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Convenient and efficient stereoselective synthesis of (2*Z*)-2-(chloromethyl)alk-2-enoates using iron(III) or indium(III) chloride ☆

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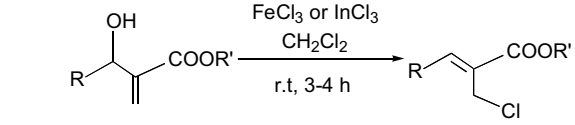
Abstract—The stereoselective synthesis of (2*Z*)-2-(chloromethyl)alk-2-enoates has been achieved efficiently and in high yields and in short reaction times from Baylis–Hillman adducts, 3-hydroxy-2-methylene-alkanoates, by treatment with $FeCl_3$ or $InCl_3$ at room temperature.

Baylis–Hillman adducts, 3-hydroxy-2-methylene-alkanoates, have recently been utilized[1] as important precursors for stereoselective synthesis of different multifunctional molecules. These adducts can be converted into (2*Z*)-2-(halomethyl)alk-2-enoates, which are employed for the synthesis of various naturally occurring bioactive compounds and their analogues such as α-methylene-γ-butyrolactones,[2a] α-alkylidene-β-lactams,[2b] and flavanoids.[2c] This conversion has been carried out in a single step using hydrogen halides together with strong acids ($HBr–H_2SO_4$, $HI–H_3PO_4$),[2a,3a–c] organic acid halides (oxalyl chloride, MsCl)[3d,e] and other reagents including the HCA–PPh_3 complex[3c] and NCS/NBS-Me_2S.[3f–h] However, most of the reported methods suffer from certain drawbacks, which include the use of concentrated acids, long reaction times, incompatibility with other functional groups and a requirement for complex experimental procedures. Here we describe a simple and efficient process for the one-step conversion of Baylis–Hillman adducts, **1** into the corresponding allyl chlorides, **2** using $FeCl_3$ or $InCl_3$. 3-Hydroxy-2-methylidenoalk-2-enoates **1** were treated with $FeCl_3$ or $InCl_3$ in CH_2Cl_2 at room temperature to afford (2*Z*)-2-(chloromethyl)alk-2-enoates **2** in high yields (Table 1). $FeCl_3$ (reaction time: 3 h) showed somewhat better activity than $InCl_3$ (reaction time: 3.5–4 h). However, the work-up procedure with the latter was easier.[4] The products were characterized by their spectral (^1H NMR and MS) data.[5] The ^1H NMR spectra of the crude products showed the formation of the (2*E*)-isomers of **2** in very small amounts (<5%). With $InCl_3$ the yields of the (2*E*)-isomers were less than with $FeCl_3$.



R = alkyl or aryl; R' =alkyl — **1**

71-88% — **2**

The reaction using either $FeCl_3$ or $InCl_3$ was found to be equally applicable to both 3-aryl or 3-alkyl-3-hydroxy-2-methylidenoalkanoates **1**. However, the yields of the products from **1** (R = alkyl) were somewhat lower. The present reaction conditions tolerate several functionalities such as halogen, nitro and ether groups. The presence of electron-donating or electron-withdrawing groups in the aromatic ring did not affect the reaction. Increasing the solvent polarity led to decreased yields of the allyl chlorides. Thus, the reaction of methyl 3-phenyl-3-hydroxy-2-methylidenopropionate (Table 1, entry a) carried out in CH_2Cl_2 using $FeCl_3$ afforded the corresponding allyl chloride in a yield of 88% but when conducted in CH_3CN, the yield was only 72%; CH_2Cl_2 was therefore preferred as a solvent for the present conversion.

Keywords: (2*Z*)-2-(Chloromethyl)alk-2-enoates; Baylis–Hillman adducts; 3-Hydroxy-2-methylene-alkanoates; $FeCl_3$; $InCl_3$.

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Table 1. Synthesis of (2*Z*)-2-(chloromethyl)alk-2-enoates **2**[a]

Entry	R	R′	Time (h)		Isolated yield (%)	
			With $FeCl_3$	With $InCl_3$	With $FeCl_3$	With $InCl_3$
a	C_6H_5	Me	3	3	88	86
b	4-$O_2NC_6H_4$	Me	3	3.5	80	77
c	2-$O_2NC_6H_4$	Me	3	3.5	78	75
d	4-$MeOC_6H_4$	Me	3	3	86	86
e	4-MeC_6H_4	Me	3	3	85	84
f	4-ClC_6H_4	Me	3	3.5	84	83
g	2-ClC_6H_4	Me	3	3.5	82	80
h	$CH_3(CH_2)_7CH_2$	Me	3	4	75	72
i	$PhCH_2CH_2$	Me	3	4	76	71
j	α-Naphthyl	Me	3	3.5	78	76
k	4-ClC_6H_4	Et	3	3	80	77
l	C_6H_5	Et	3	3	82	76
m	4-$MeOC_6H_4$	Et	3	3	78	73

[a] The structures of all the products were established from their spectral (^1H NMR and MS) data.

In conclusion, we have developed a simple and efficient one-pot synthesis of (2*Z*)-2-(chloromethyl)alk-2-enoates in high yields using the readily available reagents, $FeCl_3$ and $InCl_3$ in CH_2Cl_2 at room temperature. The reaction conditions are mild and compatible with several functional groups. The method is highly stereoselective. We feel the present procedure will find important synthetic applications.

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4. (a) Reaction with $FeCl_3$: To a solution of 3-hydroxy-2-methylidenoalkanoates **1** (1 mmol) in dry CH_2Cl_2 (10 mL) anhydrous $FeCl_3$ (0.35 equiv) was added. The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was extracted with EtOAc (3×10 mL). The extract was concentrated and subjected to column chromatography over silica gel using hexane–EtOAc (4:1) as eluent to obtain the (2*Z*)-2-(chloromethyl)alk-2-enoates **2**. (b) Reaction with $InCl_3$: To a solution of 3-hydroxy-2-methylidenoalkanoates **1** (1 mmol) in dry CH_2Cl_2 (10 mL), $InCl_3$ (0.35 equiv) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion the solution was decanted, concentrated and subjected to column chromatography over silica gel using hexane–EtOAc (4:1) as eluent to yield the (2*Z*)-2-(chloromethyl)alk-2-enoates **2**.
5. The ^1H NMR and MS data for the new products are given below. **2d**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.77 (1H, s), 7.45 (2H, d, $J = 8.0$ Hz), 6.84 (2H, d, $J = 8.0$ Hz), 4.20 (2H, s), 3.84 (3H, s), 3.79 (3H, s); EIMS: m/z 240, 242 (M^+), 205 (M^+-Cl) **2g**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.84 (1H, s), 7.63–7.34 (2H, m), 7.40 (1H, t, $J = 8.0$ Hz), 7.22 (1H, t, $J = 8.0$ Hz), 4.23 (2H, s), 3.84 (3H, s); EIMS: m/z 211, 209 (M^+-Cl), 155, 149, 127, 115. **2h**: ^1H NMR ($CDCl_3$, 200 MHz): δ 6.95 (1H, t, $J = 7.0$ Hz), 4.28 (2H, s), 3.82 (3H, s), 2.35–2.28 (2H, m), 1.44–1.23 (14H, m), 0.98 (3H, t, $J = 7.0$ Hz); EIMS: m/z 227, 225 (M^+-Cl), 193, 165, 149, 135, 109. **2i**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.20–7.02 (5H, m), 6.82 (1H, t, $J = 7.0$ Hz), 3.78 (2H, s), 3.72 (3H, s), 2.98 (2H, t, $J = 7.0$ Hz), 2.58–2.42 (2H, m); EIMS: m/z 202 (M^+-HCl), 143, 128, 115. **2j**: ^1H NMR ($CDCl_3$, 200 MHz): δ 8.32 (1H, s), 7.92–7.38 (7H, m), 4.26 (2H, s), 3.88 (3H, s); EIMS: m/z 262, 260 (M^+), 224, 165, 85. **2m**: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.78 (1H, s), 7.44 (2H, d, $J = 8.0$ Hz), 6.82 (2H, d, $J = 8.0$ Hz), 4.18 (2H, s), 3.88 (3H, s), 3.58 (2H, q, $J = 7.0$ Hz), 1.26 (3H, t, $J = 7.0$ Hz); EIMS: m/z 254, 256 (M^+), 219.