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Digest paper

Recent topics in the syntheses of β-keto carboxylic acids and the derivatives

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ABSTRACT

β-Keto carboxylic acids are key intermediates in organic syntheses, used for the development of fine chemicals, natural products, and various biologically relevant molecules. Their utilities stem from the structural features and facile bond formations, e.g., asymmetric reduction of carbonyl groups for the synthesis of β-hydroxy carboxylic acids and conjugated addition reactions through decarboxylative enolate nucleophiles, which utilize the amphiphilic reactivity of β-keto carboxylic acids. Despite their versatility and utilities, development of efficient and straightforward synthetic methods for β-keto carboxylic acids has not attracted considerable attention owing to their instability. As efficient synthetic strategies for β-keto carboxylic acids and their derivatives, reactions of α-diazoesters, acylation of malonate anions, cross-coupling reactions, and CO_2 insertion reactions are summarized in this review.

Contents

β-Keto carboxylic acids are potent key intermediates in organic syntheses,[1] used for the development of natural products and various biologically relevant molecules.[2] Their utilities seem to stem from the structural features and facile bond formations, e.g., asymmetric reduction of the carbonyl groups of β-keto carboxylic acids[3] and conjugated addition reactions through decarboxylative enolate nucleophiles.[4] These transformations are used as the carbon chain elongation methods by utilizing amphiphilic reactivity of β-keto carboxylic acids. Despite their versatility and utilities, efficient and straightforward synthetic strategies have not been yet developed, owing to the instability of β-keto carboxylic acids. In this brief review, the synthetic utilities for the efficient preparation of β-keto carboxylic acids and their derivatives such as β-keto esters and amides are summarized along with recent development and distinctive strategies.

Synthesis of β-keto esters from aldehyde and α-diazo esters

Although various methods that utilize strong bases and alkali metals have been reported for the synthesis of β-keto carboxylic acids and their derivatives,[5] Lewis acid catalyzed C—H insertion reactions of α-diazo esters into aldehydes are very effective for this purpose. In particular, Nb-catalyzed C—H insertion of α-diazoesters into α, β-unsaturated aldehydes is a transformation

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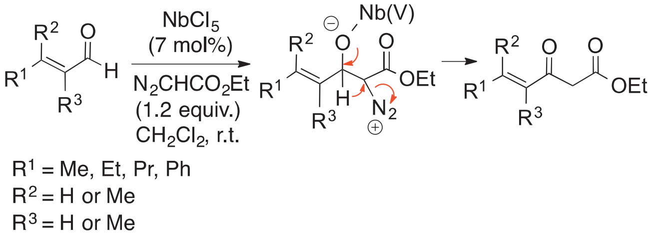


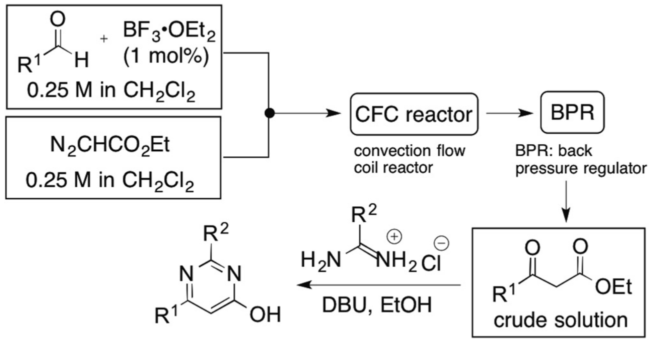
Scheme 1. Nb-catalyzed C—H activation with α-diazo esters.

with exceptional properties.[6] This reaction is likely to occur through a generation of carbene active species from ethyl diazoesters, followed by a 1,2-hydride shift with a concomitant loss of nitrogen gas (Scheme 1).

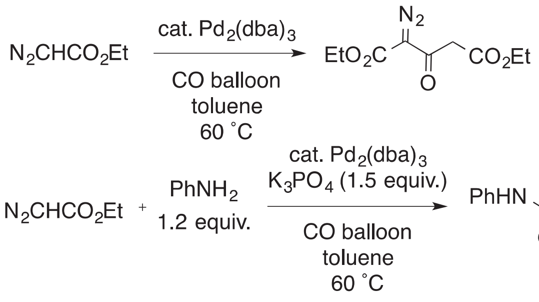
An in-flow process for the synthesis of β-keto esters through the $BF_3{\cdot}OEt_2$-catalyzed formal C—H insertion of ethyl diazoacetate into aldehyde has been developed.[7] The formed β-keto esters were condensed with various amidines, which produces various 2,6-disubstituted pyrimidin-4-ols (Scheme 2).

Pd-catalyzed carbonylation can be employed to introduce C=O groups into functional groups. The reaction of ethyl diazoacetate was catalyzed using a Pd(0) complex under an atmosphere of carbon monoxide in toluene at 60 °C to obtain diethyl 2-azo-3-oxoglutarate as a major product.[8] Decomposition of the diazo ester induced by a Pd(0) catalyst generates a Pd-carbene complex, which undergoes carbonylation that produces a ketene intermediate. Then, the obtained ketene can be attacked by ethyl diazoacetate. When a similar catalytic reaction was performed in the presence of aniline, ethyl 2-(phenylcarbamoyl) acetate was isolated in good yields. The use of inorganic bases, such as K_2CO_3 and K_3PO_4, further improved the yields (Scheme 3).

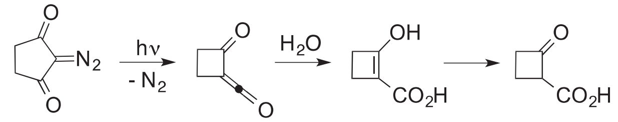
Keto-enol tautomerism can be employed as an efficient synthetic methodology for β-keto esters. A flash photolysis of 2-diazocyclopentane-1,3-dione in an aqueous medium produced 2-oxocyclobutylideneketene, which underwent hydration to the enol of 2-oxocyclobutanecarboxylic acid.[9] This β-hydroxy α, β-unsaturated carboxylic acid easily isomerizes to the keto form that provides a cyclic β-keto carboxylic acid (Scheme 4).



Scheme 2. In-flow and rapid access.



Scheme 3. Pd-catalyzed coupling with α-diazo esters.



Scheme 4. Reaction with α-diazocyclopentane-1,3-dione.

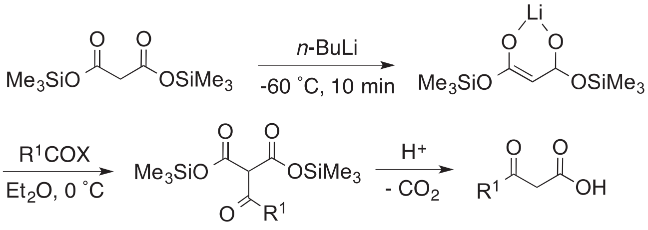
Synthesis of β-keto esters and β-keto acids from malonates

The treatment of bis(trimethylsilyl)malonate with *n*-BuLi at −60 °C generated the corresponding lithium monoanionic species, followed by the reaction with acyl halides to form α-acyl bistrimethylsilylmalonate. Then, the acidic work-up provides β-keto carboxylic acids with an instant monodecarboxylation (Scheme 5).[10]

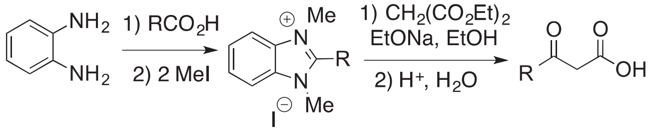
Benzimidazolium iodide is a key intermediate for the synthesis of β-keto carboxylic acid. Benzimidazole is prepared from 1,2-benzenediamine and carboxylic acid; then, a treatment with two equivalents of methyl iodide provides benzimidazole methiodide salt.[11] The addition of an ethyl malonate anion enables benzimidazolidine to convert into the corresponding β-keto carboxylic acid though acidic hydrolysis. The formation of a quaternary ammonium salt assists the addition reaction by increasing the polarity of the C=N bond, which is attacked by an ethyl malonate anion (Scheme 6).

A direct procedure for accessing β-keto esters would involve acylation of diethyl malonate, followed by a partial hydrolysis and decarboxylation processes. However, the disadvantage of this method is the possibility of diacylation, hydrolysis of both ester groups, and appearance of a *retro*-condensation reaction, which leads to the starting materials. In contrast, recently, a modified method to access β-keto esters through monoalkyl potassium malonates has been developed. Wemple et al. reported a high-yielding economical method for the preparation of β-keto esters, which involves a coupling reaction with acid chlorides and potassium ethyl malonate in a magnesium chloride-triethylamine base system (Scheme 7).[12]

Furthermore, an effective catalytic system based on palladium salt, which promotes a carbonylative arylation of potassium malonate monoesters with aryl halides under stoichiometric amounts of



Scheme 5. Acylation of lithium malonates.



Scheme 6. Synthesis of β-keto carboxylic acids from benzimidazole methiodide and ethyl malonates.