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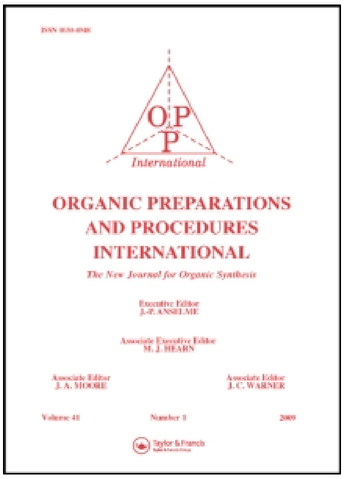

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Publication details, including instructions for authors and subscription information:
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SYNTHESIS AND USES OF β-KETO ACIDS. A BRIEF REVIEW

Lauren Oshry[a]; Stuart M. Rosenfeld[a]
[a] Department of Chemistry, Wellesley College, Wellesley, MA

To cite this Article Oshry, Lauren and Rosenfeld, Stuart M.(1982) 'SYNTHESIS AND USES OF β-KETO ACIDS. A BRIEF REVIEW', Organic Preparations and Procedures International, 14: 4, 249 — 264
To link to this Article: DOI: 10.1080/00304948209354919
URL: http://dx.doi.org/10.1080/00304948209354919

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ORGANIC PREPARATIONS AND PROCEDURES INT. 14(4), 249-264 (1982)

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Lauren Oshry and Stuart M. Rosenfeld*

Department of Chemistry
Wellesley College
Wellesley, MA 02181

II. SYNTHESIS

2. Carboxylation of Enolate Anions

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INTRODUCTION

Though β-keto acids (3-oxoalkanoic acids) have been known since before the turn of the century, the synthetic and structural aspects of their chemistry have received relatively little attention. While almost all literature pertaining to these compounds is concerned with the mechanism of decarboxylation,[1] only a relatively small number of papers describe synthetic methods and uses, purification and isolation, and spectroscopic or structural studies. Important and basic questions remain regarding the effect of solvent and structure on their tautomeric equilibria, the preferred conformations of *keto* and *enol* forms and the importance of dimeric association. Mechanistic studies of β-keto acid thermal decarboxylation have, in some instances, not taken solution phase structure into account[2] thus leading to conclusions that have later been disputed.[3] The metabolic roles of β-keto acids have been extensively studied[4] but continued high interest in this area has led to elegant work requiring well characterized and synthetically accessible substrates.[5] It is the purpose of this review to illustrate the available methods for β-keto acid synthesis, to show where our knowledge of structure is deficient, and to examine the applications found so far for β-keto acids in organic synthesis.

I. STRUCTURE

Well over thirty acyclic aliphatic (and a like number of aromatic) β-keto acids have been isolated as sharp melting solids having melting points from approximately 30° to 125° and yet the literature on their solution phase structure is sparse. Benzoylacetic acid is known to be extensively enolized in both benzene and cyclohexane[6] and cyclic dimers appear to be important under similar conditions.[7] Partial ^{1}H nuclear magnetic resonance (PMR) data have been reported for a series of aliphatic β-keto acids[8] but these incomplete data do not allow interpretation regarding tautomeric and conformational aspects of solution phase structure. Grande and Rosenfeld[9] examined the solvent dependent tautomeric equilibrium in acetoacetic acid by PMR and found a pronounced solvent dependence qualitatively similar to that observed for acetoacetic ester. This suggests that the *keto* form of the acid, as in its ethyl ester, is the more polar of the two since it apparently benefits to a greater extent from stabilization by polar solvents. Analysis of PMR shifts as a function of solvent and concentration led to the conclusion that the *enol* tautomer exists in internally hydrogen bonded form in less polar solvents and that the *keto* form does <u>not</u> benefit from a strong internal hydrogen bond, perhaps due to more favorable dimeric association. At the time of this writing, there has been no systematic examination of the relationship between structure and tautomeric and conformational equilibria in β-keto acids. However, Van der Baan *et al.*[10] have reported that the percent *enol* in $CDCl_3$ solutions of 3-oxooctanoic acid (I) and 4,4-dimethyl-3-oxopentanoic acid (II) are approximately 14 and 25 respectively. The available mass spectral

$CH_3CH_2CH_2CH_2CH_2COCH_2CO_2H$
I

$(CH_3)_3CCOCH_2CO_2H$
II

data for β-keto acids suggests that parent ions are generally observable

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and that the principal mode of fragmentation is decarboxylation as is observed in their ground state chemistry.[8,9] Though a complete X-ray structure of a β-keto acid has not appeared, Stenhagen[11] has reported crystal spacings for a series of aliphatic β-keto acids and has concluded that all those examined have the same structure near their melting point.

II. SYNTHESIS

1. Hydrolysis of Simple Esters of β-Keto Acids

In 1882 the preparation of a concentrated solution of acetoacetic (3-oxobutanoic) acid, the parent member of the series, was reported.[12] It was not until 1952, however, that Krueger[13] isolated crystalline acetoacetic acid, prepared by alkaline hydrolysis of the corresponding ester followed by careful acidification. Although alkaline hydrolysis has been used successfully to prepare several aromatic[2,14] and aliphatic β-keto acids,[15,16] it has proven to be unreliable as a general method[2,17] (Eq. 1).

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$$RCOCH_2CO_2R' + OH^- \longrightarrow RCOCH_2CO_2^- \xrightarrow{H^+} RCOCH_2CO_2H \qquad (1)$$

R = Ph, p-methoxyphenyl, p-methylphenyl, p-chlorophenyl, m-nitrophenyl, p-nitrophenyl

Mitz, Axelrod and Hofmann[17] used acid hydrolysis of a series of fatty acid derived methyl esters to prepare the corresponding acids (Eq. 2).

$$RCOCH_2CO_2R' \xrightarrow[HOAc]{HCl} RCOCH_2CO_2H \qquad (2)$$

$R = n\text{-}C_{11}H_{23},\ n\text{-}C_{13}H_{27},\ n\text{-}C_{15}H_{31},\ n\text{-}C_{17}H_{35}$

Stenhagen[11] later used the same general procedure to prepare the straight chain aliphatic β-keto acids of eight to twenty-four carbons and observed an odd-even alternation in melting point common to many homologous series of compounds. It is interesting to note that these and all other compounds cited herein are easily recrystallized and that the higher members of the series are quite stable at room temperature! (The lower members undergo slow decomposition upon standing at room temperature).

2. Carboxylation of Enolate Anions

a. Preformed Enolates

The reaction of enolate anions and related species with carbon dioxide leads to isolable β-keto acids. Both aliphatic and aromatic acids have been prepared by deprotonation of appropriate ketones with sodium, potassium and lithium phenoxides in the presence of CO_2 in inert polar solvents[18-20] and likewise by deprotonation with sodium triphenylmethide[21] or sodium amide.[22]

$$RCOCH_3 + NaNH_2 \xrightarrow[\text{ether}]{NH_3} RCOCH_2^- \xrightarrow{CO_2} \xrightarrow{H^+} RCOCH_2CO_2H \tag{3}$$

Similarly, enolates formed by reaction of Grignard reagents with sterically hindered ketones (generally mesityl or dineopentylcarbinyl ketones) react with CO_2 yielding both aliphatic and aromatic β-keto acids. In fact, this chemistry was exploited as early as 1903[25,26] for the synthesis of β-keto acids!

b. MMC Method

Carboxylation of enolate anions is simply the reverse of the previously mentioned thermal decarboxylation which has been shown to be retarded by some metal ions.[27] Stiles and Finkbeiner,[28] recognizing this, were able to reverse the decarboxylation of nitroacetic acid in the presence of magnesium methoxide in methanol. Stiles[29] later demonstrated that this reagent (referred to either as magnesium methyl carbonate,

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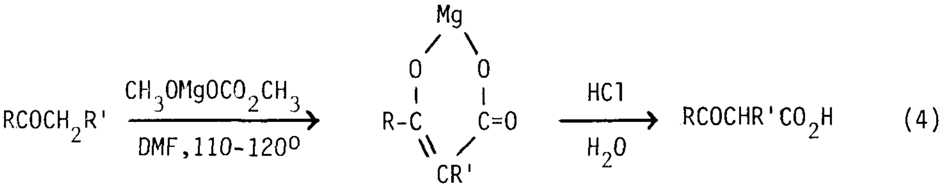
methyl magnesium carbonate or MMC) in DMF solution was capable of carboxylating ketones which have α-hydrogens, and that the intermediate chelates (III) could be alkylated or acylated at the α-carbon (Eq.4). A preferred method of acylation,[30,31] however, involves isolation of the β-keto acid



$$RCOCH_2R' \xrightarrow[DMF,110-120^o]{CH_3OMgOCO_2CH_3} \text{III} \xrightarrow[H_2O]{HCl} RCOCHR'CO_2H \qquad (4)$$

III

followed by regeneration of the chelate using the stoichiometric amount of magnesium methoxide and then addition of the acid chloride. Though the MMC method provides good yields of β-keto acids in many cases, optimum yields require large excesses (5-20 fold) of the reagent and the reaction fails when used with ketones having only one α-hydrogen or where steric factors inhibit formation of a planar chelate.[31] MMC is available commercially but is rather expensive and can be prepared on large scale relatively easily.[32-34] A typical carboxylation procedure[31] follows.

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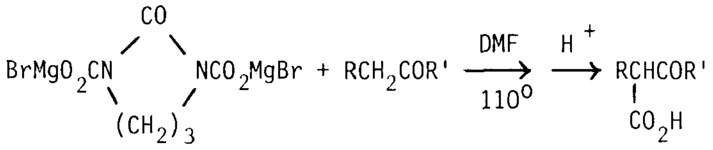
1-Indanone-2-carboxylic acid.- 1-Indanone (5g.) was treated with 128 ml of 1.86M MMC in DMF at 110-120^o for 1.5 hr. The reaction mixture was cooled and poured onto ice and excess hydrochloric acid with stirring. A white precipitate of 1-Indanone-2-carboxylic acid formed and could be collected. Better results were obtained by extraction of the acidified solution with ether, shaking the ethereal extract with 5% sodium bicarbonate solution, acidification of the bicarbonate solution at 0^o and finally extraction with ether. After drying and evaporation of ether, a 90% yield of 1-indanone-2-carboxylic acid, mp 109.5-110^o, was obtained.

A procedure similar to the MMC method but using a bromomagnesium ureide-carbon dioxide adduct as the carboxylating agent has recently been reported. The new reagent affords fair yields of β-keto acids and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R,R' = aliphatic or aromatic

appears to be sensitive to steric factors in unsymmetrical ketones, preferentially carboxylating the less hindered site.[35]

3. Solvolysis of Ketene Dimers, Enol Ethers and Trimethylsilyl Esters

Several solvolytic routes have been used to prepare β-keto acids. The reaction of ketene dimers in CCl_4 with dry HCl followed by hydrolysis with the stoichiometric amount of water affords high yields of acetoacetic acid and several halogenated derivatives.[36] In 1972, Ainsworth and Kuo[8] reported that enol ethers of β-keto acids undergo solvolysis in methanolic HCl to afford the corresponding acids. These authors also introduced a simpler, more flexible route in which intermediates formed from reaction of carboxylic acid dianions and esters were trapped using trimethylchlorosilane (TMCS). The resulting trimethylsilyl esters underwent solvolysis under neutral conditions to provide good yields of β-keto acids[37] (Eq.6).

$$R_2\bar{C}CO_2^- + R'CO_2CH_3 \longrightarrow R'COCR_2CO_2^- \xrightarrow{TMCS} \qquad (6)$$

$$R'COCR_2CO_2Si(CH_3)_3 \xrightarrow{CH_3OH} R'COCR_2CO_2H$$

2,2,4,4-Tetramethyl-3-oxopentanoic acid.[37]- The dianion of isobutyric acid was formed in THF at 0^0 using two equivalents of lithium diisopropylamide. Then one equivalent of methyl pivalate was added and the solution was stirred for 30 min. An excess of TMCS was added and the mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was concentrated and distilled under reduced pressure (50^0,

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0.05mm) to yield 70% of the trimethylsilyl β-keto ester. Solvolysis with methanol at room temp. gave a quantitative conversion to the β-keto acid, no mp reported.

More recently van der Baan and coworkers[10] have shown that acylmalonic acid diesters yield β-keto acids upon hydrolysis and decarboxylation (Eq.7), a mild route developed by these workers specifically for application in an approach to the antibiotic malonomicin.[38]

$$(Me_3SiO_2C)_2CHLi + RCOCl \xrightarrow{\text{ether}} (Me_3SiO_2C)_2CHCOR \qquad (7)$$

$$\xrightarrow[0^o]{H_2O} \left[(HO_2C)_2CHCOR\right] \xrightarrow{-CO_2} RCOCH_2CO_2H$$

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General Procedure.-[10] A 1.56 normal solution (6.5 ml) of n-butyllithium in hexane was added over 10 min. to a stirred solution of bis(trimethylsilyl) malonate (2.48 g, 10 mmol) in dry ether (20 ml) under a nitrogen atmosphere at -60°. The mixture was then allowed to warm to 0° and a solution of the acid chloride (5 mmol) in dry ether or THF (10 ml) was added in one portion. The mixture was stirred for another 10 min. at 0° and then shaken thoroughly with cold 5% aq. sodium hydrogen carbonate (50 ml) during 5-10 min. The aqueous layer was acidified to pH 1-2 with cold 4N sulfuric acid or concentrated citric acid solution, and extracted several times with ether or ethyl acetate. The extract was dried with magnesium sulfate and evaporated *in vacuo* at room temperature to give the crude β-keto acid.

An analogous though less efficient procedure provides β-keto acids by reaction of carboxylic acid dianions with acid chlorides.[39]

III. SYNTHETIC USES

β-Keto acids have served a variety of synthetic purposes in addition to their well known role as intermediates in the alkylation-hydrolysis-decarboxylation sequence of the acetoacetic ester synthesis of ketones.

In many instances where the condensation of alkyl carbonates with ketones to give β-keto esters fails[40] (e.g. for reactive or very unreactive ketones), carbonation of enolates followed by esterification of the β-keto acid[21,22] with diazomethane or use of the MMC method followed by diazomethane esterification succeeds.[41] This latter route also provides convenient regioselectivity since carbonation with MMC is reversible yielding the product derived from the more stable chelate. Pelletier and coworkers[42,43] have carboxylated a series of 2-tetralones (e.g.IV) selectively at the 3-position (Eq.8) providing β-keto acids that were then converted to their corresponding methyl esters (diazomethane). These authors suggest that steric factors favor the chelate leading to the product isolated.

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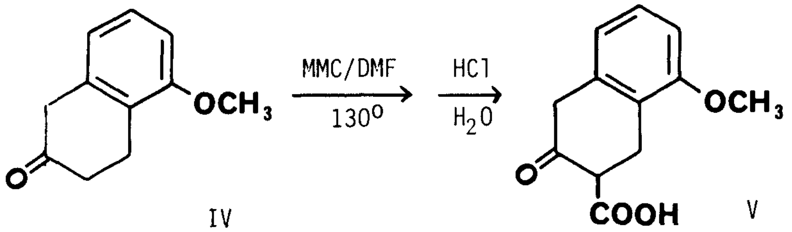
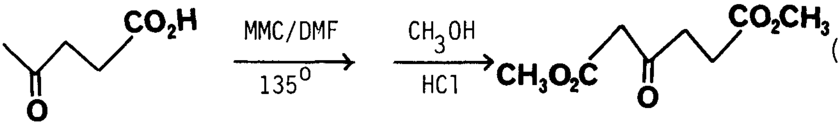


IV V (8)

The regioselectivity of the MMC method has proven useful in an efficient synthesis of dimethyl β-ketoadipate (VI) prepared by carboxylation of levulinic acid followed by Fischer esterification (Eq.9).[44]



(9)

VI

Dimethyl β-ketoadipate.[44] A solution of 10.6 g (91.4 mmol) of levulinic acid in 360 ml (920 mmol) of 2.56 M MMC in DMF was heated at 135° for 24 hrs. The DMF was removed by distillation under vacuum at 60°. Trituration of the residue with ether gave after filtration and air drying 136g of yellow solid. The solid was suspended in 820 ml of methanol in a 3 L three-necked round bottom flask equipped with mechanical stirrer, condenser, and gas inlet tube. After cooling to -10°, hydrogen chloride was passed over the mixture until saturation had occurred. After standing overnight in the ice bath the temperature had become ambient; the mixture was then concentrated at 40° under reduced pressure. The syrupy residue was poured onto ice and the aqueous solution was extracted four times with chloroform. The combined organic extract was washed with sat. bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation through a Vigreux column gave 15.8 g (92%) of dimethyl β-ketoadipate as a colorless liquid, bp. 94-96/0.35 mm.

Crombie *et al.*[45] prepared the plant natural product pyrethrolone (VII) by a route that included a quantitative and regioselective carboxylation with MMC followed by condensation of the potassium salt of the β-keto acid with pyruvaldehyde and cyclization of the hydroxydione in ethanolic NaOH (Eq.10).

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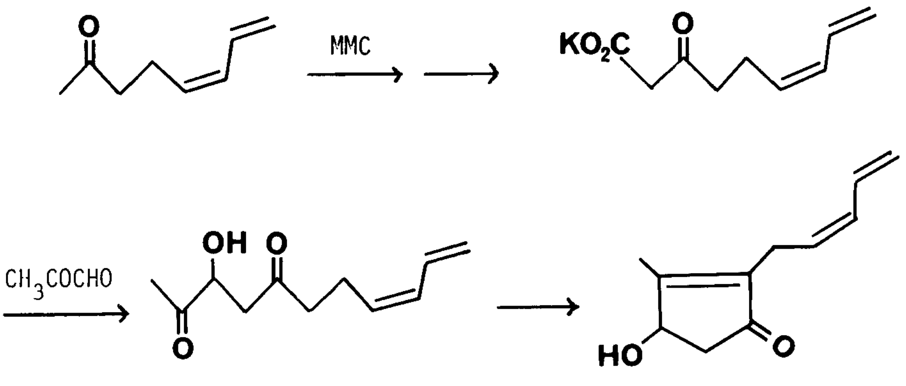


(10)

VII

n-Hexanoylmethylenetriphenylphosphorane needed for the introduction of the last portion of the carbon skeleton in the synthesis of a series of prostaglandins was prepared from 1-chloroheptan-2-one. The key step in this kilogram-scale preparation of the Wittig reagent[46] involves the chlorination-decarboxylation of 3-ketoöctanoic acid with sulfuryl chloride (Eq.11).

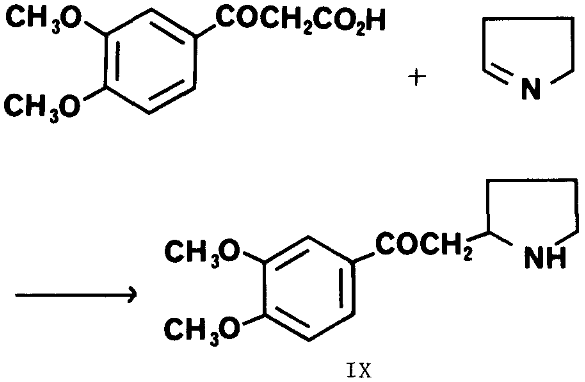
$$CH_3(CH_2)_4COCH_2CO_2H \xrightarrow[\text{2. distillation}]{\text{1. } SO_2Cl_2, CH_2Cl_2} CH_3(CH_2)_4COCH_2Cl \qquad (11)$$

β-Keto acids have been used even more directly in effecting condensation reactions. Schöpf and Thierfelder[47] as well as Stiles and coworkers[48] prepared hydroxyketones under very mild conditions by the condensation (with loss of CO_2) of aldehydes with β-keto acids (Eq.12). The

$$PhCHO + CH_3CH_2COCH_2CO_2H \xrightarrow[-CO_2]{\text{pH 7 buffer}} CH_3CH_2COCH_2CH(OH)Ph \qquad (12)$$

β-keto acids used in these procedures were neither isolated nor purified and the final yields of pure hydroxyketone were generally low (22-61%). Perhaps examination of analogous methods using pure samples of β-keto acid would be warranted.

Herbert *et al.*[49] have developed a simple and economical synthesis of the alkaloid septicine (VIII) utilizing the reaction of 3,4-dimethoxybenzoylacetic acid and Δ^1-pyrroline in aqueous methanol (pH 7) to produce the critical intermediate (IX, Eq.13). Condensation of this intermediate



(13)

IX

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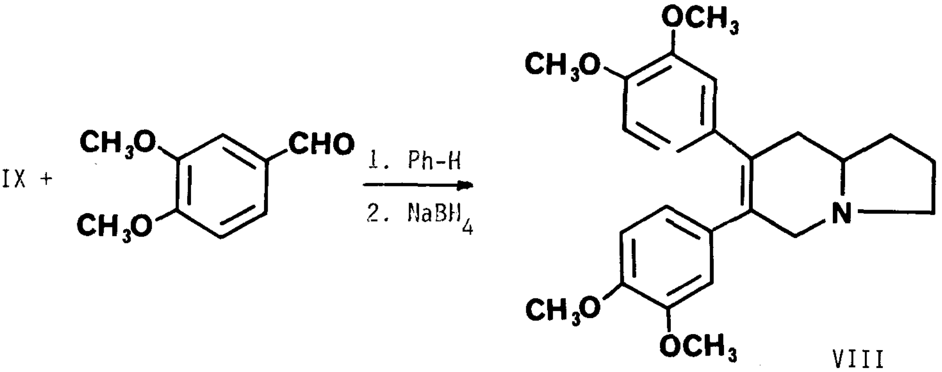
with 3,4-dimethoxybenzaldehyde followed by sodium borohydride reduction gave septicine in a yield of 24% for the steps outlined (Eq.14).



(14)

VIII

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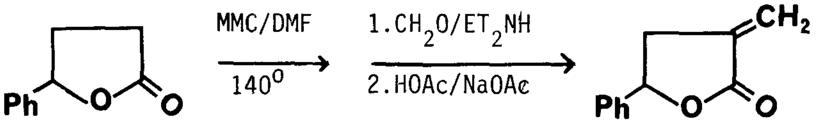
Carboxylation of carbonyl compounds other than ketones also offers promise. A method of preparation of α-methylenebutyrolactones based on carboxylation of lactones with MMC has been reported by Johnson and coworkers (Eq.15).[50,51] The method was later described in detail and applied



(15)

in the synthesis of protolichesterinic acid by these workers.[52] A similar procedure, useful in methylenation of both α- and δ-lactones, has also been reported.[53] Finally, Finkbeiner[54,55] has described a simple amino acid synthesis based on the MMC carboxylation of hydantoins followed by alkylation of the magnesium chelate and then hydrolysis to give the free amino acids.

Acknowledgment - Support of our work in this area from a William and Flora Hewlett Foundation Grant of Research Corporation is gratefully acknowledged.

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(Received September 2, 1981; in revised form February 4, 1982)

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