The Most Simple and Convenient Synthesis of the Baylis-Hillman Adducts of Cycloalkenones: Use of DMAP in Aqueous THF

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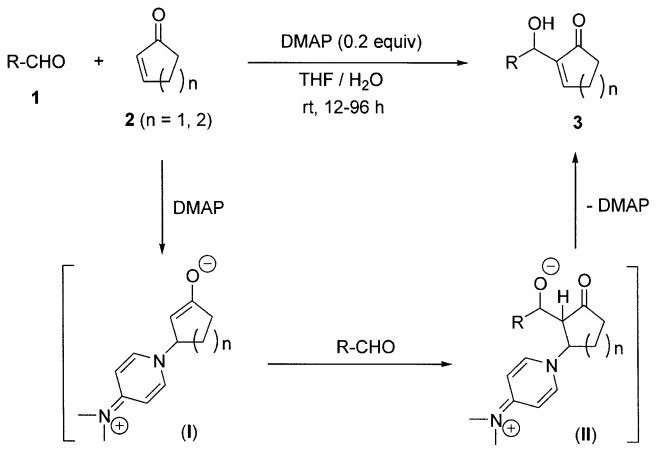
The Baylis-Hillman reaction, the coupling of aldehydes and activated vinyl compounds, is one of the most important carbon-carbon bond-forming reaction in organic synthesis.[1] The drawback to this methodology is its slow reaction rate, and many research groups have examined a variety of methods to accelerate the reaction. Among the activated alkenes cycloalkenones are famous.[1b] Under the normal reaction conditions using DABCO (1,4-diazabicyclo[2.2.2]-octane) no reaction was observed.

Recently, various methods for the synthesis of the Baylis-Hillman adducts of cycloalkenones have been developed with certain limitations. (1) The combination of 2,6-diphenyl-4*H*-chalcogenopyran-4-ones (or -4-thions) and $TiCl_4$ in methylene chloride[2a] and related methods were developed for the reactive *p*-nitrobenzaldehyde and 2-cyclohexen-1-one or 2-cyclopenten-1-one.[2] (2) The combination of lithium perchlorate ($LiClO_4$) and DABCO in ether could be used for the Baylis-Hillman reaction of benzaldehyde and 2-cyclohexen-1-one.[3] (3) The use of Et_2AlI in CH_2Cl_2 for the reaction of enone isolevoglucosenone and C-β-D-galactopyranosylformaldehyde furnished the corresponding Baylis-Hillman adduct.[4] (4) 4-(Dimethylamino)pyridine (DMAP)-catalyzed hydroxymethylation of 2-cyclohexenones with formaldehyde was carried out effectively in aqueous medium.[5] (5) Tributylphosphine combined with 1,1'-bi-2-naphthol was used effectively for cycloalkenone system.[6] (6) Lewis base effects including DMAP, tributylphosphine and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in the Baylis-Hillman reaction of 2-cyclohexen-1-one and arylaldehyde *N*-tosylimines were examined.[7] (7) Recently, it was known that $TiCl_4$ without the use of Lewis base could be applied to highly reactive aldehydes.[8] (8) Lithium phenylselenide (PhSeLi) induced Baylis-Hillman reaction was applied successively to α,β-unsaturated lactone system.[9] In summary, for the Baylis-Hillman reaction of cycloalkenone derivatives, the combination of Lewis acid and Lewis base system[2,3,6] seemed the only choice except for the reactive formaldehyde.[5] However, most of the reported methods was limited to reactive aldehydes with low to moderate yields of products.

In the course of our program for the synthesis of quinoline derivatives *via* S_N2'-S_NAr-elimination strategy,[10] we would like to extend the scope to the cycloalkenone derivatives. Thus, we needed the Baylis-Hillman adducts of 2-cyclohexen-1-one and various arylaldehydes. The use of DMAP, DBU, PBu_3 or DABCO as a base catalyst did not give the desired products in THF or CH_2Cl_2. The use of expensive 2-cyclohexen-1-one as solvent is not clever. The use of known acid-base combination methods is not conveniently accessible to us. Thus, we intended to search for the simple conditions for the reaction. Among the examined conditions, the use of DMAP (0.2 equiv) in aqueous THF (1 : 1) suffice the formation of the desired Baylis-Hillman adducts in reasonable yields.[11] As shown in Scheme 1 and in Table 1, we examined 2-cyclohexen-1-one (**2a**) and 2-cyclopenten-1-one (**2b**) and report herein the results.

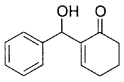
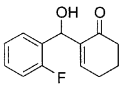
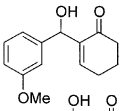
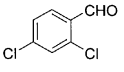
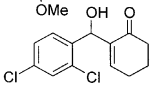
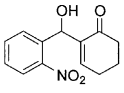
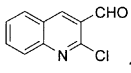
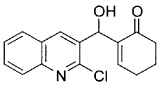
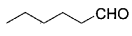
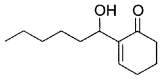
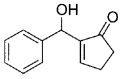
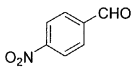
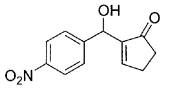
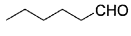
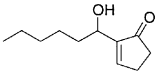
The reaction is simple and straightforward.[12] A mixture of aldehyde **1**, cycloalkenone **2** and DMAP (0.2 equiv) in aqueous THF (1 : 1) was stirred at room temperature for the time given in Table 1. After the usual workup process and column chromatographic purification (hexane/ether, 6 : 4), we could obtain the Baylis-Hillman adducts **3** and the results are summarized in Table 1.[12] During the course of this work, Aggarwal *et al*. reported on the rate acceleration of the Baylis-Hillman reaction in polar solvents such as water and formamide.[13] They examined various amines including DABCO, DMAP, 3-hydroxyquinuclidine (3-HDQ) and found that the use of 3-HDQ showed best results. However, the reaction used expensive 3-HDQ in equimolar amounts. In view of yields and the use of easily available DMAP in catalytic amounts, our conditions seemed more general and convenient than the Aggarwal's method.

The reaction mechanism is as follows as shown in Scheme 1. A conjugated addition of a Lewis base (DMAP) to



Scheme 1

Table 1. Synthesis of the Baylis-Hillman adducts of 2-cycloalken-1-ones

Entry	Aldehyde **1**	Cycloalk-enone **2**	Time (h)	Product **3**	Yield (%)[a]
1	 **1a**	 **2a**	72	 **3a**	55
2	 **1b**	**2a**	72	 **3b**	58
3	 **1c**	**2a**	96	 **3c**	63
4	 **1d**	**2a**	72	 **3d**	53 (94-95)
5	 **1e**	**2a**	72	 **3e**	56
6	 **1f**	**2a**	72	 **3f**	53
7	 **1g**	**2a**	96	 **3g**	64
8	 **1a**	 **2b**	24	 **3h**	54
9	 **1h**	**2b**	18	 **3i**	63 (136-137)
10	 **1g**	**2b**	12	 **3j**	56

[a]Mp was written in parenthesis for **3d** and **3i** and others are oil.

cycloalkenone **2** affords an enolate (**I**), which reacts with an aldehyde to give an aldol-type intermediate (**II**) followed by β-elimination of DMAP to give the product **3**. As shown the reaction sequence involves charged transition states and intermediates that could be stabilized by polar solvents such as water through intermolecular charge-dipole interactions as well as hydrogen bonding interactions to accelerate the reaction rate.[1,6,13,14]

As a conclusion we disclosed a simple and convenient reaction conditions for the Baylis-Hillman adducts of cycloalkenones.

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References and Notes

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11. When we used DABCO (0.2 equiv) as a base catalyst in THF or CH_2Cl_2, desired Baylis-Hillman adduct was not synthesized in appreciable amounts.[5a] When the reaction was performed without additional solvent (cyclohexen-1-one acts as a reagent and as a solvent in this case) product was obtained in low yield. However, this is not clever as mentioned before. The use of DABCO in aqueous THF showed intractable products. DBU or PBu_3 in aqueous THF showed complex mixtures, too. The use of DMAP in dry THF or in moisturized THF showed diminished yields of products.
12. To a stirred solution of aldehyde **1** (2 mmol) in aqueous THF (3 mL, H_2O/THF, 1 : 1) was added cycloalkenone **2** (2 mmol) and DMAP (49 mg, 0.4 mmol) at room temperature. After being stirred for the time given in Table 1, the desired Baylis-Hillman adducts **3a-j** were obtained by normal workup process and column chromatography (hexane/ether, 3 : 1). Spectroscopic data of **3a** and **3h** is as follows. **3a**[2c]: clear oil; IR (KBr) 3421, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92-2.04 (m, 2H), 2.32-2.48 (m, 4H), 3.10 (brs, 1H), 5.55 (s, 1H), 6.74 (t, J = 4.2 Hz, 1H), 7.22-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.51, 25.75, 38.56, 72.51, 126.44, 127.45, 128.28, 141.10, 141.69, 147.25, 200.31; Mass (70 eV) *m/z* (rel. intensity) 77 (23), 105 (14), 128 (23), 201 (100), 202 (M^+, 47). **3h**[6]: clear oil; IR (KBr) 3422, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40-2.45 (m, 2H), 2.54-2.60 (m, 2H), 3.59 (d, J = 3.9 Hz, 1H), 5.54 (s, 1H), 7.25-7.40 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.57, 35.16, 69.67, 126.27, 127.75, 128.40, 141.31, 147.68, 159.38, 209.54; Mass (70 eV) *m/z* (rel. intensity) 77 (30), 105 (18), 115 (17), 128 (100), 145 (18), 187 (47), 188 (M^+, 72).
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