Efficient Synthesis of Bisallylic Ethers from Baylis–Hillman Adducts Promoted by Molecular Iodine

Peichao Zhao, Jian Li, Xueshun Jia*

Department of Chemistry, Shanghai University, Shanghai 200444, P. R. of China
Fax +86(21)66132797; E-mail: xsjia@mail.shu.edu.cn

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Abstract: A straightforward and efficient synthesis of functionalized ethers from Baylis–Hillman (MBH) adducts was disclosed. In the presence of I_2, MBH adducts underwent smooth dehydration to give a series of bisallylic symmetrical ethers in moderate to good yields.

Key words: Baylis–Hillman adduct, iodine, bisallylation, symmetrical, ether

The Morita–Baylis–Hillman (MBH) reaction is 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]

Due to the synthetic importance of these structurally unique bisallylic ethers, much effort has been made towards the syntheses of such compounds.[4] Among such transformations, the use of readily available MBH adducts as substrates provides a new pathway. However, most published methods suffered from the strict conditions such as high pressure or poor yields partly due to the low reactivity of Baylis–Hillman adducts.[5] Therefore, the development of more efficient and practical methods is highly desirable. More recently, we have reported an efficient preparation of asymmetric bisallylic ethers via the dimerization of MBH adducts.[6] We are also interested in the preparation of symmetrical analogues although this still remains to be a challenge. In the past several years, we paid much attention to the application of Baylis–Hillman adducts, and many interesting results were also reported.[7] As a continuation of our interest in Baylis–Hillman chemistry, herein we wish to report a novel strategy for the symmetrical dimerization of Baylis–Hillman adducts promoted by molecular iodine.

Our initial experiments were carried out using Baylis–Hillman adduct **1a** as model substrate (Scheme 1). In a typical procedure, a catalytic amount of iodine (5 mol%) was added to a stirred suspension of 1 mmol substrate **1a** in nitromethane (10 mL) at 80 °C (Table 1, entry 1). In the presence of iodine, the Baylis–Hillman adduct underwent smooth dehydration to give the symmetrical bisallylic ether **2**[8] and its unsymmetrical isomer **3** in 60% yields. Subsequently, a series of experimental parameters including temperature and solvent were changed to optimize the reaction conditions. It was interesting that the amount of iodine added played an important role in this reaction. Notably, the ratio of the bisallylic ether **2** with **3** increased significantly along with the elevated dosage of iodine (entries 1–3). For instance, the ratio of **2**:**3** was up to 3:1 when one equivalent of iodine was used (entry 3). During our investigation, we also found that the dimerization product **2** and its isomer **3** were often obtained as an inseparable mixture. To overcome this problem, we turned our attention to further experimental modifications. To our delight, the symmetrical ether **2** was afforded exclusively when 3 equivalents of iodine were used. In such a case, no unsymmetrical isomer **3** was produced and the expected product **2** could be isolated as pure compound. On the other hand, product conversion was susceptible to temperature changes. At room temperature, the reaction was quite sluggish and the dimerization did not take place. In addition, several other solvents were also screened and nitromethane exhibited its superiority over other solvents. For example, the employment of MeCN led to long reaction times and

Table 1 Optimization on the Selective Dimerization of Baylis–Hillman Adducts Promoted by Molecular Iodine[a]

Entry	I_2 (mol%)	Solvent	Time (h)	Yield of **2** + **3** (%, **2**/**3** ratio)[b,c]
1	5	$MeNO_2$	3	67 (1:3)
2	15	$MeNO_2$	1	70 (1:1)
3	100	$MeNO_2$	0.5	65 (3:1)
4	300	$MeNO_2$	0.5	71 (100:0)
5	5	MeCN	24	8 (1:2)[d]
6	5	THF	24	–[e]
7	5	CH_2Cl_2	24	–[e]

[a] Unless otherwise noted, all attempts were carried out with 1 mmol of **1a** at 80 °C.
[b] Isolated yields.
[c] The ratio was confirmed from ^{1}H NMR spectroscopy.
[d] In such cases, the total conversion was very low even an equivalent amount of iodine was used.
[e] No reaction occurred.

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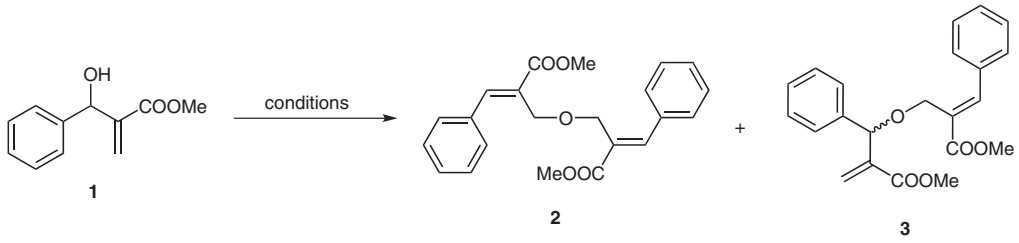
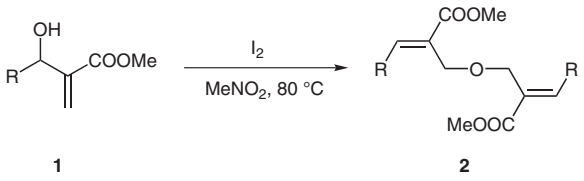


1 2 3

Scheme 1



1 2

Scheme 2

Table 2 Efficient Synthesis of Bisallylic Ether **2** from Baylis–Hillman Adducts Promoted by Iodine[a]

Entry	R	Time (min)	Yield (%)[b,c]
1	Ph	30	71
2	4-MeC_6H_4	15	66
3	4-*t*-BuC_6H_4	10	81
4	4-ClC_6H_4	30	75
5	3-ClC_6H_4	100	52
6	2-ClC_6H_4	50	45
7	4-BrC_6H_4	40	66
8	3-$O_2NC_6H_4$	100	–[d]
9	4-$MeOC_6H_4$	100	–[e]

[a] Unless otherwise noted, all reactions proceeded with Baylis–Hillman adduct **1** (1 mmol), I_2 (3 mmol) at 80 °C in $MeNO_2$ (10 mL).
[b] All new compounds were characterized by ^1H NMR, ^{13}C NMR, elemental analysis, and IR spectroscopy.
[c] Isolated yields.
[d] In such case, only a little amount of allylic iodine derivative was afforded.
[e] Substrate was transformed to unrecognized mixture.

low yields, whereas no reaction occurred when CH_2Cl_2 or THF was used as solvent (entries 5–7).

In addition, the present transformation also manifested excellent *E*-stereoselectivity and no *Z*-isomer was observed.[9]

We then focused our attention to substrate generality using the optimized reaction conditions (Scheme 2). Several Baylis–Hillman adducts were examined under the optimal conditions and the results were summarized in Table 2. In most cases, the reaction proceeded smoothly to give the corresponding bisallylic ethers **2** in moderate to good yields. It was noteworthy that the presence of electron-donating groups seemed to facilitate this dehydration process and shortened the reaction time (Table 2, entries 2 and 3). However, 2-chloro-substituted substrate resulted in a lower yield (45%), which could be contributed to the steric hindrance (entry 6). We also noticed that no dimerization product was formed when a 3-nitro group was present (entry 8). In such case, only a small amount of the corresponding allylic iodide was isolated. Furthermore, methoxy-group-substituted substrate also failed to give the desired bisallylic ether **2** under optimized conditions. Notably, the present methodology showed excellent *E*-stereoselectivity and no *Z*-isomer was detected. To further establish the generality of the present strategy, an analogue of **1** (R = 4-*t*-BuC_6H_4), in which the COOMe group was replaced by a CN group, was prepared and subjected to the same reaction conditions. To our delight, the corresponding dimerization ether was isolated in 78% yield, and the symmetrical ether was also produced as major product in a 5:1 ratio with the unsymmetrical one as the minor product.

In summary, we reported here a facile and novel methodology for the synthesis of symmetric bisallylic ether **2** from Baylis–Hillman adducts.[10] Indeed, the usefulness of this reaction lays in the high degree of functionality present in the products for further transformations. We believed that our current procedure would be an excellent alternative to existing methods. Further applications of the bisallylic ether **2** in organic synthesis are underway in our laboratory.

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

(9) The stereochemistry of product **2** was assigned according to published report.[7d]

(10) **General Procedure for the Synthesis of the Symmetrical Bisallylic Ether**

To a stirred solution of Baylis–Hillman adduct **1** (1 mmol) in $MeNO_2$ (10 mL), I_2 (3 mmol) was added. The resulting mixture was then allowed to react at 80 °C in air. After completion of the reaction, H_2O was added to quench the reaction, and the mixture was successively exacted with Et_2O (3 × 20 mL). The organic phase was washed with sat. $Na_2S_2O_3$ (15 mL), sat. brine (10 mL), 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 petroleum ether as eluent.

Selected Spectroscopy Data of Product 2

Compound **2a** (R = Ph): white solid, mp 96.3–97.4 °C. IR (KBr): 3404, 2948, 1714, 1629, 1244, 1006, 768, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (s, 2 H), 7.63–7.40 (m, 10 H), 4.41 (s, 4 H), 3.87 (s, 6 H) ppm. ^{13}C NMR (125 MH_Z, $CDCl_3$): δ = 168.18, 145.47, 134.83, 130.27, 129.68, 128.78, 128.39, 64.93, 52.40 ppm. MS: *m/z* (%) = 389 [M + Na]$^+$. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.13; H, 6.01. Found: C, 72.29; H, 5.97.

Compound **2d** (R = 4-ClC_6H_4): white solid, mp 123.1–123.8 °C. IR (KBr): 3408, 1711, 1631, 1237, 816 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (s, 2 H), 7.57 (d, 4 H, *J* = 8.5 Hz), 7.41 (t, 4 H, *J* = 8.5 Hz), 4.36 (s, 4 H), 3.87 (s, 6 H). ^{13}C NMR (125 MH_Z, $CDCl_3$): δ = 167.86, 144.21, 133.95, 133.20, 131.61, 129.12, 128.70, 64.85, 52.53. MS: *m/z* (%) = 457 [M + Na]$^+$. Anal. Calcd for $C_{22}H_{20}Cl_2O_5$: C, 60.69; H, 4.59. Found: C, 60.63; H, 4.76.