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Selective Synthesis of α,β-Unsaturated Ketones by Dibutyltin Dimethoxide-Catalyzed Condensation of Aldehydes with Alkenyl Trichloroacetates

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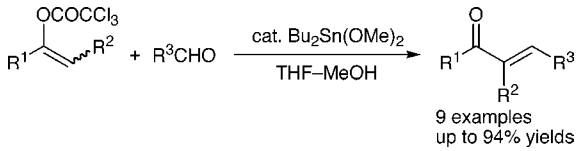
ABSTRACT



Various α,β-unsaturated ketones were stereoselectively synthesized in high yields up to 94% by a condensation reaction between alkenyl trichloroacetates and aldehydes using dibutyltin dimethoxide as a catalyst in the presence of methanol. This process is superior to the classical Claisen–Schmidt condensation with respect to mildness of the base catalyst and product selectivity.

α,β-Unsaturated carbonyl compounds are versatile organic molecules which have been frequently used as substrates for carbonyl addition,[1] conjugate addition,[1] the Morita−Baylis−Hillman reaction,[2] etc. The Claisen−Schmidt condensation is recognized to be a classical and still useful method to prepare a α,β-unsaturated ketone or aldehyde from an aromatic aldehyde and an aliphatic ketone or aldehyde. However, since this method employs a relatively strong base such as metal hydroxide or metal alkoxide, it is often accompanied by side reactions, e.g., bis-condensation and aliphatic aldehyde dimerization.[3,4] In addition, the narrow substrate diversity does limit the applicability of this process. An elegant solution to these problems is a Mukaiyama aldol reaction and subsequent dehydration catalyzed by a Lewis acid in place of strong base catalysts.[5] In contrast, we have found that dibutyltin dimethoxide is a milder base catalyst effective in converting alkenyl esters and aldehydes into the

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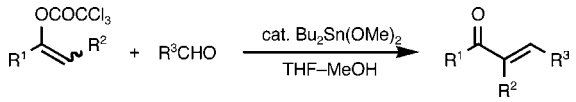
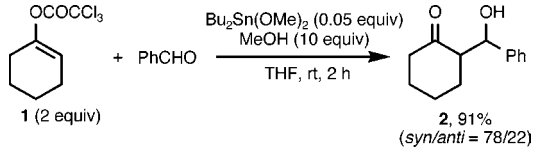
Scheme 1. $Bu_2Sn(OMe)_2$-Catalyzed Condensation between Alkenyl Trichloroacetates and Aldehydes



corresponding α,β-unsaturated ketones. Here, we wish to report a novel method for preparing α,β-unsaturated ketones by a tandem aldol condensation/dehydration under the influence of the tin catalyst (Scheme 1).

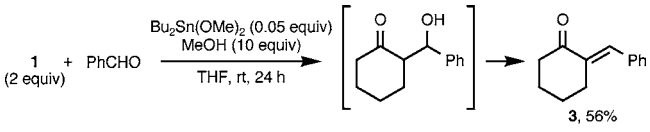
As previously reported, the $Bu_2Sn(OMe)_2$−MeOH system promotes the aldol reaction of alkenyl trichloroacetates.[6] For example, treatment of 1-trichloroacetoxycyclohexene[7] (**1**, 2 equiv) with benzaldehyde (1 equiv) in the presence of 5 mol % of $Bu_2Sn(OMe)_2$ and 10 equiv of MeOH in THF at room temperature (20−25 °C) for 2 h gave the aldol adduct **2** in 91% yield with a *syn*/*anti* ratio of 78/22 (Scheme 2). We

Scheme 2. Aldol Reaction of 1-Trichloroacetoxycyclohexene with Benzaldehyde Catalyzed by $Bu_2Sn(OMe)_2$



envisaged that if the reaction was performed for a longer time, the corresponding α,β-unsaturated ketone might be formed due to a subsequent dehydration reaction of the resulting aldol adduct. In fact, when the aforementioned aldol reaction was carried out for 24 h under similar reaction conditions, the desired enone **3** was obtained in 56% yield as the sole stereoisomer (*E*-isomer, Scheme 3). Thus, we

Scheme 3. Attempt at Tandem Aldol Reaction/Dehydration



next optimized the reaction conditions of the tandem aldol/dehydration reaction to obtain higher yields of the product, and the results are summarized in Table 1. First, an increase in the amount of MeOH to 20 equiv caused definite improvement in the chemical yield (entry 2). Then, several

(6) (a) Yanagisawa, A.; Sekiguchi, T. *Tetrahedron Lett.* **2003**, *44*, 7163. See also: (b) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892. (c) Yanagisawa, A.; Matsumoto, Y.; Asakawa K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331. Alkenyl trichloroacetates are the best substrates for the present condensation reaction and other alkenyl esters, such as simple acetates show almost no reactivity under the standard reaction conditions.

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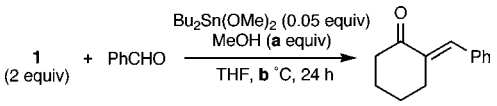
Table 1. Optimization of Reaction Conditions of Condensation of 1-Trichloroacetoxycyclohexene with Benzaldehyde Catalyzed by Dibutyltin Dimethoxide[a]



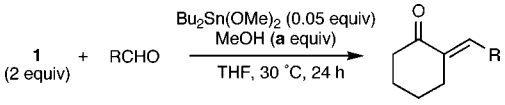
entry	**a** (equiv)	**b** (°C)	yield[b] (%)
1	10	rt	56
2	20	rt	71
3	20	30	94[c]
4	20	35	85
5	20	40	82
6	10	30	87
7	30	30	76

[a] Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.05 equiv), 1-trichloroacetoxycyclohexene (2 equiv), and benzaldehyde (1 equiv) in dry THF containing MeOH (10−30 equiv) at the specified temperature for 24 h. [b] Isolated yield. [c] 95% purity.

reaction temperatures were examined, and reaction at 30 °C gave the best result (entries 2−5). However, the reaction at 30 °C using 10 or 30 equiv of MeOH decreased the yield (entries 3, 6, and 7).

Optimal conditions were established, and we then employed these conditions in a catalytic coupling reaction of 1-trichloroacetoxycyclohexene with typical aromatic, α,β-unsaturated, and aliphatic aldehydes (Table 2). All reactions

Table 2. $Bu_2Sn(OMe)_2$-Catalyzed Coupling Reaction of 1-Trichloroacetoxycyclohexene with Various Aldehydes[a]



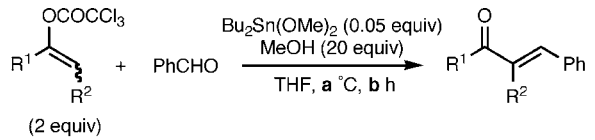
entry	RCHO	**a** (equiv)	yield[b] (%)
1	PhCHO	20	94[c]
2	4-$MeOC_6H_4CHO$	10	88
3	4-BrC_6H_4CHO	20	74
4	(*E*)-PhCH=CHCHO	20	89[d]
5	$Ph(CH_2)_2CHO$	10	62[e]

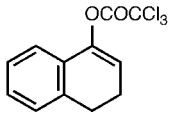
[a] Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.05 equiv), 1-trichloroacetoxycyclohexene (2 equiv), and aldehyde (1 equiv) in dry THF containing MeOH (10 or 20 equiv) at 30 °C for 24 h. [b] Isolated yield. [c] 95% purity. [d] 98% purity. [e] 96% purity.

furnished moderate to high yields under the influence of 5 mol % of $Bu_2Sn(OMe)_2$ at 30 °C for 24 h; with the α,β-unsaturated aldehyde, exclusive 1,2-addition occurred to provide a conjugated (*E*,*E*)-dienone (entry 4). In the reaction with *p*-anisaldehyde and hydrocinnamaldehyde, 10 equiv of MeOH was effective for obtaining satisfactory yields (entries 2 and 5).

We further studied the generality of substrates for the present $Bu_2Sn(OMe)_2$-catalyzed coupling reaction and the

Table 3. $Bu_2Sn(OMe)_2$-Catalyzed Coupling Reaction of Various Alkenyl Trichloroacetates with Benzaldehyde[a]



entry	R^1	R^2	**a** (°C)	**b** (h)	yield (%)[b]
1	$-(CH_2)_3-$		40	24	65[c]
2	$-(CH_2)_4-$		30	24	94[d]
3	$-(CH_2)_5-$		30	24	92
4	Et	Me[e]	30	24	20
5			40	24	89
6	Ph	Me[f]	40	24	<1[g]
7			50	72	83

[a] Unless otherwise noted, the reaction was carried out using dibutyltin dimethoxide (0.02−0.1 equiv), enol trichloroacetate (2 equiv), and benzaldehyde (1 equiv) in dry THF containing MeOH (5−20 equiv) at room temperature for 1−24 h. [b] Isolated yield. [c] 97% purity. [d] 95% purity. [e] The *E*/*Z* ratio was 23/77. [f] The *E*/*Z* ratio was 82/18. [g] The corresponding aldol adduct was obtained in 64% yield.

results using alkenyl trichloroacetates prepared from different types of ketones are listed in Table 3. In addition to cyclic ketone derivatives (entries 1−3), 3-pentanone-derived (*Z*)-enriched alkenyl trichloroacetate, an acyclic substrate also reacted with benzaldehyde in high yield, though higher reaction temperature (40 °C) was necessary (entries 4 and 5). In contrast, in the reaction with (*E*)-enriched alkenyl trichloroacetate of propiophenone under similar reaction conditions no dehydration took place and the desired enone was not obtained at all (entry 6). To our surprise, however, a α-tetralone derivative, a cyclic analogue of the acyclic substrate in entry 6, gave the corresponding enone in 83% yield in the reaction at 50 °C for 72 h (entry 7).

In conclusion, we have developed a new class of coupling reaction of alkenyl trichloroacetates with aldehydes using a catalytic amount of dibutyltin dimethoxide. The reaction can be performed on a substantial scale employing ordinary laboratory equipment and readily available chemicals and can furnish various α,β-unsaturated ketones stereoselectively in high yields up to 94%. The present method is superior to the classical Claisen−Schmidt condensation because of the mildness of the tin catalyst and high product selectivity.[8] Further work is now in progress on application of the catalytic tandem reaction and the reaction mechanism.

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Supporting Information Available: Experimental procedures and spectral data for all products in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) We tried a Claisen−Schmidt condensation between cyclohexanone and benzaldehyde in the presence of 2 mol % of NaOMe in MeOH under similar conditions (rt, 24 h); however, the desired enone **3** was produced in only 2% yield accompanied by the aldol adduct **2** (49%).