Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Amination of the Baylis-Hillman Acetates in Ethanol

Young Sang Park [a] , Min Young Cho [b] , Young Bum Kwon [b] , Byung Woo Yoo [b] & Cheol Min Yoon [b]

[a] Graduate School of Biotechnology, Korea University, South Korea

[b] Department of New Material Chemistry, Korea University, South Korea

Published online: 14 Aug 2007.

To cite this article: Young Sang Park , Min Young Cho , Young Bum Kwon , Byung Woo Yoo & Cheol Min Yoon (2007) Amination of the Baylis-Hillman Acetates in Ethanol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:16, 2677-2685, DOI: 10.1080/00397910701465370

To link to this article: http://dx.doi.org/10.1080/00397910701465370

Synthetic Communications®, 37: 2677–2685, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701465370

Amination of the Baylis–Hillman Acetates in Ethanol

Young Sang Park
Graduate School of Biotechnology, Korea University, South Korea

Min Young Cho, Young Bum Kwon, Byung Woo Yoo, and Cheol Min Yoon
Department of New Material Chemistry, Korea University, South Korea

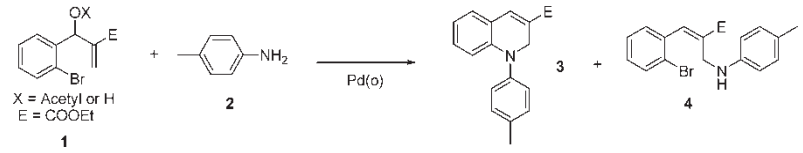
Abstract: Baylis–Hillman acetates in EtOH were substituted by various nitrogen nucleophiles to give the corresponding trisubstituted alkenes in high yields.

Keywords: Baylis–Hillman acetates, amination, trisubstituted alkene

The Baylis–Hillman reaction is one of the carbon–carbon bond-forming reactions in organic synthesis.[1] The Baylis–Hillman adducts were prepared by the reaction of activated alkenes such as ethyl acrylate, acrylonitrile, and methyl vinyl ketone with aldehydes or imines in the presence of nucleophilic catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO), quinuclidine, 4-(N,N-dimethylamino)pyridine (DMAP), and phosphine.[2] In addition to the usefulness of the Baylis–Hillman adducts by themselves, they and their acetates are very useful precursors for the preparation of a variety of trisubstituted alkenes with various functional groups such as ester, ketone, and nitriles by the reaction with a variety of nucleophiles.[3,4] Quinoline and dihydroquinolines are the important moiety of biological active compounds in medicinal chemistry[5–7] and prepared from the Baylis–Hillman adducts.[3b,4]

During a study for the palladium-catalyzed one-pot synthesis of dihydroquinolines **3** by the reaction of the Baylis–Hillman adducts or their acetates **1**

Received July 21, 2006
Address correspondence to Cheol Min Yoon, Department of Advanced Material Chemistry, Korea University, Jochiwon, Chungnam Korea. E-mail: cmyoon@korea.ac.kr

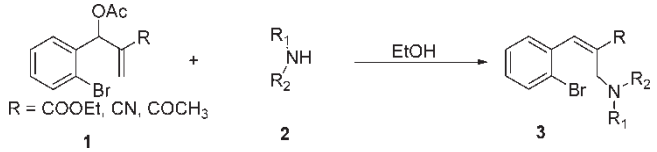


Scheme 1.

with *p*-toluidine (Scheme 1), Baylis–Hillman acetates **1** were found to undergo the substitution to give the corresponding substituted amines **4**.

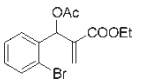
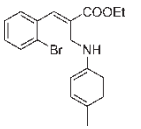
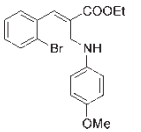
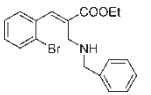
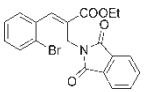
Amination of the Baylis–Hillman acetates was one of the most straightforward reactions to synthesize the corresponding trisubstituted alkenes with amino functional group. However, only two methods have been reported, to the best of our knowledge: the substitution of the Baylis–Hillman acetates with amine nucleophile in THF under reflux[8] and the palladium-catalyzed substitution of the Baylis–Hillman acetate in THF using Pd $(PPh_3)_4$ at rt.[9] The two reactions posed some problems such as relatively low yield, extended reaction time, high reaction temperature, low regioselectivity, and generality. Here we are going to report a mild, efficient, and convenient protocol for the nucleophilic displacement of the Baylis–Hillman acetates by aromatic amine, benzylamine, and potassium phthalimide in EtOH at rt to give the corresponding trisubsituted alkenes **3** in good to high yields (Scheme 2).

The optimum condition was investigated using ethyl 2-(acetoxy(2-bromo-phenyl)methyl)acrylate as a model substrate and *p*-toluidine as an amine nucleophile in various solvent systems such as acetonitrile, THF, DMSO, ethanol, and water in the presence or absence of palladium catalyst. Various palladium reagents did not have any role in the reaction, and EtOH turned out to be the choice of solvent. The reaction of ethyl 2-(acetoxy(2-bromophenyl)methyl)- acrylate in ethanol after 8 h gave the trisubstituted product in 87% isolated yield as shown in entry 1 of Table 1. With this result in hand, the substitution of ethyl 2-(acetoxyarylmethyl)acrylates with *p*-anizidine, benzylamine, potassium phthalimide, *p*-toluenesulfonylamide, diethylamine, and *N*-benzylmethylamine under optimized condition were attempted to give the corresponding products with (*E*)-stereoselectivity (entries 2–13). The reaction of ethyl 2-(acetoxyphenylmethyl)acrylate with amides such as acetamide and *t*-butoxycarbamate did not proceed at



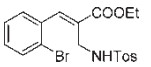
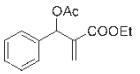
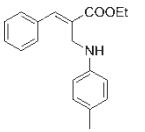
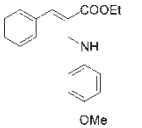
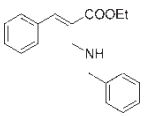
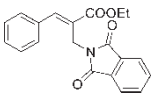
Scheme 2.

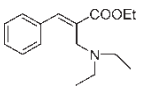
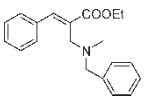
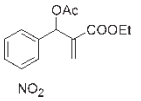
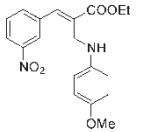
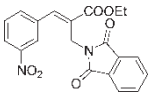
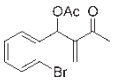
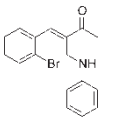
Table 1. Amination of the Baylis–Hillman acetates in EtOH

Entry	Acetate	Nucleophile	Product	Time (h)	Yield (%)[a]
1		*p*-Toluidine		8	87.0
2		*p*-Anisidine		8	82.0
3		Benzylamine		8	90.0
4		Potassium phthalimide		8	83.6

(*continued*)

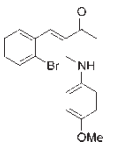
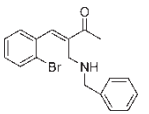
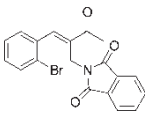
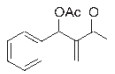
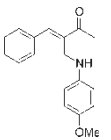
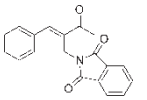
Table 1. Continued

Entry	Acetate	Nucleophile	Product	Time (h)	Yield (%)[a]
5		*p*-Toluenesulfonylamide		8	71.2
6		*p*-Toluidine		8	94.6
7		*p*-Anisidine		8	92.0
8		Benzylamine		4	87.3
9		Potassium phthalimide		4	80.1

10		Diethylamine		2	84.5
11		*N*-Bezylmethylamine		2	92.3
12		*p*-Anisidine		5	90.5
13		Potassium phthalimide		6	86.0
14		*p*-Toluidine		4	92.0

(*continued*)

Table 1. Continued

Entry	Acetate	Nucleophile	Product	Time (h)	Yield (%)[a]
15		*p*-Anisidine		3	94.0
16		Benzylamine		6	82.0
17		Potassium phthalimide		5	82.3
18		*p*-Anisidine		1	94.8
19		Potassium phthalimide		3	87.2

20		*p*-Anisidine		8	97.0
21		Potassium phthalimide		3	91.4
22		*p*-Toluidine		8	97.0
23		*p*-Anizidine		1	89.3
24		Benzylamine		2	85.0
25		Potassium phthalimide		4	81.0

[a]Isolated yields.

all, even under reflux condition. β-Acetoxy-α-methylene ketones reacted with *p*-toluidine, *p*-anizidine, benzylamine, and potassium phthalimide in ethanol at rt to afford the corresponding products (*E*)-stereoselectively in good to high isolated yields (entries 14–19). Further, the reactions of 3-acetoxy-2-methylene-3-phenylacrylonitriles with *p*-toluidine, *p*-anizidine, benzylamine, and potassium phthalimide in ethanol produced the corresponding alkenes having (*Z*)-stereochemistry in good to high yields (entries 20–25).

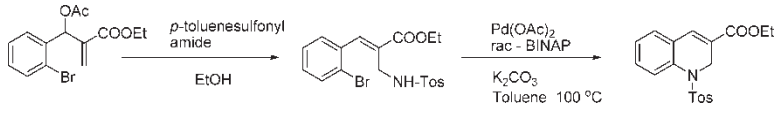
The amination product prepared from Baylis–Hillman adduct was attempted for the cyclization.[10] A amine obtained by the reaction of Baylis–Hillman acetate and *p*-toluenesulfonylamide in ethanol at rt undergoes the cyclization in the presence of palladium acetate and BINAP in toluene at 100°C for 12 h to give a dihydroquinoline in 82% yield (Scheme 3). The dihydroquinoline generated during the reaction seemed to be quite stable under the reaction condition even after a long reaction time (48 h), based on thin-layer chromatography (TLC). The further study for the one-pot synthesis of dihydroquinolines from Baylis–Hillman acetate using palladium catalyst are under way.[11]

In summary, we have described a simple, convenient, and efficient protocol for the substitution reaction by various amines and amides on Baylis–Hillman acetates in EtOH at rt to give the corresponding trisubstituted alkenes in good to high yields. A success of palladium-catalyzed cyclization of a Baylis–Hillman amine opened the possibility of new synthetic route for the dihydroquinoline.

EXPERIMENTAL

General Procedure

The mixture of Baylis–Hillman acetate (0.1528 mmol) and amine (0.3056 mmol, 2 equiv) in EtOH (1 mL) was stirred at room temperature for the appropriate time (see Table 1). After the reaction was complete (monitored by TLC using a solution of EA and hexane), the reaction mixture was concentrated under reduced pressure, and the concentrate was chromatographed on a short silica-gel pad using a solution of ethyl acetate and hexane (1:10) to give the corresponding products in good to high yield.



Scheme 3.

ACKNOWLEDGMENT

The authors acknowledge the financial support of the Korea Science and Engineering Foundation in the proceeding program in 2005.

REFERENCES

1. (a) Baylis, A. B.; Hillman, M. E. D. German Patent 1972, 2155113; (b) Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 34174q; (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
2. Basabaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
3. (a) Kim, J. N.; Im, Y. J.; Gong, J. H.; Lee, K. Y. *Tetrahedron Lett.* **2001**, *42*, 4195; (b) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343; (c) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613; (d) Lee, H. J.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **1999**, *40*, 4363; (e) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223; (f) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85; (g) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett.* **2001**, *42*, 477; (h) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729; (i) Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375; (j) Madapa, S.; Singh, V.; Batra, S. *Tetrahedron Lett.* **2006**, *62*, 8740.
4. (a) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2563; (b) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809; (c) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2612; (d) Amri, H.; El Gaied, M. M.; Ben Ayed, T.; Villieras, J. *Tetrahedron Lett.* **1992**, *33*, 6159; (e) Amri, H.; El Gaied, M. M.; BenAyed, T.; Villieras, J. *Tetrahedron Lett.* **1992**, *33*, 7345; (f) Jungheim, L. N. *Tetrahedron Lett.* **1989**, *30*, 1889.
5. (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605; (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p. 245.
6. Jones, G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees and C. W., Scriven, E. F. V. Eds.; Pergamon: Oxford, 1996; Vol. 5, p. 167.
7. (a) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531; (b) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499; (c) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett.* **1999**, 401; (d) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977; (e) Katritzky, A. R.; Arend, M. *J. Org. Chem.* **1998**, *63*, 9989; (f) Ruhland, T.; Kunzer, H. *Tetrahedron Lett.* **1996**, *37*, 2757; (g) Radl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143; (h) Qiang, L. G.; Baine, N. H. *J. Org. Chem.* **1988**, *53*, 4218.
8. Lee, C. G.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409.
9. Rajesh, S.; Banerji, B.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 7852.
10. (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737; (b) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341.
11. (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369; (b) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, A. Z. *J. Org. Chem.* **2005**, *70*, 596–602.