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Substoichiometric $TiCl_4$-mediated vicinal difunctionalization of α,β-acetylenic ketones for the synthesis of β-halo Baylis–Hillman olefins

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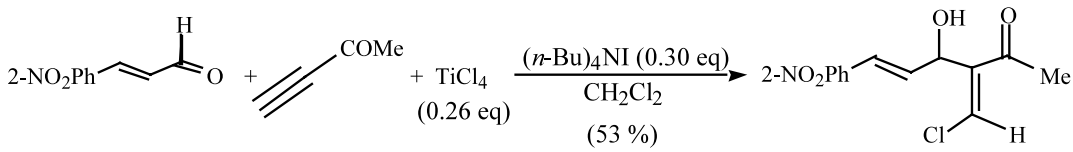
Abstract—A substoichiometric amount of titanium tetrachloride was found to be effective to promote and participate in the tandem α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones in the presence of $(n\text{-Bu})_4NI$. This method provides the concise synthesis of (*E*)-β-halo Baylis–Hillman adducts. No β-iodo products were detected when using this combination of halogen sources. The reaction process involves 1,4-addition of chloro anion released from $TiCl_4$ onto α,β-acetylenic ketones to give $TiCl_3$–allenolate intermediates followed by the titanium Lewis acid-promoted carbonyl addition. Modest to good yields (53–77%) and excellent *E*/*Z* stereoselectivity (>95%) have been obtained for 10 examples.

The study of methodologies for the synthesis of multifunctionalized alkenes in stereoselective fashions has been an important goal in organic chemistry.[1–4] Among these alkenes, the Baylis–Hillman adducts are particularly useful for serving as chemically and biologically important precursors.[5] Recently, we and others have developed several methods for the synthesis of β-alkyl and β,β-dialkyl α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates which cannot be normally generated under the Baylis–Hillman conditions.[6–8] However, so far little work has been reported for the synthesis of β-halo Baylis–Hillman adducts. We thus developed the concise α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones using a slightly excess amount of titanium tetrachloride as the promoter and as chlorine sources for the synthesis of β-chloro Baylis–Hillman adducts.[9–11] In this letter, we report that when the mixture of $(n\text{-Bu})_4NI$ and $TiCl_4$ was used for this reaction, only a substoichiometric amount of titanium tetrachloride (0.26 equiv.) was necessary to promote and participate in the tandem α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones to give β-chloro Baylis–Hillman ketones. Surprisingly, no β-iodo products were observed when using this combination of halogen sources. This new process is represented in Scheme 1 with results summarized in Table 1.

The reaction was carried out by simply mixing aldehyde, α,β-acetylenic ketone, $TiCl_4$ and $(n\text{-Bu})_4NI$ in dichloromethane solution in a capped vial of appropriate size with no need to protect it using either argon or nitrogen gases. The reaction goes to completion in a period of about 2 h at room temperature as indicated by TLC or ^1H NMR analysis. Modest to good yields were obtained for 10 examples which we examined. The products were predominantly produced as *E* configura-



(no iodo product was found)

Scheme 1.

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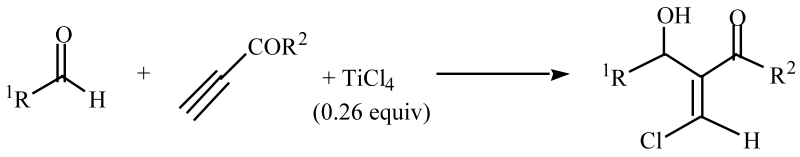
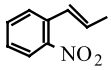
Table 1. Results of the tandem *cis* Cl–C/C–C bond formation[12]



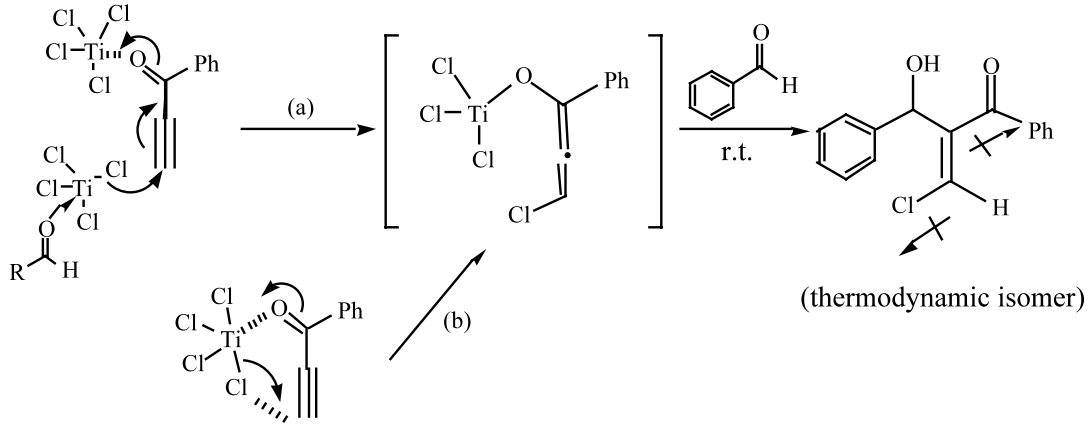
entry	R^1	R^2	*E*/*Z*[a] selectivity (%)	yield (%)[b]
1[c]	*p*-NO_2Ph	Me	>95	74
2	Ph	Me	>95	65
3		Me	>95	53
4[c]	*p*-CF_3Ph	Me	>95	66
5	*p*-CH_3Ph	Me	>95	71
6	*p*-F-Ph	Me	>95	64
7[c]	*p*-NO_2Ph	Pr	>95	77
8	*n*-C_9H_{19}	Ph	>95	60
9		Ph	>95	76
10	*n*-C_5H_{11}	Me	>95	76

[a] > 95% means only one isomer was observed by crude ^{1}H-NMR determination. [b] Purified yields after column chromatography. [c] m.p. of the solid products: 114-116°C for **1**, 68-70°C for **4**, 86-88°C for **7**.

tion for all cases as revealed by ^{1}H NMR analyses of the crude products. The absolute *E* configuration was confirmed by comparing with a known sample which was unambiguously determined by ^{1}H NMR NOE experiments. Five percent of NOE was observed between the signals of vinyl proton and methyl protons of the product.[9]

The careful analysis of the data showed in Table 1 tells that this reaction can be carried out for both aromatic and nonaromatic α,β-acetylenic ketones as the conjugate addition acceptors. Meanwhile, both aromatic and aliphatic aldehydes can be employed as the electrophilic acceptors to react with a substoichiometric amount of titanium tetrachloride. For aromatic aldehydes, substitutions on aromatic rings give no obvious effect on reaction efficiencies in both yield and stereoselectivity. Interestingly, electron deficient aromatic aldehydes did not show a faster rate under this new system.

Similar to the previous system, an excess of α,β-acetylenic ketone (1.4 equiv.) was necessary for this reaction. In addition, at least 0.3 equiv. of $(n\text{-Bu})_4$NI was required for complete conversion of aldehydes. Furthermore, 0.35 equiv. of $TiCl_4$ is needed for the complete consumption of aliphatic aldehydes (entries 8 and 10 of Table 1). It should be pointed out that the use of the $(n\text{-Bu})_4$NI/$TiCl_4$ combination for similar synthesis was pioneered by Kishi, Oshima and co-workers.[13] In the known processes, β-iodo Baylis–Hillman adducts were predominantly produced. However, under the current system, only β-chloro Baylis–Hillman adducts were observed for all cases with no β-iodo Baylis–Hillman adduct detected at all.



Scheme 2.

The mechanistic explanation proposed by Kishi and Taniguchi can be directly adopted here to understand the resulting high Z/E-stereoselectivity.[13] The exclusive Z-stereoselectivity of β-iodo Baylis–Hillman ketones was achieved at −78°C in the known systems, while the high E-stereoselectivity was observed at 0°C. It was suggested the Z-stereoisomer is kinetically controlled product, while the E-stereoisomer is thermodynamically controlled. In the present system, the exclusive E-stereoselectivity was observed for all cases we studied. It suggests that the thermodynamic effect played a key rule in determining the geometric selectivity of the products. Z-β-Chloro Baylis–Hillman ketones are more stable due to the dipole–dipole interaction of the carbonyl substituent and polar C–Cl bond (Scheme 2). So far, no study has been conducted to see if the vinylic organotitanium intermediates[14] can coexist with titanium alleneoates under the new system.

The working hypothesis of this process is represented in Scheme 2.[9] The initial reaction step involves the addition of $TiCl_4$ to the α,β-acetylenic ketone to generate the $TiCl_3$–allenoate. The formation of this intermediate is accelerated by the coordination of carbonyl oxygen to the Lewis acidic titanium center (C=O–Ti interaction).[15] Both (a) and (b) pathways are possible for the formation of $TiCl_3$–allenoate intermediate. The second step proceeds through the nucleophilic attack of the allenoate intermediate to the aldehyde. The later C–C bond forming step is also activated by the coordination of aldehyde oxygen onto the Lewis acidic species.

In summary, a new system of the tandem α-hydroxyalkylation/β-chlorination of α,β-acetylenic ketones was developed for the synthesis of (*E*)-β-chloro Baylis–Hillman ketones. The new protocol utilizes a substoichiometric amount of $TiCl_4$ as the chlorine anion source and as the Lewis acid promoter. The reaction can be easily performed at room temperature without the need for inert atmosphere protection.

Acknowledgements

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12. Typical procedure: Into a clean dry vial was loaded benzaldehyde (0.1 mL, 1.0 mmol), 3-butyn-2-one (95.0 mg, 1.40 mmol), $(n\text{-Bu})_4NI$ (111 mg, 0.30 mmol) and freshly distilled dichloromethane (1.0 mL). A solution of $TiCl_4$ in dichloromethane (1.0 M, 0.26 mL, 0.26 mmol) was then added into the resulting solution dropwise via syringe. The capped vial was immersed in a room temperature bath and was stirred for 2 h at this temperature without the use of an inert gas. TLC or ^1H NMR determination were used to monitor the reaction which was quenched by the dropwise addition of aqueous $NaHCO_3$ solution (satd, 2 mL). After the CH_2Cl_2 was distilled off, the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed sequentially with water and brine, dried over anhydrous magnesium sulfate and concentrated. Purification by flash chromatography (EtOAc/hexane, 1/5, v/v) provided product **1** (136 mg, 65% yield) as colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.45 (m, 5H), 5.95 (d, $J=11.3$, 1H), 4.44 (d, $J=11.3$, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.2; 143.2, 141.4, 135.6, 128.4, 127.4, 125.1, 70.7, 27.0; IR (THF) 3474, 1666 cm^{-1}; HRMS (FAB) m/z (M+Na) found 233.0340, calcd for $C_{11}H_{11}ClO_2Na$ 233.0345.

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