

The intramolecular Baylis–Hillman reaction: easy preparation of versatile substrates, facile reactions, and synthetic applications†

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We have developed a general and highly efficient method for the preparation of diverse ω -formyl- α,β -unsaturated carbonyl compounds and optimized the conditions for the intramolecular Baylis–Hillman reactions of these compounds to provide various biologically important polycyclic compounds.

More than 500 research papers during the last decade have reported the ever-increasing importance of the Baylis–Hillman reaction in organic synthesis, where efficient formation of the C–C bond between Michael acceptors and carbonyl or imine compounds with diverse functional group compatibility can be realized under mild reaction conditions.¹ Moreover, highly functionalized molecules can be assembled by this reaction, which can be utilized for the construction of complicated molecular frameworks.^{1,2} The study of the intramolecular version³ of this reaction that would lead to versatile cyclization products, however, is still in its infancy partially due to the limited access to these rather unstable substrates, e.g. ω -formyl- α,β -unsaturated carbonyl compounds. Instead of applying the mono Wittig reaction to symmetrical dialdehydes, which not only lowered the reaction yield but also limited the possible substituents within the molecule,³ we devised a new approach to produce ω -formyl- α,β -unsaturated carbonyl compounds with various substituents in decent yields. We optimized the intramolecular Baylis–Hillman reaction conditions of these versatile substrates to give rise to a variety of conjugated cycloalkenones containing an α -carbinol moiety. Further cyclizations of these well-equipped Baylis–Hillman products led to useful polycyclic compounds such as chromones and the 6,8-dioxabicyclo[3.3.1]octane ring.

As delineated in Table 1, our synthetic approach to ω -formyl- α,β -unsaturated carbonyl compounds **3** relied on the $\text{Pb}(\text{OAc})_4$ -promoted oxidative ring cleavage⁴ of cycloalkene-1,2-diols **2** that can be readily obtained by the 1,2-addition of various nucleophiles to α' -acetoxy-substituted conjugated cycloalkenones **1**. Commer-

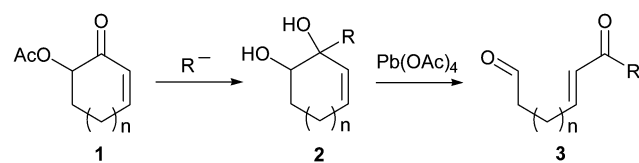


Table 1 An efficient method of preparation of versatile substrates for the intramolecular Baylis–Hillman reaction

Compound	<i>n</i>	R	Yield of 2 ^a (%)	Yield of 3 ^b (%)
a	1	H	81	68 (85)
b	1	Ph	71	70 (98)
c	1	Me	89	89 (99)
d	1	Et	76	62 (83)
e	1	Bu	81	93 (99)
f	2	H	96	97 (99)

^a A mixture of diastereomers. ^b Crude yields are given in parentheses.

† Electronic Supplementary Information (ESI) available: experimental procedures, characterization data, and ¹H NMR spectra. See <http://www.rsc.org/suppdata/cc/b3/b311951c/>

cially available 2-cyclohexene-1-one and 2-cycloheptene-1-one were acetoxyated by $\text{Pb}(\text{OAc})_4$ at the reflux temperature of toluene yielding cycloalkenones **1** in 85% and 97% yield, respectively.⁴ Various nucleophiles including NaBH_4 , PhLi , MeLi , EtMgBr , and $n\text{-BuLi}$ were utilized for the 1,2-addition to cycloalkenones **1**. Cycloalkene-1,2-diols **2** can be obtained directly when more than 2 eq. of nucleophiles are used, or by hydrolysis of the acetate of the initial adduct. A mixture of diastereomers was obtained in these addition reactions. Oxidative ring cleavage of 1,2-diols **2** by $\text{Pb}(\text{OAc})_4$ proceeded efficiently in MeCN to give **3**. This reaction was so fast that it took only ~30 s for 50% conversion and less than 10 min for completion, with the initially formed *Z*-isomer isomerizing to the more stable *E*-isomer. The *Z*-isomer was isolated when the reaction was stopped within 5 min. The crude products were pure enough to be used for the Baylis–Hillman reaction without further purification.

Only a few intramolecular Baylis–Hillman reactions have been reported, most of which suffered from low yields.³ In our initial study this reaction seemed to be impractical for **3a** presumably due to its easy polymerization through the intermolecular Michael reaction. However, we were able to optimize the intramolecular Baylis–Hillman reaction of **3a** after careful studies with several nucleophiles and various solvents and conditions (entries 1–7,

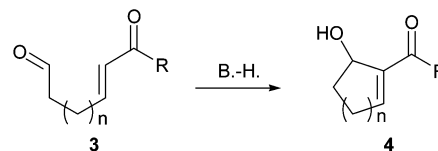


Table 2). A stoichiometric amount of nucleophile was required to induce the intramolecular cyclization to give **4a**, while a catalytic amount of nucleophile produced no cyclization product at all. PPh_3

Table 2 Intramolecular Baylis–Hillman reactions

Entry	3	Nucleophile ^a	Solvent ^b	Conditions	Yield of 4 (%)
1	a	PPh_3	THF	20 °C, 38 h	14
2	a	PPh_3	CH_2Cl_2	20 °C, 29 h	36
3	a	PPh_3	Acetone	20 °C, 24 h	48
4	a	PPh_3	MeCN	20 °C, 72 h	48
5	a	PPh_3	<i>t</i> -BuOH	30 °C, 12 h	98
6	a	DABCO	<i>t</i> -BuOH	30 °C, 18 h	33
7	a	PMe_3	<i>t</i> -BuOH	30 °C, 3 h	— ^c
8	b	PPh_3	MeCN	20 °C, 22 h	99
9	b	PPh_3	EtOAc	70 °C, 2 h	20
10	b	PPh_3	<i>t</i> -BuOH	30 °C, 6 h	78
11	c	PPh_3	MeCN	20 °C, 24 h	83
12	c	PPh_3	<i>t</i> -BuOH	80 °C, 10 h	76
13	c	PMe_3	<i>t</i> -BuOH	30 °C, 22 h	— ^c
14	d	PPh_3	MeCN	20 °C, 43 h	48
15	d	PPh_3	CH_2Cl_2	20 °C, 48 h	36
16	d	PPh_3	<i>t</i> -BuOH	40 °C, 15 h	78
17	e	PPh_3	MeCN	20 °C, 22 h	60
18	e	PPh_3	<i>t</i> -BuOH	30 °C, 25 h	83
19	f	PPh_3	<i>t</i> -BuOH	80 °C, 29 h	73
20	f	PPh_3	MeCN	80 °C, 29 h	53

^a 1.0 equiv of nucleophile was used. ^b 0.1 M solution. ^c decomposition of the starting material was observed.

was found to be superior to DABCO, and only the decomposition of the starting material was noticed when PMe_3 was used. A dramatic solvent effect was observed in these reactions; polar solvents such as *t*-BuOH and MeCN provided high yields of the desired cyclic products, while less polar solvents such as THF, CH_2Cl_2 , acetone and EtOAc gave only marginal yields, in accord with the results of Roush⁵ and Krische⁶ for the vinylogous intramolecular Morita–Baylis–Hillman reaction. Dilution may help the intramolecular reactions, however, it was not critical in the above cases and the reactions were conducted at 0.1 M concentration. Good to excellent yields of **4b–f** were also obtained using this optimized reaction condition. A higher temperature and longer reaction time were required for cyclization to a 6-membered ring.

The general applicability of our present process was demonstrated in the efficient preparation of the required substrates **3g–i** for the intramolecular Baylis–Hillman reaction leading to chromones **5g–i** (Table 3). MOM-protected *o*-bromophenol and *o*-bromothiophenol were lithiated by *t*-BuLi, and the resulting nucleophiles were added to 6-acetoxy-2-cyclohexene-1-one or 7-acetoxy-2-cycloheptene-1-one to give 1,2-diols **2g–i**. The intramolecular Baylis–Hillman reaction of compounds **3g–i**, prepared by the oxidation of **2g–i** by $\text{Pb}(\text{OAc})_4$, proceeded smoothly under the above-optimized conditions (PPh_3 in MeCN at reflux or *t*-BuOH at 30 °C) to produce the cyclic products **4g–i**. Deprotection of the MOM group by 3 M HCl in THF followed by reflux in benzene with catalytic *p*-TsOH induced a further cyclization to provide chromones in decent yields. It is noteworthy that the deprotection of the MOM group was accompanied by $\text{Pb}(\text{OAc})_4$ -promoted oxidation of **2g** to **3g** ($\text{P} = \text{H}$). No direct double cyclization of **3g** to **5g** through the intramolecular conjugate addition of the phenolic OH followed by the aldol reaction was observed under the Baylis–Hillman reaction conditions. In the case of **4i**, deprotection of the MOM group in 3 M HCl triggered a spontaneous cyclization to **5i** at 30 °C.

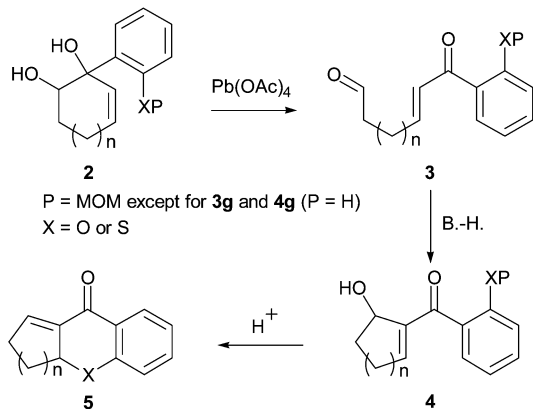
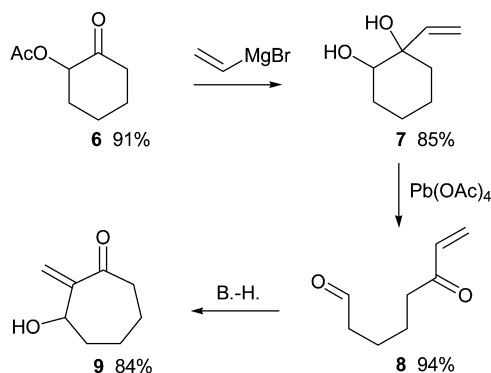


Table 3 Reaction yields of the intermediate compounds in chromone synthesis

Comp.	<i>n</i>	X	Yield (%)			
			2	3	4	5
g	1	O	58	98 ^a	91 ^{a,b}	93 ^c
h	2	O	84	84	75 ^d	85 ^e /71 ^c
i	2	S	87	75	65 ^b	81 ^e

^a A phenol product was obtained in which the MOM group was deprotected.
^b *t*-BuOH at 30 °C. ^c *p*-TsOH in benzene at reflux. ^d MeCN at reflux. ^e 3 M HCl in THF at 30 °C.



Scheme 1 A ring expansion protocol.

The preparation of the above ω -formyl- α,β -unsaturated carbonyl compounds and the intramolecular Baylis–Hillman reaction overall constitutes a ring-contraction protocol, *e.g.* from cyclohexanone to cyclopentenol. We wanted to show the possibility of ring-expansion by the application of our present sequence (Scheme 1). Acetoxylation (91% yield) of cyclohexanone by $\text{Pb}(\text{OAc})_4$ and the addition of vinylmagnesium bromide (85% yield) to **6** followed by the oxidative ring cleavage (94% yield) of **7** produced the novel ω -formyl- α,β -unsaturated carbonyl compound **8** containing a terminal methylene unit. The facile intramolecular Baylis–Hillman reaction (PPh_3 in *t*-BuOH at 20 °C for 4 h) of **8** produced the ring-expanded cycloheptanone **9** in 84% yield. Compound **9** has been reported to produce the polycyclic compound containing the 6,8-dioxabicyclo[3.2.1]octane ring,⁷ which constitutes the basic structure of a number of pheromones.⁸

In conclusion, we have developed an efficient method of preparation of diverse ω -formyl- α,β -unsaturated carbonyl compounds and optimized the conditions for the intramolecular Baylis–Hillman reactions of these compounds. Our present sequence is quite general and applicable to the syntheses of various biologically important polycyclic compounds, as demonstrated by the syntheses of chromones and the precursor of the compound containing the 6,8-dioxabicyclo[3.2.1]octane ring.

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