BULLETIN

OF THE

KOREAN CHEMICAL SOCIETY

ISSN 0253-2964
Volume 21, Number 9

BKCSDE 21(9) 839-946
September 20, 2000

Communications

Synthesis of Cinnamyl Amines from the Baylis-Hillman Adducts: Transformation of Allylic Alcohols to Allylic Amines

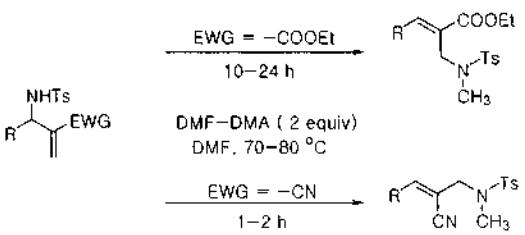
Hong Jung Lee, Yun Mi Chung, Ka Young Lee, and Jae Nyoung Kim*

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

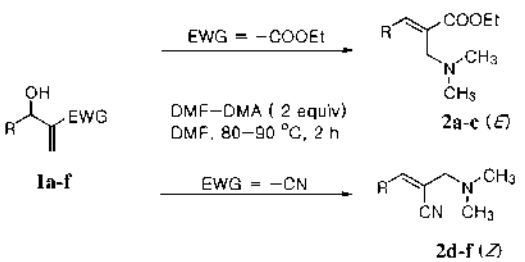
Received June 1, 2000

The Baylis-Hillman reaction is one of the most powerful carbon-carbon bond-forming methods in organic synthesis.[1] The Baylis-Hillman adducts, which are allylic alcohol derivatives, can be formed most often by the reaction of activated vinyls and carbonyl compounds.[1] Besides the usefulness of these Baylis-Hillman adducts themselves, further derivatization with various nucleophilic reagents toward synthetically useful compounds has been studied in depth by us and other groups.[2]

Recently, we have reported on the reaction of the Baylis-Hillman adducts of *N*-tosylimines and *N,N*-dimethylformamide dimethyl acetal (DMF-DMA).[3] We could obtain the *N*-methyl-*N*-tosylallylic amine derivatives stereoselectively as shown in Scheme 1.[3] As a continueous work, we tried on the reaction of the Baylis-Hillman adducts of benzaldehydes **1a-f** and *N,N*-dimethylformamide dimethyl acetal. From the reaction we could obtain *N,N*-dimethylcinnamyl amine derivatives **2a-f** in moderate to good yields stereoselectively (Scheme 2). *N,N*-Dialkylcinnamyl amine moiety constitutes an important scaffold in many biologically active compounds.[4]



Scheme 1

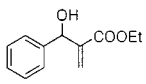
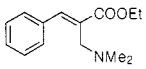
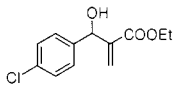
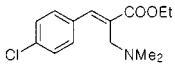
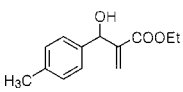
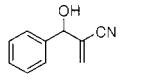
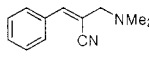
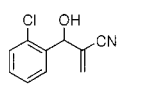
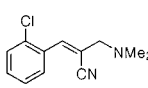
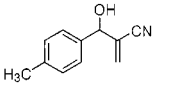
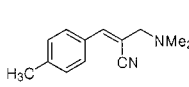


1a-f

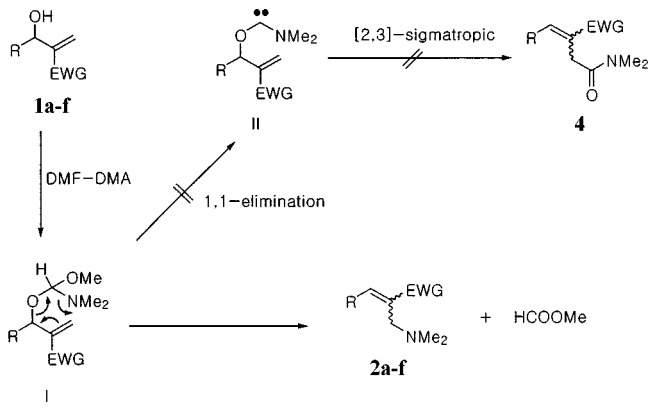
Scheme 2

As shown in Scheme 2 and in Table 1, the reaction of the Baylis-Hillman adducts **1a-f** and DMF-DMA in DMF afforded the corresponding amines **2a-f** in 63-88% isolated yields in a highly stereoselective manner. Ester substituted derivatives **1a-c** gave the *E* isomer **2a-c** selectively, while for nitrile substituted derivatives **1d-f** the *Z* isomer **2d-f** pre-

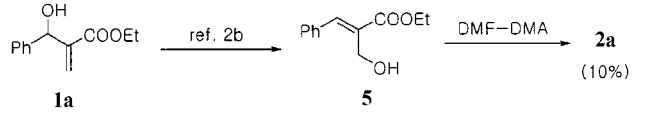
Table 1. Synthesis of *N,N*-dimethylcinnamyl amine derivatives

Entry	B-H adducts		Products (% yields)	
1		**1a**		**2a** (*E*, 73)[a]
2		**1b**		**2b** (*E*, 69)[b]
3		**1c**		**2c** (*E*, 72)[a]
4		**1d**		**2d** (*Z*, 83)[c]
5		**1e**		**2e** (*Z*, 88)[c]
6		**1f**		**2f** (*Z*, 63)[c]

[a]*Z* isomer was observed in trace amounts on tlc. [b]*Z* isomer was isolated in 20% yield. [c]*E* isomer was observed in trace amounts on tlc.



Scheme 3



Scheme 4

dominates. The reaction did not proceed at room temperature. Xylene can replace DMF as solvent (76% of **2a** was isolated in the case of **1a**). Without DMF-DMA no reaction was observed. The reaction of **1a** and dimethylamine hydrochloride (3.0 equiv) in DMF (reflux, 48 h) gave **2a** in 43% yield. However, the *E*:*Z* ratio was about 2 : 1 in this case. The reaction of **1a** and *N*,*N*-dimethylacetamide dimethyl acetal (2 equiv) in *N*,*N*-dimethylacetamide gave the expected γ,δ-unsaturated amide derivative (**3**, 2-(2-dimethylcarbamoyl ethyl)-3-phenyl acrylic acid ethyl ester) *via* the normal Claisen rearrangement pathway in 69% isolated yield.[5,6]

The stereochemistry of the products (*E* for ester, *Z* for nitrile) can be explained as we have already proposed.[2b,3] Some representative spectroscopic data of selected products **2a**, **2d**, and **3** were presented.[6]

We tentatively propose the reaction mechanism as follows: (1) exchange of methoxy group in DMF-DMA with the Baylis-Hillman adduct **1a-f** to form the intermediate **I**, (2) concerted Michael type addition of dimethylamino group[2b] and concomitant elimination of methyl formate gave **2a-f** (Scheme 3).

In a brilliant works of Buchi and co-workers,[7] treatment of some allylic alcohols with DMF-DMA gave the homologous β,γ-unsaturated amides *via* the formation of carbene and subsequent [2,3]-sigmatropic rearrangement (Scheme 3). However, in our reaction conditions, we could not observe the corresponding amide products **4** at all. This discrepancy could be explained as follows. In the cases of simple allylic alcohols the carbene mechanism works.[7] However, for the good Michael acceptor such as **1a-f**, Michael type addition of dimethylamino group is the preferred pathway leading to **2a-f**. To confirm the hypothesis we examined the reaction of ethyl 2-hydroxymethyl-3-phenyl-2-propenoate (**5**)[2b] and DMF-DMA in the same reaction conditions (Scheme 4). In this case the β-position is not a good Michael acceptor, and as a result, **2a** was isolated in low yield (10%) with 90% of the recovered starting material.

Acknowledgment. We wish to thank the Ministry of Korea (BK-21 project) for financial support of this work.

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6. Some representative spectroscopic data of products are as follows:
   2a: clear oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 2.24 (s, 6H), 3.30 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 7.34-7.62 (m, 5H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.30, 45.17, 54.37, 60.93, 128.39, 128.78, 130.32, 130.61, 135.40, 142.62, 168.58; Mass (70 eV) *m*/*z* (rel intensity) 58 (100), 91 (24), 115 (40), 131 (17), 172 (19), 204 (19), 218 (36), 233 (M^+, 21).
   2d: clear oil; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 3.21 (s, 2H), 7.08 (s, 1H), 7.40-7.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 44.95, 63.84, 108.97, 118.64, 128.84, 128.90, 130.37, 133.24, 145.08.
   3: clear oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 2.53-2.60 (m, 2H), 2.85-2.91 (m, 2H), 2.94 (s, 3H), 3.01 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 7.30-7.42 (m, 5H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.24, 23.49, 32.76, 35.32, 37.15, 60.82, 128.51, 128.57, 129.20, 131.80, 135.22, 139.93, 168.05, 172.11.
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