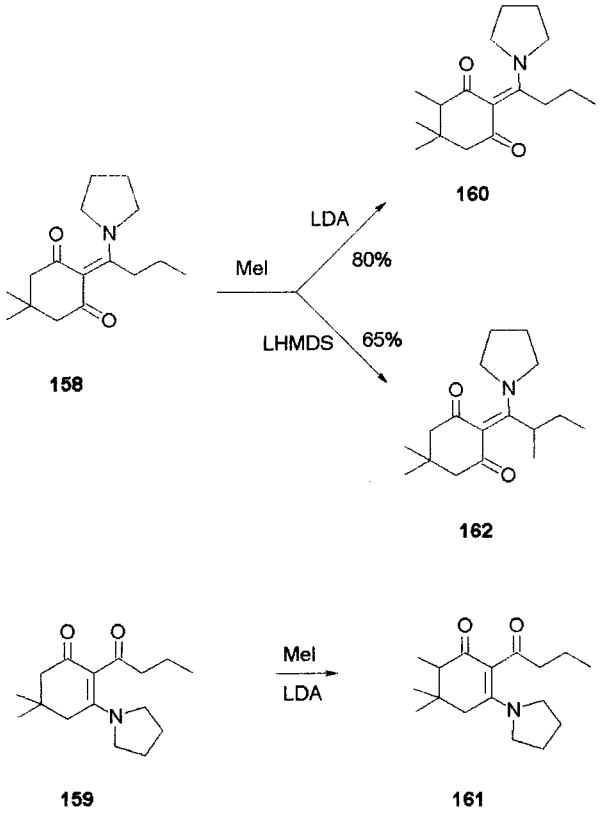
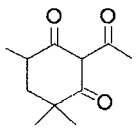


Chart 14

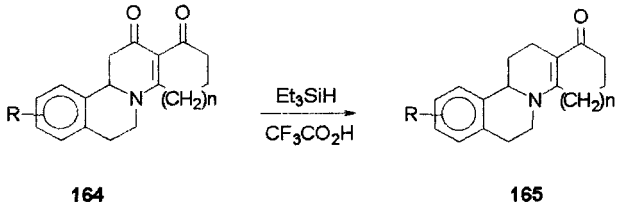


ethyl- or allyloxyamines.[104] It is clear from the IR and PMR data that enaminoimines (**155**), inclined to tautomerism, occur preferably in the enaminoimino ketone form (**155a**) (Scheme 33).[103]

A procedure for the regioselective C-alkylation of cyclohexane β-triketone enamino derivatives in the presence of strong bases has been proposed.[105] Pyrrolidine enamines (**158, 159**) can be alkylated at the α-position by LDA and methyl iodide in THF yielding 80% and 65% of the ring-methylated products (**160, 161**), respectively (Scheme 34). The use of lithium bis(trimethylsilyl)amide as a base permits the methylation of the enamine (**158**) to be directed toward the acyl chain with the exclusive formation of the γ-methylated enamino diketone (**162**). Due to the easy preparation of enamino diketones such as **158** as well as the simple regeneration of the β-triketone by hydrolysis,[79b] this reaction followed by a double α-alkylation has been used for the synthesis of the naturally occurring β-triketone angustione (**163**) (Chart 14).[106]

Both *exo*- and *endo*-cyclic vinylogous amides such as **114**, **115**, and **131** cannot be hydrogenated catalytically using common procedures. Under harsh hydrogenation conditions, the process results in the formation of a complex mixture of products. A similar situation is observed in the reduction with lithium

Scheme 35

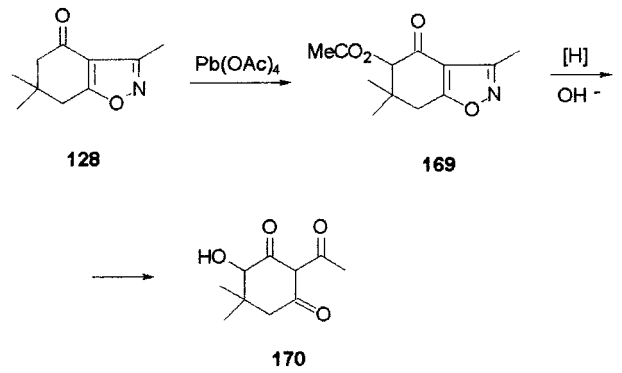


164 165

166, 168 167

164-165: R = H, OMe; n = 0,1;
166-167: R^1= H, CO_2Me; R^2,R^3 = H, H; H, Me;
168: R^1= H, CO_2Me; R^2,R^3 = Et, Et; $(CH_2)_4$

Scheme 36



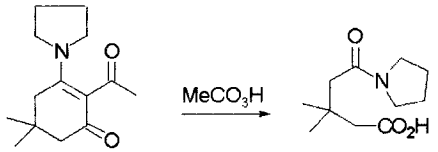
128 169 170

aluminum hydride and sodium borohydride.[79c]

The ionic hydrogenation of the 8-aza steroid enamino diketones (**164**) has been shown to proceed chemoselectively with the reduction of the 12-keto group to give enamino ketones (**165**) (Scheme 35).[107] *Endo*-cyclic cyclohexane enamino diketones (**166**), containing primary and secondary amino groups in the ring, have been reduced regioselectively under the same conditions to give 2-alkyl-substituted β-diketones (**167**) in high yield (Scheme 35). *Endo*-compounds (**168**), bearing tertiary amino groups, suffer deacylation to give enamino ketones such as **136** (Scheme 28). Pyrrolidine and morpholine enamino diketones (**137**), lacking the 4-methoxycarbonyl group, remain unchanged under ionic hydrogenation conditions, probably because of the higher degree of conjugation of the enamino ketone system with the acyl carbonyl group. Derivatives of the type (**114, 115**) containing an *exo*-enamino substituent are also not reduced by ionic hydrogenation even in the presence of Lewis acids.[44]

Isoxazole (**128**) can be considered as a latent vinylogous amide which protects the β-tricarbonyl system and permits modification of the cyclohexane ring. Thus, 4-hydroxy functionalization of cyclohexane β-triketones has been achieved by lead tetraacetate oxidation of isoxazoles (**128**) followed by

Scheme 37



134 171

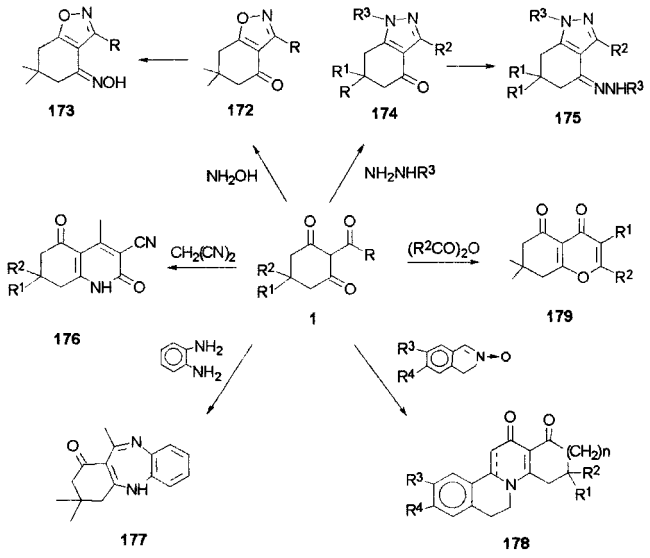
catalytic hydrogenation and alkaline hydrolysis of the intermediate (**169**), affording naturally occurring β-triketones of the type **170** (Scheme 36).[108] The cyclohexane ring in *endo*-pyrrolidinyl-substituted **134** (R^4 = Me) has been shown to be destroyed by peracetic acid oxidation to yield the glutaric acid monoamide (**171**) (Scheme 37).[109]

VII. Heterocycles from 2-Acylcycloalkane-1,3-diones

Both cyclic β-triketones and their enol derivatives represent useful building blocks for the construction of various heterocyclic systems due to their high degree of functionalization and their high reactivity. Examples of such heterocycle synthesis are presented in the previous sections. Heterocycles from the reaction of 2-acylcyclohexane-1,3-diones with malononitrile are reviewed elsewhere.[110] This review considers it in the general context of cyclic β-triketones chemical properties.

The reaction of 2-formyl- and 2-acetyldimedone with hydroxylamine, proceeding through nucleophilic attack at the *exo*-cyclic carbonyl with the formation of an acyl oxime intermediate, has been used as a synthetic route to isoxazoles (**172**) (Scheme 38).[73a,c,111] 2-Acetyldimedone, condensing with 2 equiv of hydroxylamine, gives rise to oxime isoxazole (**173**).[73a,c] Similarly, 2-acylcyclohexane-1,3-diones react with

Scheme 38



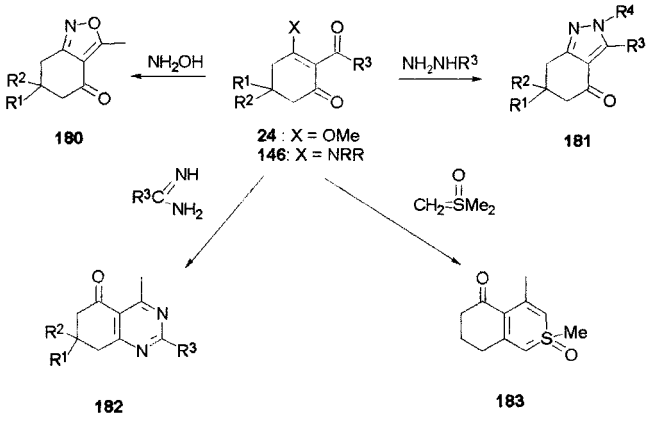
173 172 174 175

176 1 179

177 178

172-173: R = H, Me
174-175: R^1 = H, Me, Ph; R^2 = Me, Et, Pr; R^3 = H, Ph, p-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, $CH_2CH_2CH_2OH$, phenanthridine
176: R^1 = H, Me; R^2 = H, Me, Ph, α–furyl
178: R^1,R^2 = H, Me; R^3,R^4 = H, OMe; n = 0,1
179: R^1 = H, Me, Et; R^2 = H, Me, Pr, C_5H_{11}, CO_2Et

Scheme 39



180: R^1,R^2 = H, Me, Ph
181: R^1,R^2 = H, Me, OH; R^3,R^4 = H, Me, Ph
182: R^1,R^2 = H, Me; R^3 = H, Me, Ph

hydrazine, as well as with alkyl- and arylhydrazines, to yield pyrazoles (**174**) or pyrazole hydrazones (**175**), respectively.[73a,112] Condensation of 5-substituted 2-acetylcyclohexane-1,3-diones with malononitrile in the presence of bases appears to begin with an attack at the acetyl carbonyl group. The main products of this reaction have been shown to be the quinoline derivatives (**176**).[113]

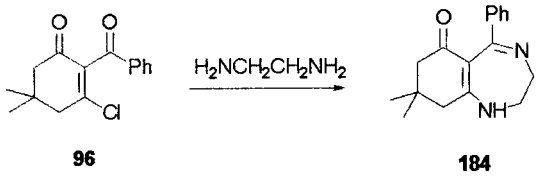
1,4-Diazepine derivatives (**177**) have been obtained by the interaction of 2-acyldimedone and *o*-aminoaniline.[114] The annelation of cyclic β-triketones by 3,4-dihydroisoquinolines realizes an approach to the 8-aza steroids (**178**) (Scheme 38).[115] The latter reaction as well as the biological properties of these steroid analogues have been reviewed in detail.[116] The factors influencing the regio- and stereoselectivity of this annelation have been carefully investigated in recent years.[117]

It has been shown that γ-pyrones (**179**) are formed as byproducts in the acylation of cyclic β-diketones by acyl anhydrides in the presence of sodium hydroxide (Scheme 38).[66] It has been assumed that the process proceeds through enolacylate (**57**) formation followed by an intramolecular ester condensation. This has been confirmed by research on the properties of the enolacylate (**57**). An effective procedure for the preparation of γ-pyrones has been elaborated.[49] The formation of γ-pyrones has been noted in the cyclization of compounds such as **21**,[31] as well as a result of the interaction of 2-acyldimedone with ethyl orthoformate in the presence of perchloric acid.[118]

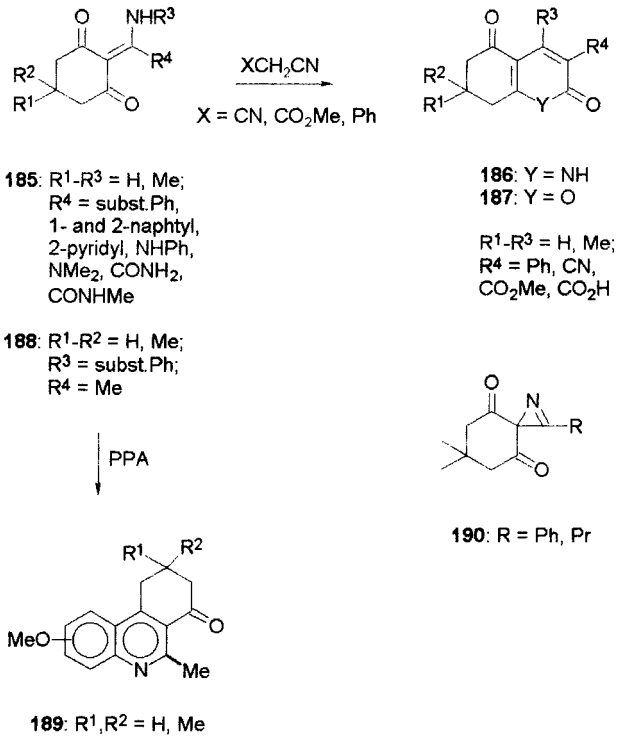
Condensed isoxazoles (**180**) and pyrazoles (**181**), which are isomeric to the heterocycles (**172, 174**) obtained from β-triketones, have been synthesized by the reaction of enol methyl ethers (**24**)[119] and *endo*-cyclic enamino diketones (**146**)[82,89a] with hydroxylamine and hydrazines, respectively (Scheme 39).

Condensed pyrimidines (**182**) have been prepared by the reaction of 2-acyldimedone enol methyl ether (**24**) with both formamidines and acetamidines.[120] An unusual reaction of 2-acyldimedone enol methylate (**24**) with dimethyloxosulfonium methylide yields 5,6,7,8-tetrahydro-2,4-dimethyl-5-oxo-2-thianaphthalene 2-oxide (**183**) (Scheme 39).[121]

Scheme 40



Scheme 41



The reaction of *endo*-cyclic vinyl chlorides (**96**) under these conditions yields heterocycles such as **172** and **174** similar to the β-triketones.[41] Condensation of 2-benzoyl-5,5-dimethyl-substituted chloride (**96**) with 1,2-ethanediamine leads to the 1,4-diazepine derivative (**184**) (Scheme 40).[122]

Exo-cyclic enamino diketones (**185**) have been used as starting materials for the synthesis of tetrahydroquinolines (**186**)[83a,84,123] and tetrahydrocoumarines (**187**)[83c] from the reaction of malononitrile and other compounds containing active methylene groups, in the presence of base (Scheme 41). Heating with polyphosphoric acid converts enamines (**188**) into tetrahydrophenanthridines (**189**), which are useful as a key synthon in 6-aza steroid synthesis.[124] The flash vacuum pyrolysis of ethyl and allyl oximes (**119**) yields azirines (**190**) in addition to oxazoles and isoxazoles.[125]

VIII. Conclusion

Cyclic β-triketone research remains an important and potentially growing focus area of organic chemistry. The reactions described in this review give a clear view of methods used in 2-acylcycloalkane-1,3-dione chemistry as well as the synthetic potential of this class of compounds as universal building blocks for the synthesis of biologically active naturally occurring substances and their analogues. Due to the

versatile multifunctionality of the β-tricarbonyl group, which permits the selective chemical modification of each carbonyl group, as well as selective reactions at other reactive centers according to general synthetic schemes, cyclic β-triketones and their various derivatives have the potential for wider application in modern organic synthesis for the preparation of both important synthetic and naturally occurring substances for medicine and agriculture.

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