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Stobbe Condensation

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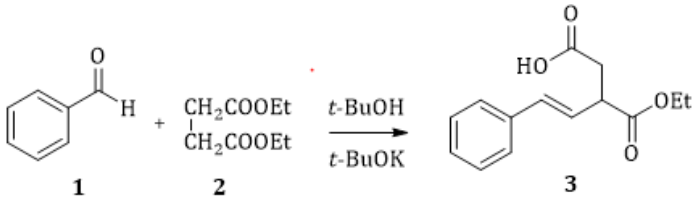
Abstract

The Stobbe condensation, a widely used reaction in synthetic organic chemistry, involves the reaction of a diester of succinic acid with a carbonyl compound in the presence of an alkoxide to lead to the formation of alkylidine succinic acids [1]. The formation of an intermediary lactone ester is suggested although rarely observed. The reaction condition, particularly the nature of the metal steers the Stobbe reaction in different directions. The reaction has been widely used for the synthesis of cyclopentanone, cyclohexanone derivatives as well as carbonyl compounds with propionic acid as a side chain. It has also been applied for the synthesis of substituted tetralones, tetrahydronapthalenes, and oestrone derivatives.

Keywords: Dialkylsuccinate; Benzaldehyde; Tetralones; Rishitinol

Introduction

This is a condensation between dialkyl succinates and aldehydes or ketones in presence of a base like sodium hydride, potassium t-butoxide, or sodium ethoxide to form salts of α, β-unsaturated half esters [1]. The condensation of benzaldehyde 1 with diethylsuccinate 2 in presence of base produces the salt of ethyl α-benzylidene esters of succinic acid which on acidification furnishes halfester 3 (Scheme 1).



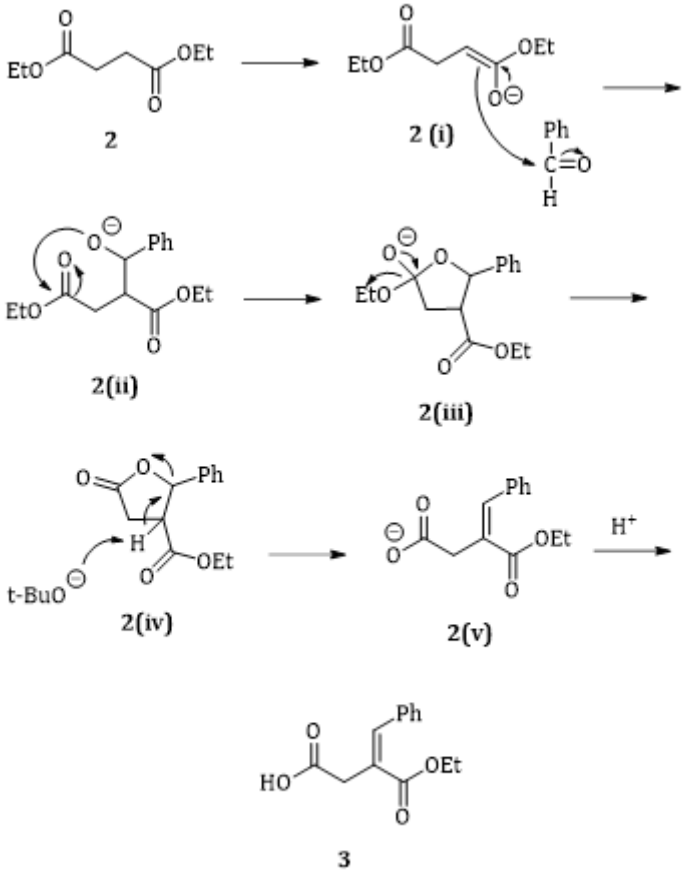
1 2 3

Scheme 1

A variety of condensing agents has been used including sodium ethoxide, potassium t-butoxide, and sodium hydride. Sodium methoxide, metallic sodium, and sodium triphenylmethyl have limited applications. The succinic esters that have been employed are diethyl, dimethyl, and di-t-butylsuccinate. Although ketones usually do not condense with the active methylene group of the diacid ester as readily as aldehydes, ketones are found to react equally well with succinates in the Stobbe condensation in comparison with aldehydes [2]. In addition, it has been reported the Stobbe condensation involving a ketone usually gives a better yield, and pure substituted Stobbe acid ester if potassium t-butoxide [3] or sodium hydride [4] is used in a short reaction period than sodium ethoxide.

Mechanism

The first step of the Stobbe condensation is the formation of the enolate anion 2(i) of the succinic ester 2 which attacks the benzaldehyde 1 to yield the lactone 2 (iv) through the vias 2(ii) and 2(iii) [2]. The cleavage of the lactone yields the anion 2 (v) which on acidification furnishes the halfester 3 (Scheme 2).



Scheme 2

Drawbacks

(i) Self-condensation of the aldehydes or ketone substrate, (ii) Cannizaro reaction of the aromatic aldehyde, (iii) If the ketone is highly enolizable under the reaction condition yields tend to be slow, (iv) too reactive ketones may undergo acylation (Claisen reaction) at their α-position by the dialkyl succinate.

Modifications

The reaction has been extended to dialkyl adipates [5], diethyl β,β-dimethylglutarate [6], diethyl diglycolate [7], and homophthalic ester [8]. A Silyl-Stobbe condensation has been developed [9]. It is worthwhile to mention here that the Stobbe condensation reaction is affected by steric hindrance [10].

Applications

Numerous examples of the Stobbe condensation have been cited [1,11]. The Stobbe condensation has been applied for the synthesis of substituted cyclopentanone, cyclohexanone, decalone, etc. In addition, the Stobbe condensation has been applied for the synthesis of natural products related to terpenes, flavones, oestrones, etc. A few examples are described below.

The Stobbe condensation of the keto ester 4 with di-t-butylglutarate 5 (Scheme 3) affords the triester 6 [12] which on deprotection and dehydration affords the acid 7. PPA cyclization of the acid affords the unsaturated keto acid 8. The overall yield of the acid 8 (34%) is superior to the method employed (overall yield of 5%) [13]. The acid 8 has been converted to β-eudesmol 9 by Huffman [13] and Heathcock [14].

The Stobbe condensation reaction is applied for the synthesis of 8-methoxy-1-tetralone 14 [15]. The synthetic route has been depicted in Scheme 4. The condensation of m-methoxy – benzaldehyde 10 with dimethyl succinate 11 yields an unsaturated ester which on alkaline hydrolysis followed by catalytic hydrogenation affords the diacid 12. Bromination of the diacid and

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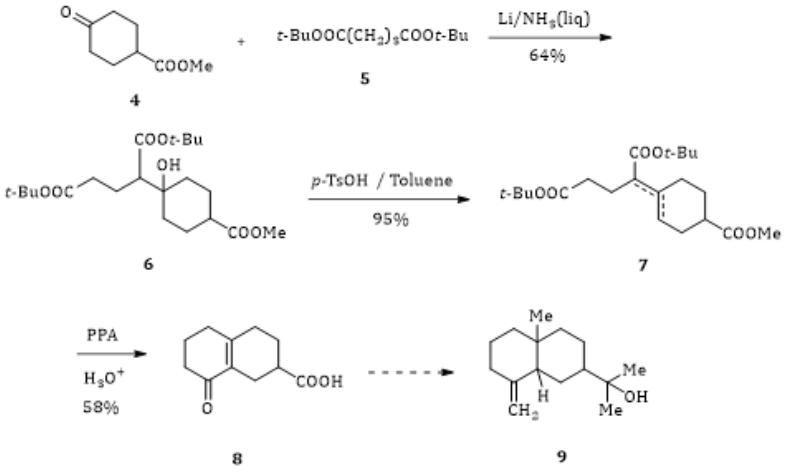
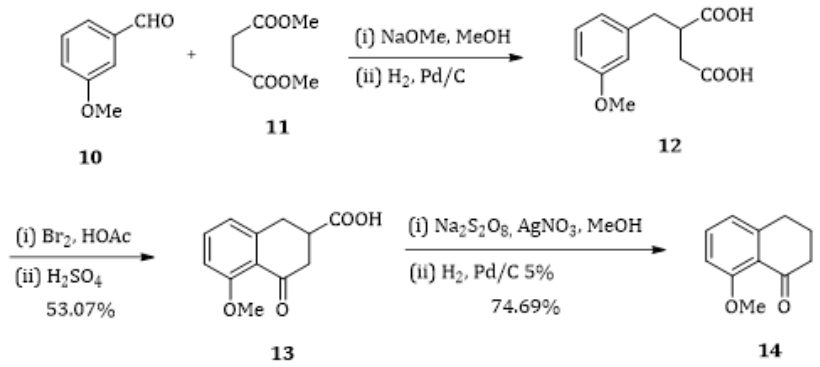
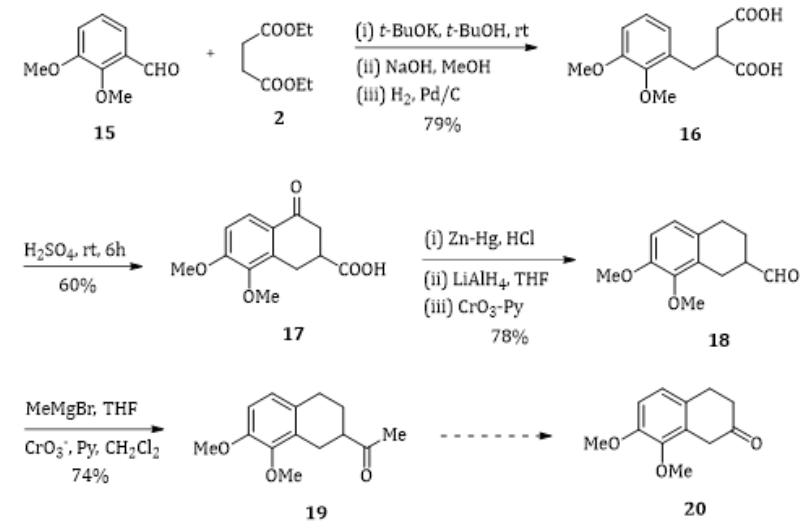
then cyclization with sulfuric acid furnishes bromotetralone 13 whose transformation to the 8-methoxy-1-tetralone 14 is affected by (i) decarboxylation, achieved by heating with sodium bisulphite and (ii) dihydrobromination, realized by catalytic hydrogenation. Tetralone 14 is useful for the synthesis of ARQ-501, a metabolite of human blood. In addition, tetralone 14 is useful for the study of dopamine (DA) and serotonin receptors.



Scheme 3



Scheme 4.



Scheme 5

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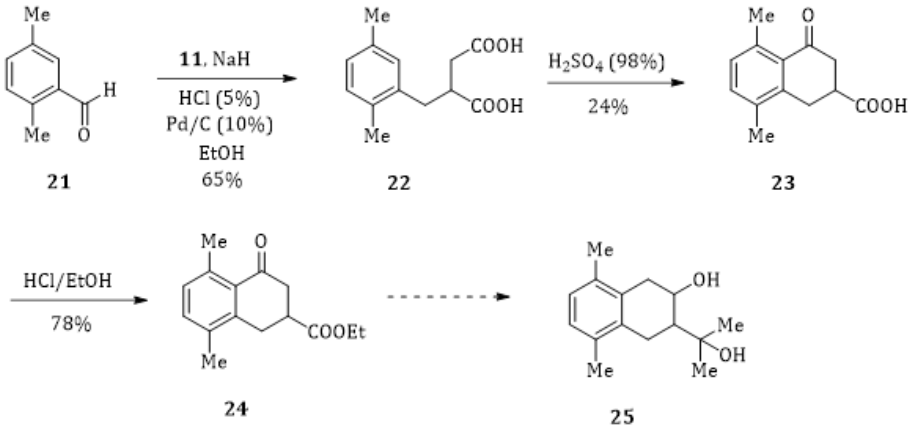
The applications of the Stobbe condensation have been noted during the synthesis of 2-acetyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 19 (Scheme 5) which can easily be converted to the reported [16] 2-keto-7,8-dimethoxy-1,2,3,4-tetrahydro- naphthalene 20, an important intermediate which is useful for the synthesis of biologically active compounds. The Stobbe condensation of the 2,3-dimethoxybenzaldehyde 15 with dimethylsuccinate 2 yields an unsaturated compound which is converted to diacid 16 by alkaline hydrolysis and catalytic hydrogenation respectively. The cyclization of the acid 16 with sulfuric acid affords the tetralone 17 whose transformation to the aldehyde 18 is affected in three steps: (i) Clemmensen reduction [17], (ii) metal hydride reduction, and (iii) chromic acid oxidation respectively. Treatment of the aldehyde with Grignard reagent followed by chromic acid oxidation furnishes the desired compound 19 which can be converted to the reported tetrahydro-naphthalene 20 in three steps (Baeyer Villiger oxidation, alkaline hydrolysis, and chromic acid oxidation).

Banerjee and collaborators [18] have utilized the Stobbe condensation to accomplish a formal total synthesis of Rishitinol 25 [19], a phytoalexin sesquiterpene, which is produced in stressed white potato (solanum tuberosum) as a response to the infection by Phytophtora infestans [20] fungus. In order to accomplish the objective, the commercially available aldehyde 21 (Scheme 6) is subjected to the Stobbe condensation by heating at reflux with dimethylsuccinate 11 and sodium hydride. The resulting compound, on hydrolysis with hydrochloric acid (5%) and catalytic hydrogenation with palladium on carbon in ethanol affords the diacid 22 which on cyclization with sulfuric acid (98%) leads to the formation of the tetralone 23. Esterification of 23 with ethanolic hydrochloric acid furnishes the ester 24 (overall yield 12%) which is superior to the reported [19] overall yield (6%). As the conversion of the ester 24 to rishitinol 25 has been accomplished in two steps the present approach constitutes a formal total synthesis of rishitinol.



Scheme 6

The Stobbe condensation has been applied for the synthesis of ventiloquinone F and Isoventiloquinone F [21]. A stereoselective Stobbe condensation of ethyl methyl diphenylmethylene succinate with aromatic aldehydes has been studied by Liu and Brooks [22]. The Stobbe condensation proved useful to develop different indole derivatives depending on the reaction condition [23]. A convenient synthesis of 5-methylene-4-substituted-2(5H)-furanones has been developed by applying Stobbe condensation [24].

We believe that in near future more applications of the Stobbe condensations will be developed.

The Stobbe condensation has been applied for the synthesis of 4-oxo-4H-quinolizine-2-carboximide derivatives [25] and substituted furanones [26].

Conclusion

The present review describes very briefly the applications of the Stobbe condensation in synthesis of substituted tetralones and in synthesis of natural products Eg: β-eudesmol, rishitinol. The applications of the Stobbe condensation in synthesis of heterocyclic compounds have been mentioned.

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