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The Reaction of the Baylis–Hillman Adducts of *N*-Tosylimines with *N,N*-Dimethylformamide Dimethylacetal

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Abstract

The reaction of *N,N*-dimethylformamide dimethylacetal (DMF-DMA) and the Baylis-Hillman adducts of *N*-tosylimines afforded *N*-methyl-*N*-tosyl allylic amine derivatives stereoselectively in moderate yields.

Keywords: *N,N*-dimethylformamide dimethylacetal, Baylis-Hillman adducts, *N*-tosylimines, *N*-methyl-*N*-tosyl allylic amine derivatives

Baylis-Hillman reaction is one of the most powerful carbon-carbon bond forming reactions in organic chemistry.[1] Most of the Baylis-Hillman reaction constitutes the reaction of activated vinyl compounds and carbonyl compounds to produce the Baylis-Hillman adducts *viz* allylic alcohol derivatives.[1] Besides the usefulness of these Baylis-Hillman adducts themselves, further derivatization with various nucleophilic reagents toward synthetically useful compounds has been studied deeply.[2] However, there were no reports on the reaction of the Baylis-Hillman adducts of *N*-tosylimines with amine or its equivalent nucleophiles.[2e]

During the course of our recent studies on the Friedel-Crafts reaction of arene nucleophiles with the Baylis-Hillman adducts of *N*-tosylimines,[3] we need *N*-alkyl derivatives of the Baylis-Hillman adducts in order to examine the effects of *N*-alkyl groups on the stereochemistry. Thus, we examined the reaction of *N,N*-dimethylformamide dimethylacetal (DMF-DMA) and the Baylis-Hillman adducts **1** in DMF to prepare the *N*-methyl derivatives of **1**. DMF-DMA has been used as a methylating agent of various compounds.[4] However, to our surprise in the reaction we could isolate the rearranged *N*-methyl-*N*-tosyl allylic amine derivatives **2**-**3**[5] in moderate yields as shown in Scheme 1. The reaction mechanism for the formation of **2**-**3** was proposed as follows as shown in Scheme 1. Michael type addition of methoxide, which might be present in DMF-DMA in small amounts,[4] to **1** gave a tetrahedral intermediate **I**. The intermediate **I** was converted to the product by three successive steps: (1) loss of tosylamide anion, (2) nucleophilic displacement of methoxy group of **II** or Michael type reaction of **1** by the tosylamide anion, and (3) *N*-methylation by DMF-DMA. More interestingly, depending upon the EWG in starting materials, stereochemistry of the generated allylic amines could be controlled. As shown in Table 1, *E*-allylic amine derivatives **2** were obtained stereoselectively where EWG is ester functionality, while the corresponding *Z* form **3** was obtained in the cases of nitrile derivatives. The assignment of the stereochemistry of **2**-**3** was based on their ^{1}H and ^{13}C NMR spectra.[2c,3]

These remarkable discrepancy in stereochemistry could be explained by the relative stabilities of the possible tetrahedral intermediates **A**-**D** as shown in Figure 1. Steric bulkiness of the ethoxycarbonyl group might be bigger than methoxymethyl which in turn is bigger than the cyano group. Thus, the energies of the intermediate **A** and **D** might be lower than the corresponding energies of **B** and **C**.[2b,2d-e] The reaction of **1a** and *N*-methyl

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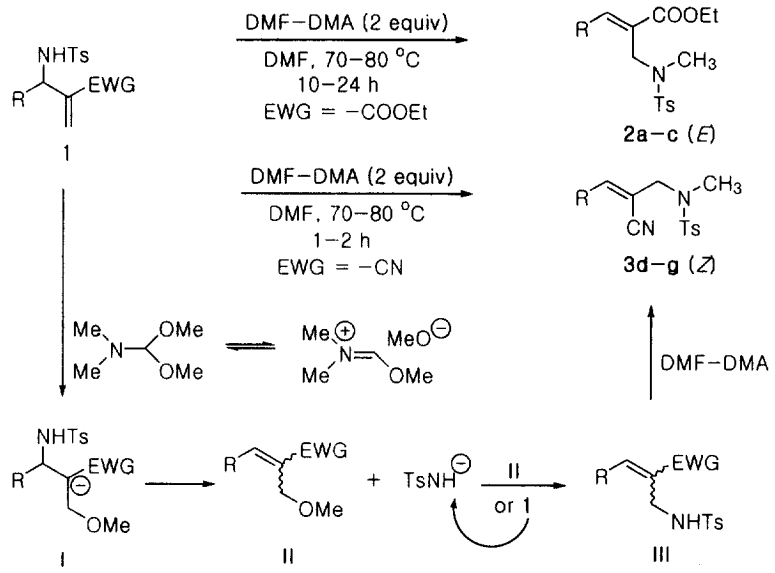


Scheme 1

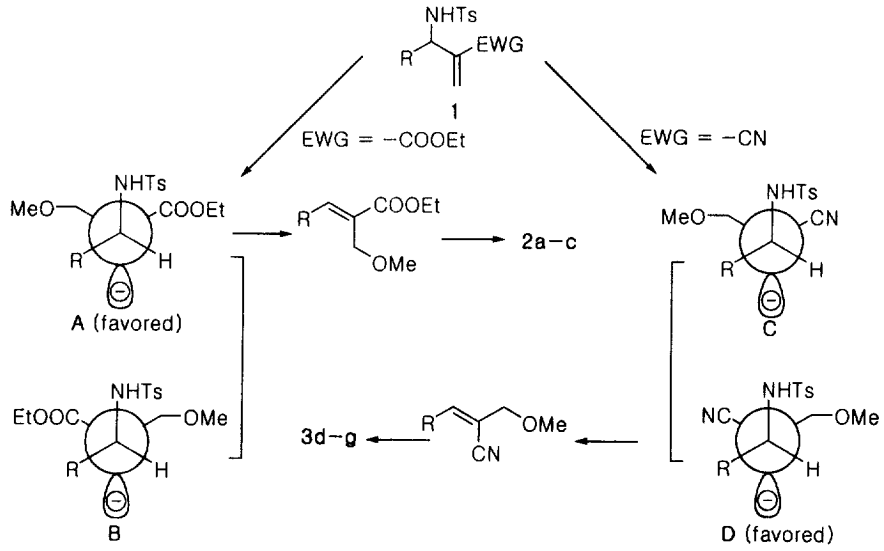
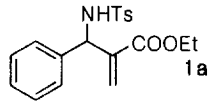
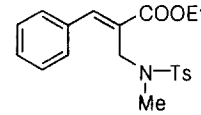
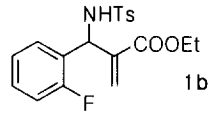
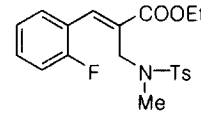
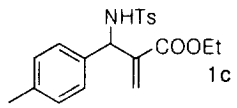
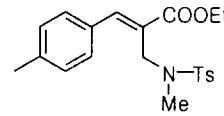
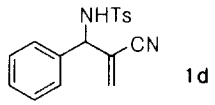
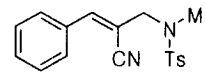
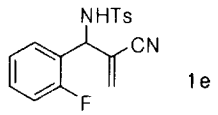
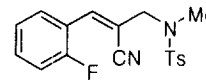
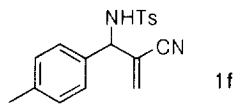
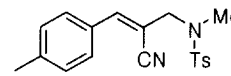
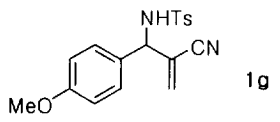
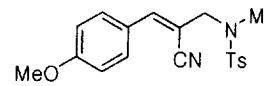
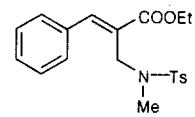
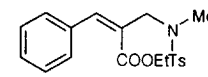
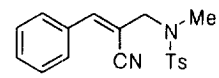


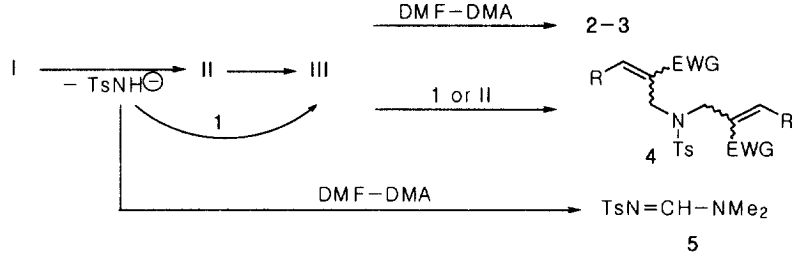
Figure 1. Conformations of tetrahedral intermediate I leading to the (*E*)–2 and (*Z*)–3.

Table 1. Synthesis of *N*-methyl-*N*-tosyl allylic amine derivatives 2-3.

entry	substrate	conditions[a]	product (% yield)
1	 1a	DMF-DMA (2 equiv) 12 h	 2a (39)
2	 1b	DMF-DMA (2 equiv) 10 h	 2b (41)
3	 1c	DMF-DMA (2 equiv) 24 h	 2c (40)
4	 1d	DMF-DMA (2 equiv) 2 h	 3d (38)
5	 1e	DMF-DMA (2 equiv) 1 h	 3e (47)
6	 1f	DMF-DMA (2 equiv) 2 h	 3f (46)
7	 1g	DMF-DMA (2 equiv) 2 h	 3g (35)
8	1a	TsNHMe (1 equiv) K_2CO_3, 12 h	  2a (33, *E/Z* = 65:35)[b]
9	1d	TsNHMe (1 equiv) K_2CO_3, 12 h	 3d (45)

[a]All reactions were carried out in 10 mmol scale of 1a-g in DMF at 70-80 °C for time indicated.
[b]Ratio determined by ^{1}H NMR spectrum.

p-toluenesulfonamide in the presence of K_2CO_3 in DMF gave also the corresponding **2a** in 33% isolated yield. However, in this case *E* and *Z* form was obtained as a mixture (entry 8). The energies of the corresponding tetrahedral intermediates **A** and **B** in this case become comparable due to the comparable bulkiness of -COOEt and $-CH_2N(CH_3)Ts$. Whereas, the reaction of **1d** in the same reaction conditions gave *Z*-isomer **3d** stereoselectively as in the cases of using DMF-DMA (entry 9). The yields of **2-3** were moderate due to the formation of side products **4** (0-12%) and/or **5**[6] (trace-49%) in the reaction conditions as shown in Scheme 2.[7] These results also state that *N*-methylation occur in the final stage and the presence of tosylamide in the reaction mixtures. Thus our proposed mechanism for the reaction seems plausible.



Scheme 2

Our initial target compound *N*-methyl derivatives of **1** could be prepared easily by CH_3I/K_2CO_3 in DMF, and the effects of alkyl substituents on the Friedel-Crafts reactions[3] are under study. As a summary, in this report we developed a stereoselective preparation method of allylic amine derivatives from the easily available Baylis-Hillman adducts. Further studies on the substitution reaction with various kinds of nucleophiles are undergoing.

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References and Notes

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4. Paquette, L. A. Encyclopedia of Reagents for Organic Synthesis, John Wiley & Sons, vol 3, pp 1987-1989.
5. As an example, ^1H and ^{13}C NMR spectral data of **2a** and **3d** were as follows. **2a**: ^1H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 2.59 (s, 3H), 4.08 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 7.28-7.61 (m, 9H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.15, 21.50, 34.63, 45.77, 61.29, 126.71, 127.84, 128.62, 129.43, 129.59, 130.14, 133.10, 134.22, 143.47, 144.60, 167.60. **3d**: ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.84 (s, 3H), 3.97 (s, 2H), 7.18 (s, 1H), 7.30-7.60 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.50, 35.16, 53.86, 105.83, 117.60, 127.52, 128.92, 129.05, 129.88, 130.89, 132.68, 134.57, 143.94, 146.02.
6. (a) Lee, G.; Oka, M.; Takemura, H.; Miyahara, Y.; Shimizu, N.; Inazu, T. *J. Org. Chem.* **1996**, *61*, 8304. (b) Han, Y.; Cai, L. *Tetrahedron Lett.* **1997**, *38*, 5423 and references cited therein.
7. In certain cases the corresponding intermediate **II** and **III** were isolated in trace amounts.