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Halo Aldol Reaction of a,b-Unsaturated Ketones and Aldehydes Mediated by Titanium Tetrachloride‡,1

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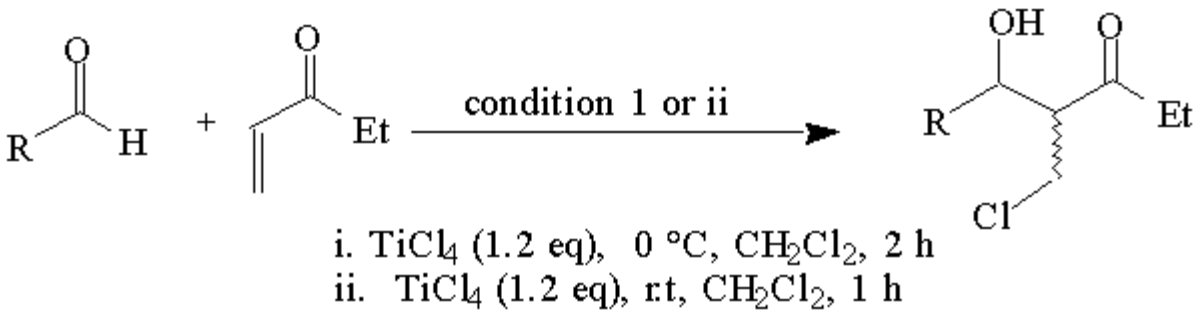
Abstract

A three-component halo aldol reaction has been developed by using titanium tetrachloride as the halogen source as well as the Lewis acid mediator. The dehydration and elimination of hydrogen chloride were inhibited conducting the reaction at 0˚C in dichloromethane or at room temperature within a shortened period. Seven examples were examined to give good to high yields (61 - 92%) and modest stereoselectivity (*syn/anti*: 2.2/1.0 - 8.4/1.0).

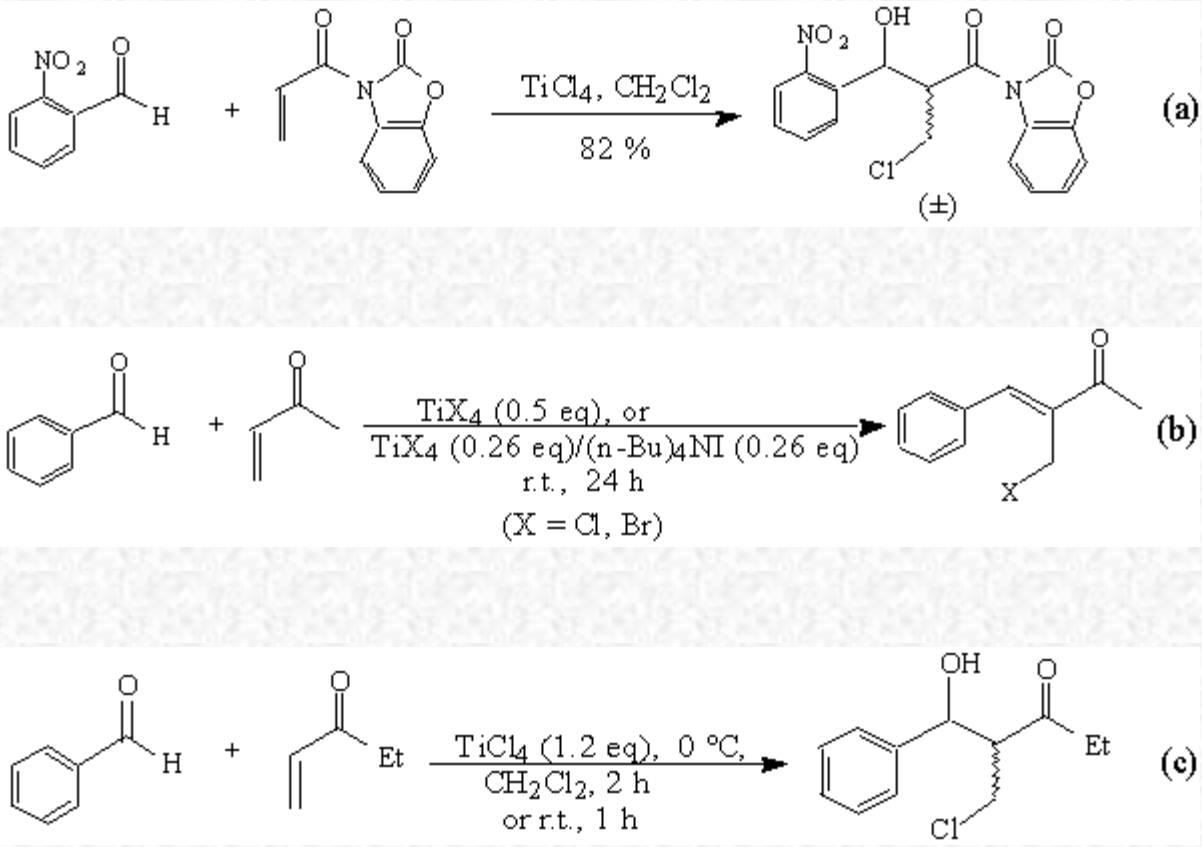


61 - 92%
(7 examples)

Introduction

The formation of C(sp^3)-C(sp^3) bond via aldol reaction represents an important topic in organic chemistry.[2-4] It also acts as the key step of the Baylis-Hillman reaction.[5-6] Recently, we developed the $TiCl_4$-mediated Baylis-Hillman-type reaction without the direct use of a Lewis base,[7a] which was confirmed to proceed through halogeno aldol reaction by using a,b-unsaturated *N*-acyl benzoxalinone as the Michael acceptor (Scheme 1a). When we attempted to extend the reaction scope to the use of a,b-unsaturated ketones, we failed to obtain the anticipated Baylis-Hillman adducts or halo aldol products under the established conditions.[7b] The dehydration products of C=C bond formation were produced dominantly. Only 0.5 equivalent of titanium (IV) halides or 0.25 equivalent of $TiX_4/(n\text{-}Bu)_4NI$[8] were needed to furnish the reaction with high stereoselectivity and yield (Scheme 1b). While the further study of the new C=C bond formation is ongoing in our laboratories, we concurrently made efforts to control the ketone-based system

to produce halo aldol adducts prior to dehydration. In this report, we describe the preliminary results of this method which is represented in Scheme 1c.



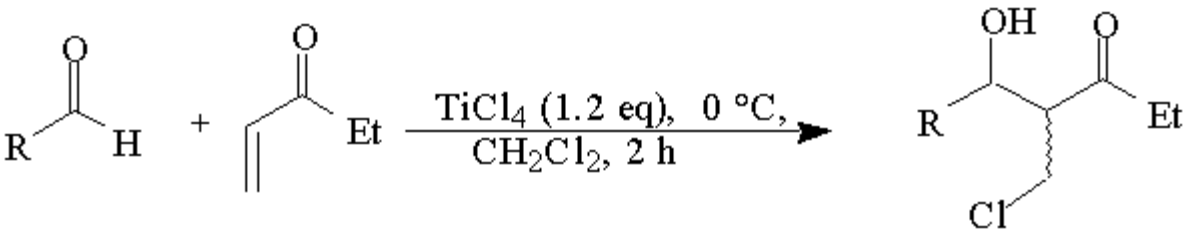
Scheme 1

Results and Discussion

This halo aldol reaction was achieved by using an excess amount of a,b-unsaturated ketone (2.0 eq) and $TiCl_4$ (1.2 eq) and performed at 0˚C in dichloromethane. The three-component starting materials, a,b-unsaturated ketone, aldehyde and $TiCl_4$, were simply mixed together in a convenient vial without the protection of inert gases. The reaction was completed within a shortened period (2 h) as revealed by gas chromatography monitoring. Unlike the C=C formation system, the combination of $TiCl_4/(n\text{-}Bu)_4NI$ was proven to be inefficient for the present ketone-based halo aldol reaction. Indeed, only a trace amount of the desired halo aldol adducts were observed in more than 2 hours. The data in Table 1 shows that good to excellent yields have been obtained for both aromatic and aliphatic aldehyde substrates. The stereoselectivity for aromatic cases were well controlled. However, the individual *syn*/*anti* stereoisomers of all seven cases failed to be separated via flash column chromatography.

The *anti/syn* stereoselectivity was determined by ^1H NMR analysis where the chemical shift of b proton (CHOH) of the *anti* isomer is farther downfield as compared with that of the corresponding *syn* isomer for most cases. The *syn* and *anti* isomers can be distinguished by the coupling constants between a and b protons of aldol adducts.[9] For entry 1 of Table 1, b proton (CHOH) triplet of the *anti* isomer (d 5.11, J = 6.35 Hz) and doublet-doublet of *anti* isomer (d 5.05, J = 2.75, 6.08 Hz) were observed. The stability of these ethyl vinyl ketone-derived products and the resolution of their ^1H NMR spectra made this determination possible. In contrast, the methyl vinyl ketone-derived products can be very easily dehydrated under the current conditions. The *syn* selectivity suggests that this aldol reaction is dynamically controlled. This is similar to a,b-unsaturated aldehyde-based system where the dynamically controlled *syn* stereoselection was proven to be dominant at -78 ˚C in the same solvent in which $TiCl_4/(n\text{-}Bu)_4NI$ combination was employed as the halogen source (I^-).[8c]

Table 1. Results of $TiCl_4$-Mediated Halo Aldol Reaction



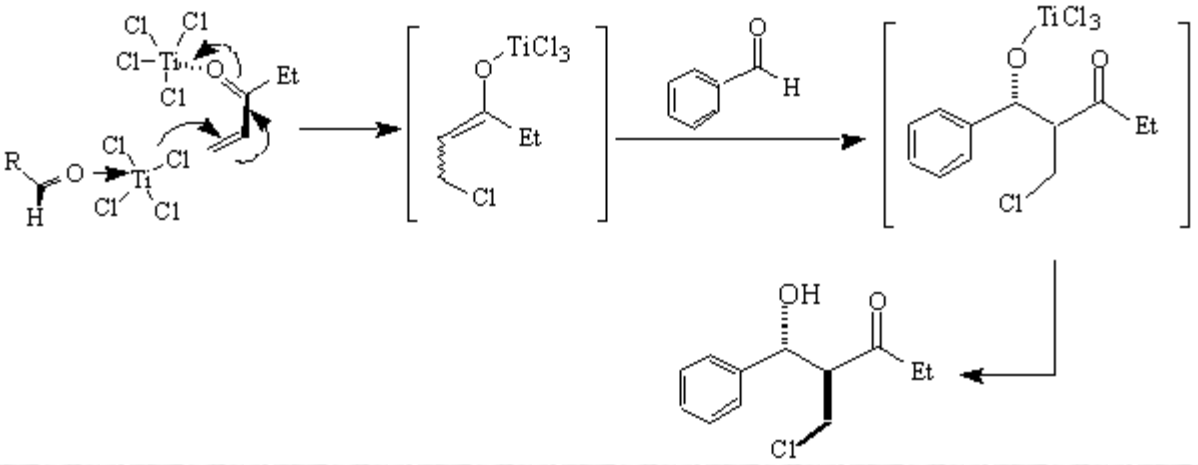
Entry	R	yield[a]	*syn/anti*[b]
1	O_2N–	80	2.9/1.0
2	F–	67	5.4:1.0
3	Cl–	68	8.4:1.0
4	Br–	81	5.1:1.0
5		61	7.2:1.0
6	Me–	87	3.5:1.0
7		79	4.0:1.0
8		92	2.2:1.0

[a] Yield of *syn/anti* mixture. [b] Determined by ^{1}H NMR analysis

The typical procedure is represented by the reaction of entry 1 in Table 1. Into a dry vial was added freshly distilled dichloromethane (1.0 mL), 4-nitrobenzaldehyde (0.151 g, 1.0 mmol) and ethyl vinyl ketone (0.17 mL, 2.0 mmol). The vial with the stirring reaction mixture was cooled to 0 ˚C, and then added titanium tetrachloride (1.2 mL, 1.0 M solution in dichloromethane, 1.2 mmol). The resulting solution in the capped vial was stirred at the same temperature

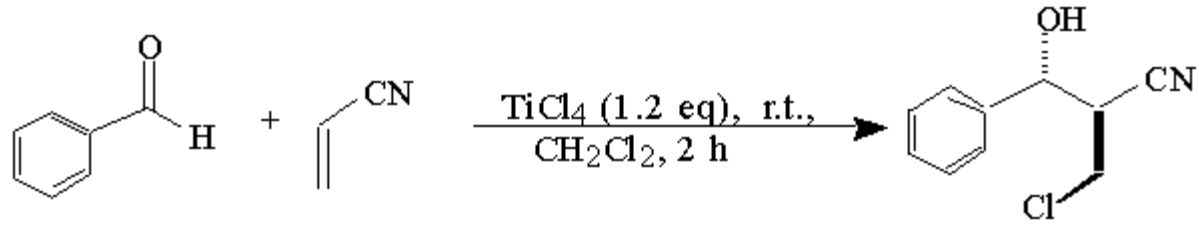
for 2 h without argon protection. The reaction was finally quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (2.0 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/5, v/v) provided **1** (216 mg, 80 %) as colorless oil.

The working hypothesis of this reaction is proposed as shown in Scheme 4.[7,10] The initial step involves the addition of $TiCl_4$ to the a,b-unsaturated ketone to generate the titanium enolate. The formation of this enolate intermediate could be accelerated by the coordination of carbonyl oxygen to the titanium center (C=O--Ti interaction),[11] to further polarize the a,b-conjugate double bond and to free the chlorine anion from $TiCl_4$ prior to the a,b-conjugate addition. The resulting Lewis acidic species can also activate aldehyde for the subsequent aldol reaction by coordinating with aldehyde oxygen.



Scheme 2

The resulting halo aldol adducts can be transformed into Baylis-Hillman adducts by treating with DBU at room temperature. These products can also be converted to dehydration products in prolonged reaction period. Interestingly, the dehydration products are much easier to form even at 0 ˚C when ethyl vinyl ketone was employed as the Michael acceptor. Acrylonitrile can also be used as the starting material by reacting at room temperature to give >70% yield (Scheme 3).



Scheme 3

Conclusion

The vinyl ketone-based halo aldol reaction has been achieved by using an excess amount of ketone and titanium tetrachloride. The reaction can occur to completion at 0˚C in dichloromethane within two hours or at room temperature for 1 hour. The scope of this reaction will be extended to the use of other substrates. Titanium tetrabromide and related chiral metal halides will also be employed as the halogen sources and Lewis acids in the future.

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‡ The preliminary results of this paper were reported at the Gorden Research Conference on Organic Reaction and Processes (paper no. 25), Bristol, RI, July 16 - 21, 2000.

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