Metallic Samarium Promoted Self-Coupling of Baylis–Hillman Adducts to Functionalized 1,5-Hexadienes in the Presence of the I_2/$ClCO_2Et$/$BiCl_3$ System

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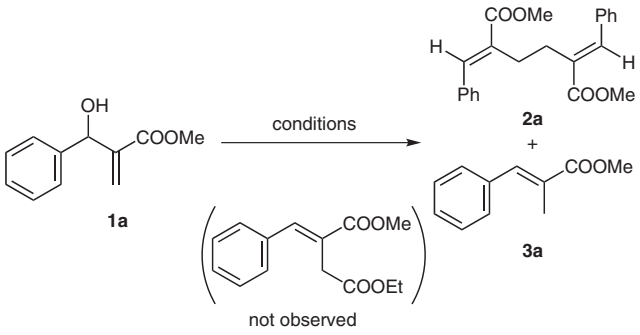
Abstract: A facile strategy for the self-coupling of Baylis–Hillman adducts to functionalized 1,5-hexadienes has been described. Promoted by the Sm/I_2/$ClCO_2Et$/$BiCl_3$ system, the present method allows for the conversion of MBH adducts to their corresponding 1,5-hexadienes.

Keywords: Baylis–Hillman adduct, metallic samarium, self-coupling, functionalized 1,5-hexadiene, Lewis acid

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 possessing hydroxy, alkenyl, and electron-withdrawing groups in close proximity, which makes it valuable in a number of stereoselective transformation processes.[2] Furthermore, many strategies/methodologies have been successfully employed in the syntheses of biologically active molecules and natural products.[3] Among these transformations, however, using their acetates as substrates other than the Baylis–Hillman adducts themselves predominates since the direct elimination of 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.

In the past several years, we paid much attention to the application of Baylis–Hillman adducts. For instance, we have developed a novel strategy to synthesize structurally unique γ-keto esters via the stereoselective C-acetylation of Baylis–Hillman adducts.[4] In addition, we have just reported an efficient preparation of symmetric bisallylic ethers via the dimerization of MBH adduct.[5] On the other hand, the coupling of Baylis–Hillman adducts to the functionalized 1,5-hexadienes remains a challenge although SmI_2 has proved to be a good choice for such a transformation.[6] However, the application of samarium diiodide is limited since it is expensive and sensitive to air and water. Therefore, the development of more facile and straightforward method is highly desirable. Recently, 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 a strong reducing power (Sm^{3+}/Sm = –2.41 V). Moreover, it is also cheap and easy to handle. Herein we wish to report a facile strategy for the self-coupling of Baylis–Hillman adducts promoted by metallic samarium.



Scheme 1

Our initial experiment was carried out by using Baylis–Hillman adduct **1a** as a model substrate (Scheme 1). Firstly, we investigated the direct transformation of Baylis–Hillman adducts with metallic samarium and $ClCO_2Et$ in the absence of any additives. At room temperature, no reaction occurred when substrate **1a** was mixed with Sm/$ClCO_2Et$ in THF. Fortunately, 23% yield of self-coupling product **2a** was isolated together with large amount of reduction product **3a** when the reaction was carried out under refluxing temperature (Table 1, entry 1). Subsequently, a series of experimental parameters including additive loading were changed to optimize the reaction conditions. As usual additives, molecular iodine was then added to activate the metallic samarium powder. It was noteworthy that the presence of iodine was crucial to the self-coupling of starting material **1a** (Table 1, entry 3). We tried different amount of iodine added and found that excessive iodine only led to low yield of product **2a** (entry 4). To our delight, applying $FeCl_3$ to this system brought great improvement. As we can see from Table 1, in the presence of 5 mol% $FeCl_3$, the self-coupling product **2a** and the reduction product **3a** were afforded in 53% and 31% yields, respectively (entry 5). Notably, the reaction time was greatly shortened to 3 hours from 20 hours. Several other Lewis acids were also screened to optimize the reaction conditions, and the experimental data showed that 5 mol% amount of $BiCl_3$ appeared to be the best

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Table 1 Optimization on the Self-Coupling of Baylis–Hillman Adducts Promoted by Metallic Samarium[a]

Entry	$ClCO_2Et$ (equiv)	I_2 (mol%)	Lewis acid	Time (h)	Yield (%)[c]	
					2a	**3a**
1	1	–	–	20	23	52
2	2	–	–	20	28	50
3	2	5	–	20	50	36
4	2	20	–	20	32	42
5	2	5	$FeCl_3$[b]	3	53	31
6	2	5	$RuCl_3$[b]	3	47	16
7	2	5	$AlCl_3$[b]	3	43	31
8	2	5	$ZnCl_2$[b]	3	31	36
9	2	5	$BiCl_3$[b]	3	61	23
10	2	5	$BiCl_3$ (15 mol%)	3	42	31
11	2	–	$BiCl_3$[b]	3	20	37
12	–	5	$BiCl_3$[b]	3	0	56

[a] All attempts were carried out with 1.5 equiv samarium powder and in 15 mL THF under reflux.
[b] In such cases, 5 mol% Lewis acid is added.
[c] Isolated yields.

choice (entry 6–10). In addition, lower yield of **2a** was also observed without molecular iodine (entry 11). In spite of the important role played by Lewis acid, the employment of $ClCO_2Et$ was also important. During our investigation, no direct C-acylation product from $ClCO_2Et$ could be detected (Scheme 1). The self-coupling of Baylis–Hillman adduct did not occur when the corresponding reaction was conducted in the absence of $ClCO_2Et$ (entry 12). In addition, the present transformation also manifested excellent *E*-stereoselectivity and no *Z*-isomer was observed.[8]

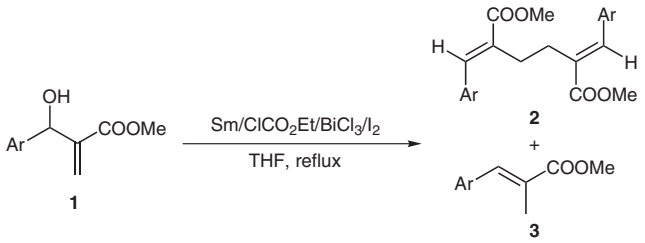
With the $Sm/I_2/ClCO_2Et/BiCl_3$ system optimized, we then turned our attention to the substrate generality (Scheme 2). Various Baylis–Hillman adducts were examined under the optimal conditions, and the results were summarized in Table 2.[9] In all cases, Baylis–Hillman adducts bearing both electron-withdrawing and electron-donating groups on aromatic rings underwent smooth transformation to the corresponding self-coupling product **2** and reduction product **3** (Table 2, entry 2–7). It seemed that the presence of electron-withdrawing group on the aromatic ring was favorable to the formation of product **2** together with higher yields (entry 2, 5, and 6). Furthermore, the yields of desired products **2** decreased to some extent due to the increasing steric hindrance (entry 4).

As to the mechanism, the presence of $BiCl_3$ was considered to facilitate the elimination of the hydroxyl group in

Table 2 Facile Self-Coupling of Baylis–Hillman Adducts Promoted by $Sm/I_2/ClCO_2Et/BiCl_3$ System[a,b]

Entry	Ar	Coupling product	Yield (%)[c]	
			2	**3**
1	Ph	**2a**	61	23
2	4-ClC_6H_4	**2b**	66	24
3	4-MeC_6H_4	**2c**	56	32
4	4-*t*-BuC_6H_4	**2d**	48	30
5	2-BrC_6H_4	**2e**	63	22
6	4-BrC_6H_4	**2f**	65	26
7	3-$MeOC_6H_4$	**2g**	59	27

[a] Unless otherwise noted, all reactions proceeded with 1 mmol Baylis–Hillman adduct **1**, 1.5 mmol Sm powder in the presence of 2 mmol $ClCO_2Et$, 5 mol% $BiCl_3$ and 5 mol% I_2.
[b] All reactions were carried out in 15 mL THF under reflux.
[c] It referred to isolated yields.



Scheme 2

Baylis–Hillman adducts. The employment of $ClCO_2Et$ was also crucial to the present conversion. At present stage, however, we are not quite sure about their exact role. Further studies on reaction mechanism are still under way in our laboratory.

In summary, we provided a facile methodology for the self-coupling of Baylis–Hillman adducts. This new protocol allows for the direct conversion of Baylis–Hillman adducts to the functionalized 1,5-hexadienes. We believe that our present procedure and the functionalized 1,5-hexadiene products will find their application in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) The stereochemistry of products **2** is all *E*, and the ^{1}H NMR spectra and the melting points of **2** were well in coincidence with the reported ones.[6]

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

General Procedure for the Synthesis of 1,5-Hexadiene 2

To a stirred solution of Sm powder (1.5 mmol) and $ClCO_2Et$ (2 mmol) in THF (15 mL), $BiCl_3$ (5 mol%), I_2 (5 mol%), and Baylis–Hillman adduct **1** (1 mmol) 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 EtOAc (2 × 20 mL). The organic phase was washed with sat. brine (15 mL), dried over anhyd Na_2SO_4, filtered. The solvent was removed under reduced pressure to give the crude products, which were purified by column chromatography using EtOAc and PE (1:20) as eluent.

Selected Spectroscopic Data of Product 2

Compound **2d**: white solid, mp 171.8–172.3 °C. IR (KBr): 1705, 1629, 1436 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (s, 2 H), 7.70 (s, 2 H), 7.46–7.39 (m, 8 H), 3.78 (s, 6 H), 2.83 (s, 2 H), 1.33 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): d = 169.1, 151.8, 140.4, 132.7, 131.4, 129.6, 125.5, 52.1, 31.4, 27.0 ppm. MS: *m/z* (%) = 462 (10) [M$^+$], 371 (17), 175 (100). Anal. Calcd for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found C, 77.78; H, 8.19.

Compound **2e**: white solid, mp 168.6–169.0 °C. IR (KBr): 1707, 1560, 1432 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (s, 2 H), 7.60–7.17 (m, 8 H), 3.69 (s, 6 H), 2.58 (s, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 139.9, 136.2, 133.6, 132.8, 130.4, 129.7, 127.3, 124.1, 52.1, 27.0 ppm. MS: *m/z* (%) = 508 (6) [M$^+$], 397 (52), 174 (70), 115 (100). Anal. Calcd for $C_{22}H_{20}Br_2O_4$: C, 51.99; H, 3.97. Found C, 52.08; H, 3.83.