Facile Synthesis of Baylis-Hillman Adducts Bearing the Carbamate or Amide Functional Group at the Secondary Position

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Received August 4, 2004

Key Words : Baylis-Hillman adducts, Carbamates, Secondary position, DABCO

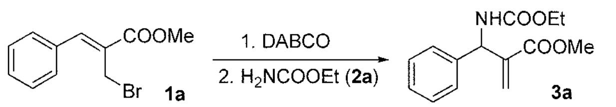
Recently, we and other groups have reported on the selective introduction of various nucleophiles onto the secondary position of the Baylis-Hillman adducts.[1,2] Introduction of nucleophile at the secondary position of the Baylis-Hillman adducts was carried out in aqueous THF via the corresponding DABCO salt, which was generated in situ from the corresponding acetate or bromides.[1,2] The nucleophiles include hydride ($NaBH_4$),[1a] *p*-toluenesulfonamide,[1e,1g] cyanide (KCN),[1f] water surrogate ($NaHCO_3$),[1d] primary nitro alkane,[1b] 2,4-pentanedione,[1h] allyl alcohol,[1g] and various kinds of *N*-containing heterocyclic compounds such as isatin, benzotriazole, phthalimide, and barbituric acid.[1c] But, we failed to introduce somewhat weaker nucleophiles such as ethyl carbamate, acetamide, or 2-amino-4-methoxy-6-methylpyrimidine in aqueous THF medium. The introduction of such nucleophiles is highly required in view of the usefulness of the products toward various types of chemical transformations.[3]

We thought the nucleophilicity of ethyl carbamate or diethyl phosphoramidate could be increased in polar and aprotic solvent such as CH_3CN, DMSO, or DMF. Thus, we reasoned that if the DABCO salt formation in non-aqueous solvent could be successfully carried out, we might use the solvent as the reaction medium. In the same contexts, we reasoned that we can use NaOH or KOH in order to deprotonate partially the hydrogen atom of ethyl carbamate of diethyl phosphoramidate and increase the nucleophilicity of them as a result. In this paper, we wish to disclose the results for the successful introduction of some nucleophiles at the secondary position of Baylis-Hillman adducts regioselectively. The nucleophiles included ethyl carbamate (**2a**), diethyl phosphoramidate (**2b**), diacetamide (**2c**), acrylamide (**2d**), and 2-amino-4-methoxy-6-methylpyrimidine (**2e**). Our synthetic rationale for **3a** is depicted in Scheme 1 as a representative example.

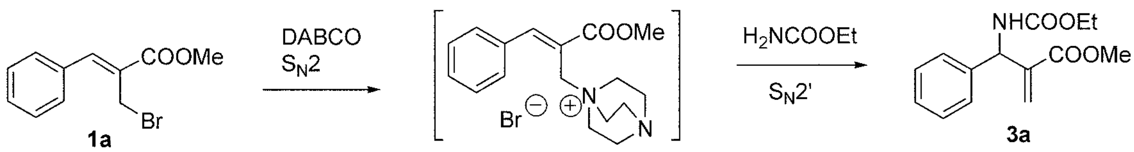
As a first trial, we examined the salt formation between DABCO and **1a** in different solvents and we found that the salt formation could be carried out in CH_3CN, DMSO, or DMF although the rates were different according to the solvent. The corresponding DABCO salt formation occurred at room temperature within 30 min completely in all cases (TLC observation).[4]

As a next, we examined the S_N2' type reaction of the DABCO salt and ethyl carbamate (**2a**) under various conditions (Table 1). The use of aqueous THF as solvent did not produce desired product **3a** at all irrespective of the base, DABCO (entry 1), K_2CO_3 (not shown), NaOH (entry 2). Moderate yields of products were obtained when we used CH_3CN, DMF, or DMSO as shown in Table 1. Best result was obtained (48%) when we carried out the reaction in

Table 1. Optimization of conditions for the conversion of **1a** into **3a**



Entry	Conditions	Yield (%)
1	1. aq THF, DABCO, rt, 30 min. 2. $H_2NCOOEt$, rt, 72 h	not formed
2	1. aq THF, DABCO, rt, 30 min. 2. NaOH, $H_2NCOOEt$, rt, 72 h	not formed
3	1. CH_3CN, DABCO, rt, 30 min. 2. NaOH, $H_2NCOOEt$, rt, 72 h	40%
4	1. DMF, DABCO, rt, 30 min. 2. NaOH, $H_2NCOOEt$, rt, 72 h	44%
5	1. DMSO, DABCO, rt, 30 min. 2. NaOH, $H_2NCOOEt$, rt, 48 h	15%
6	1. CH_3CN, DABCO, rt, 30 min. 2. NaOH, $H_2NCOOEt$, 50 °C, 48 h	48%



Scheme 1

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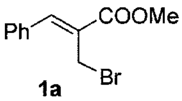
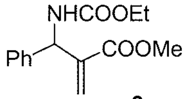
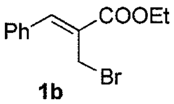
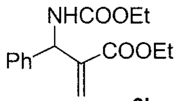
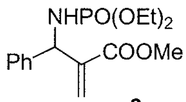
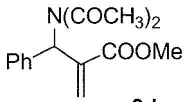
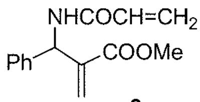
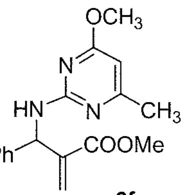
Table 2. Introduction of amine nucleophiles at the secondary position of Baylis-Hillman bromide

Entry	B-H adduct	Conditions	Products	Yield (%)
1	 **1a**	1. CH_3CN, DABCO (1.2 equiv) rt, 30 min. 2. NaOH (1.2 equiv) $H_2NCOOEt$ (**2a**, 1.2 equiv), 50 °C, 70 h	 **3a**	48
2	 **1b**	1. CH_3CN, DABCO (1.2 equiv) rt, 30 min. 2. NaOH (1.1 equiv) **2a** (1.1 equiv), 40 °C, 90 h	 **3b**	59
3	**1a**	1. CH_3CN, DABCO (1.2 equiv) rt, 30 min. 2. NaOH (1.1 equiv) $H_2NPO(OEt)_2$ (**2a**, 1.1 equiv), 50 °C, 60 h	 **3c**	38
4	**1a**	1. CH_3CN, DABCO (1.2 equiv) rt, 30 min. 2. NaOH (1.1 equiv) $HN(COCH_3)_2$ (**2c**, 1.1 equiv), rt, 40 h	 **3d**	46
5	**1a**	1. CH_3CN, DABCO (1.2 equiv) rt, 20 min. 2. NaOH (1.1 equiv) $H_2NCOCH{=}CH_2$ (**2d**, 1.1 equiv), 50 °C, 12 h	 **3e**	65
6	**1a**	1. CH_3CN, DABCO (1.2 equiv) rt, 20 min. 2. NaOH (1.1 equiv) 2-amino-4-methoxy-6-methyl-pyrimidine (**2e**, 1.1 equiv), 50 °C, 15 h	 **3f**	58

CH_3CN in the presence of NaOH at 40-50 °C. The reaction with Baylis-Hillman acetate instead of **1a** was less effective.[5]

By using the optimized conditions (entry 6 in Table 1) we examined the reaction with other nucleophiles, which were unsuccessful under the published reaction conditions.[1,2] As shown in Table 2, ethyl carbamate (entries 1 and 2), diethyl phosphoramidate (entry 3), diacetamide (entry 4), acrylamide (entry 5), and 2-amino-4-methoxy-6-methylpyrimidine (entry 6) showed similar results. Easily exchangeable ethoxy- (for diethyl phosphoramidate, entry 3) or methoxy- (for 2-amino-4-methoxy-6-methylpyrimidine, entry 6) groups survive after the reaction. However, unfortunately, the reaction of **2a** and the Baylis-Hillman bromide derived from acrylonitrile failed completely under the same reaction conditions.

In summary, we successfully introduced some interesting nucleophiles at the secondary position of Baylis-Hillman adducts regio-selectively although the yields were moderate. Currently we are trying further chemical transformation of the prepared compounds including synthesis of heterocycles and ring-closing metathesis reaction.

Experimental Section

Typical procedure for the synthesis of **3a**: To a stirred solution of Baylis-Hillman bromide (**1a**, 255 mg, 1.0 mmol) in CH_3CN (5 mL) was added DABCO (135 mg, 1.2 mmol) and stirred at room temperature for 30 min. To the reaction mixture NaOH (48 mg, 1.2 mmol) and ethyl carbamate (**2a**, 107 mg, 1.2 mmol) was added and heated to 50 °C for 70 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 4 : 1) we obtained **3a** as clear oil, 127 mg (48%). Other compounds were synthesized similarly and their spectroscopic data are as follows.

3a: oil; IR (neat) 3336, 1724, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 3.67 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 5.72 (br s, 2H), 5.92 (s, 1H), 6.38 (s, 1H), 7.22-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.54, 51.91, 56.53, 61.10, 126.39, 126.93, 127.52, 128.56, 139.66, 139.75, 155.76, 166.03; Mass (70 eV) m/z (rel. intensity) 49 (100), 84 (56), 115 (31), 174 (33), 190 (38), 231 (12), 263 (M^+, 3).

3b: oil; IR (neat) 3340, 2981, 1720, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 4.06-4.17 (m, 4H), 5.74 (br s, 2H), 5.88 (s, 1H), 6.36 (s, 1H), 7.22-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.81, 14.44, 56.35, 60.73, 60.93, 126.37 (2C), 127.35, 128.40, 139.72, 140.01, 155.67, 165.46.

3c: oil; IR (neat) 3217, 1724, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (td, J = 7.2 and 0.6 Hz, 3H), 1.28 (td, J = 7.2

and 0.6 Hz, 3H), 3.65 (s, 3H), 3.80-4.10 (m, 4H + NH), 5.17 (t, J = 10.5 Hz, 1H), 5.95 (s, 1H), 6.33 (d, J = 0.6 Hz, 1H), 7.20-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.97 (d, $^3J_{CP}$ = 7.1 Hz), 16.06 (d, $^3J_{CP}$ = 6.9 Hz), 51.80, 57.12, 62.30 (d, $^2J_{CP}$ = 5.5 Hz), 62.37 (d, $^2J_{CP}$ = 5.2 Hz), 126.10, 126.29, 127.26, 128.35, 140.98 (d, $^3J_{CP}$ = 5.4 Hz), 141.29 (d, $^3J_{CP}$ = 4.0 Hz), 165.93.

3d: oil; IR (neat) 1712, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6H), 3.77 (s, 3H), 5.63 (s, 1H), 6.29 (s, 1H), 6.52 (s, 1H), 7.21-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.74, 52.27, 60.44, 127.71, 127.88, 128.58, 129.43, 136.94, 138.16, 166.67, 174.14.

3e: oil; IR (neat) 3278, 1724, 1658, 1531 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 5.64 (dd, J = 9.9 and 1.8 Hz, 1H), 5.92 (s, 1H), 6.09 (d, J = 8.7 Hz, 1H), 6.12-6.33 (m, 2H), 6.36 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.12, 54.83, 126.65, 127.18, 127.58, 127.71, 128.74, 130.80, 139.15, 139.52, 164.73, 166.41.

3f: oil; IR (neat) 3425, 1720, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 5.71 (d, J = 8.4 Hz, 1H), 5.90 (s, 1H), 5.92 (s, 1H), 6.17 (d, J = 8.4 Hz, 1H), 6.35 (s, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.93, 52.00, 53.21, 56.32, 96.49, 126.18, 127.03, 127.51, 128.67, 140.76, 140.98, 161.32, 166.59, 168.31, 170.95.

References and Notes

1. For our recent publications on the selective introduction of nucleophiles at the secondary position of Baylis-Hillman adducts by using the amine salt concepts, see: (a) Im, Y. J.; Kim, J. M.; Mun, J. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2001**, *22*, 349. (b) Kim, J. M.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 657. (c) Gong, J. H.; Kim, H. R.; Ryu, E. K.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 789. (d) Kim, J. N.; Lee, H. J.; Gong, J. H. *Tetrahedron Lett*. **2002**, *43*, 9141. (e) Kim, J. N.; Lee, H. J.; Kee, K. Y.; Gong, J. H. *Synlett* **2001**, 173. (f) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett*. **2001**, *42*, 9023. (g) Kim, J. M.; Lee, K. Y.; Lee, S.-K.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 2805. (h) Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2004**, *25*, 328.
2. For the synthetic applications of the DABCO salt concepts of other groups, see: (a) Saxena, R.; Patra, A.; Batra, S. *Synlett* **2003**, 1439. (b) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett*. **2001**, *42*, 477. (c) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett*. **2001**, *42*, 85. (d) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun*. **2000**, *30*, 1045. (e) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem*. **2002**, *67*, 7135. (f) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S.; Reddy, R. M. *Tetrahedron* **2001**, *57*, 8167.
3. For the synthesis and applications of carbamate- or amide-containing Baylis-Hillman adducts, see: (a) Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Gambacorta, A. *Tetrahedron Lett*. **2002**, *43*, 3017. (b) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 319. (c) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869. (d) Mamaghani, M.; Badrian, A. *Tetrahedron Lett*. **2004**, *45*, 1547. (e) Shi, M.; Zhao, G.-L. *Tetrahedron Lett*. **2002**, *43*, 9171. (f) Shi, M.; Zhao, G.-L. *Tetrahedron Lett*. **2002**, *43*, 4499.
4. We examined the formation of DABCO salt in ionic liquid medium, 1-butyl-3-methylimidazolium tetrafluoroborate. Appreciable salt formation between **1a** and DABCO was not detected at room temperature.
5. When we used the Baylis-Hillman acetate instead of the bromide, rearranged acetate was formed in appreciable amounts during the reaction.