Samarium Metal Promoted Facile C-Acetylation of Baylis–Hillman Adducts in the Presence of Iron(III) Chloride and Iodine

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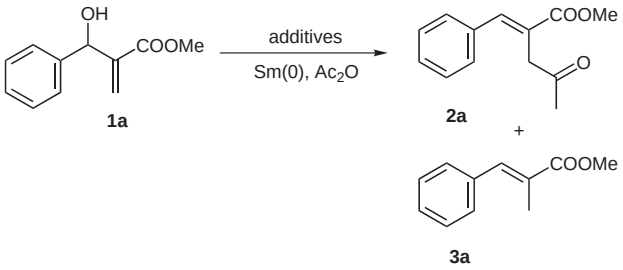
Abstract: A novel and efficient strategy for the C-acetylation of Baylis–Hillman adducts has been described. Promoted by Sm(0)/Ac_2O/$FeCl_3$/I_2, the present method allows for the efficient conversion of Morita–Baylis–Hillman adducts to their corresponding 2-alkylidene-4-oxoalkanoate derivatives and reduction products.

Key words: Baylis–Hillman adduct, metallic samarium, C-acetylation, stereoselective

The Morita–Baylis–Hillman (MBH) reaction has become one of the powerful carbon–carbon bond-forming methods in organic synthesis.[1] The MBH reaction provides molecules with hydroxy, alkenyl, and electron-withdrawing groups in close proximity, which makes it valuable for further chemical transformations.[2] Furthermore, the reaction has also been successfully employed in the syntheses of biologically active molecules and natural products.[3] Among these transformations, using their corresponding acetates as substrates other than the original MBH adducts is more popular since direct transformation of the hydroxyl group is usually difficult. As a result, the direct use of Baylis–Hillman alcohols in organic synthesis without O-acetylation continues to be a challenge.

Due to the synthetic importance of γ-ketoesters and 1,4-diketones, much effort has been put towards the synthesis of such compounds. As reported previously, using readily available MBH adducts as substrates provide a new pathway.[4] Recently, Kim described a new synthesis of 2-alkylidene-4-oxoalkanoate from Baylis–Hillman acetates.[5] However, this synthetic method suffers from the complicated operation which included a S_N2' conversion followed by Nef reaction,[6] thus posing a barrier to their further applications. Therefore, development of a more efficient and straightforward method is highly desirable.

The direct use of metallic samarium as a reducing agent in organic synthesis has attracted much attention in the past several years.[7] This is due to the fact that metallic samarium is stable in air and has strong reducing power (Sm^{3+}/Sm = –2.41 V). Moreover, it is also cheap and easy to handle. Recently, we have reported the acylation of alcohols with acid chlorides as well as the reduction of MBH adducts promoted by metallic samarium.[8] As a continuation of our interest in Baylis–Hillman chemistry,[9] herein we wish to report a novel and efficient strategy for the stereoselective C-acetylation of MBH adducts promoted by metallic samarium. To the best of our knowledge, this is the first example for the direct C-acylation of MBH adducts.



Scheme 1

Our initial experiments were carried out by using MBH adduct **1a** as a model substrate (Scheme 1 and Table 1). First, we investigated the direct transformation of compound **1a** with metallic samarium and acetic anhydride in the absence of any additives. At room temperature, no reaction occurred when substrate **1a** was mixed with Sm(0) and Ac_2O in THF. At elevated temperature, the formation of a small amount of O-acetylation product was noted (Table 1, entry 1). Addition of 4% of molecular iodine resulted in the formation of a small amount of C-acetylation product (11%) **2a** and a reduction product **3a** (12%, Table 1, entry 2).[10]

We also tried adding other amounts of iodine, but most reactions suffered from low conversion. On the other hand, excessive iodine resulted in very complex mixtures (Table 1, entry 3). Notably, addition of $FeCl_3$ to this system brought about great improvement. In the presence of 5 mol% of $FeCl_3$, the reaction conversion increased dramatically to 100% and the corresponding C-acetylation product **2a** and reduction product **3a** were afforded in 61% and 27% yields, respectively (Table 1, entry 5). Subsequent experiments showed that 5 mol% amount of $FeCl_3$ appeared to be the best choice (entries 5–7). In spite of the important role played by $FeCl_3$, the use of iodine is also indispensable (Table 1, entry 4). A series of experiments were carried out to determine the optimal dosage of iodine and 4 mol% was found to give the best results (Table 1, entry 5). Decreasing amount of iodine led to low conversion ratios, while the excessive amount resulted in

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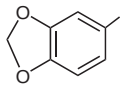
Table 1 Optimization on the C-Acetylation of Baylis–Hillman Adducts **1a** Promoted by Metallic Samarium[a]

Entry	Additive (%)	Time (h)	Conversion (%)	Yield (%)[b]	
				2a	**3a**
1	No additive	48	–[c]		
2	I_2 (4)	24	30	11	12
3	I_2 (50)	10	–[d]		
4	$FeCl_3$ (5)	24	50	20	26
5	I_2 (4), $FeCl_3$ (5)	10	100	61	27
6	I_2 (4), $FeCl_3$ (10)	8	100	57	33
7	I_2 (4), $FeCl_3$ (15)	8	100	50	42
8	I_2 (1), $FeCl_3$ (5)	24	54	27	24
9	I_2 (3), $FeCl_3$ (5)	10	100	54	35
10	I_2 (5), $FeCl_3$ (5)	10	100	41	50

[a] All reactions were carried out with samarium powder (6 equiv) and Ac_2O in THF (15 mL) under reflux.
[b] Isolated yields.
[c] Only a small amount of O-acetylation product was obtained.
[d] A very complex mixture was formed.

Table 2 Stereoselective C-Acetylation of Baylis–Hillman Adducts Promoted by Sm(0)/Ac_2O System[a]

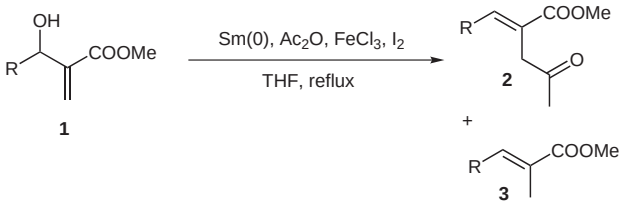
Entry	R	Time (h)	Yield (%)[b]	
			2	**3**
1	Ph	10	61	27
2	4-MeC_6H_4	22	63	28
3	4-$MeOC_6H_4$	24	65	23
4	3-$MeOC_6H_4$	8	60	31
5	4-*t*-BuC_6H_4	14	69	18
6		10	56	30
7	2-ClC_6H_4	6	50	47
8	4-ClC_6H_4	12	40	49
9	4-BrC_6H_4	18	57	33
10		40	30	28

[a] Unless otherwise noted, all reactions proceeded with MBH adduct **1** (1 mmol), Sm powder (6 mmol) and Ac_2O (6 mmol) in the presence of $FeCl_3$ (5 mol%) and I_2 (4 mol%) in THF (15 mL) under reflux.
[b] Isolated yields.

poorer selectivity (Table 1, entry 8–10). In addition, the present transformation was highly *E*-stereoselective and no *Z*-isomer was observed.[11]

With the Sm(0)/Ac_2O/$FeCl_3$/I_2 system optimized, we then turned our attention to other reaction substrates (Scheme 2). Various MBH adducts were examined under the optimal conditions and the results were summarized in Table 2. First, a series of electron-rich MBH adducts were applied to the above conversion and excellent selectivities were observed in all cases (Table 2, entry 2–5). As can be seen, the C-acetylation products were obtained as major products (60–69% yield) even though long reaction time was needed. On the other hand, the presence of electron-withdrawing group shortened the reaction time but the yields of desired products **2** decreased to some extent and more reduction products **3** were isolated. Notably, the present methodology showed excellent *E*-stereoselectivity and no *Z*-isomer was detected.

As to the mechanism, an acyl anion intermediate formed in situ by Sm and Ac_2O mixture may be involved in this



Scheme 2

conversion produced.[12] Furthermore, the presence of $FeCl_3$ was also considered to facilitate the elimination of the hydroxyl group in MBH adducts.[13] Further studies on reaction mechanism are still under way in our laboratory.

In summary, we have provided a facile and novel methodology for the synthesis of γ-ketoesters from MBH adducts.[14] This new protocol allows for the direct C-acetylation of MBH adducts. We believe that this procedure will be an excellent alternative to existing literature methods.

Acknowledgment

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(10) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis.

(11) The stereochemistry of product **2** was all *E*, as was that of product **3**.[9c] The ^{1}H NMR spectrum of **2** was in good agreement with the reported data.[5]

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(14) **General Procedure for C-Acetylation of Baylis–Hillman Adducts**

To a stirred solution of 6 mmol Sm powder (0.9 g) and 6 mmol Ac_2O (0.6 g) in 15 mL THF, 5 mol% $FeCl_3$, 4 mol% I_2 and 1 mmol Baylis–Hillman adduct **1** were added. The resulting mixture was then allowed to reflux in the air. Until completion of the reaction, 3 mL HCl (1 M) was then added to quench the reaction and the mixture was successively exacted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with 15 mL sat. brine, dried over anhyd Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give the crude products, which were purified by column chromatography using EtOAc and PE (1:10) as eluent. Selected spectroscopic data for compounds **2** follow.

Compound **2a** (R = Ph): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.37–7.27 (m, 5 H), 3.80 (s, 3 H), 3.62 (s, 2 H), 2.25 (s, 3 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 206.1, 167.8, 142.2, 135.0, 128.9, 128.7, 128.6, 126.6, 52.2, 42.5, 30.1. IR (film): 3058, 2952, 2847, 1703, 1639, 1575, 1492, 1437, 1359, 1264, 1098, 764, 700 cm^{-1}.

Compound **2b** (R = 3-MeOC_6H_4): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1 H), 7.30–6.84 (m, 4 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.63 (s, 2 H), 2.26 (s, 3 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 206.6, 168.4, 160.1, 142.8, 136.9, 130.2, 127.4, 121.6, 115.2, 114.5, 55.8, 52.8, 43.2, 30.7. IR (film): 3001, 2953, 2850, 1706, 1637, 1600, 1580, 1488, 1433, 1359, 1247, 1098, 790, 690 cm^{-1}.