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Morita–Baylis–Hillman Reaction and Cyclization of 1-(*p*-Toluenesulfonyl)-1,3-butadiene with Aldimines

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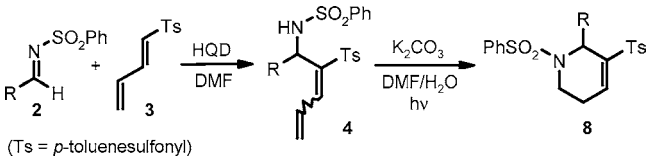
ABSTRACT

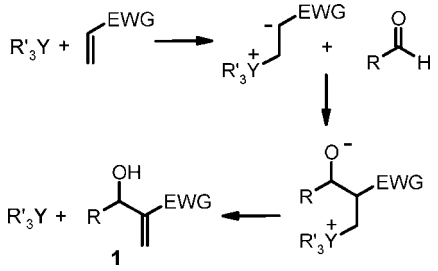


Aldimines 2 underwent Morita–Baylis–Hillman reaction with 1-(*p*-toluenesulfonyl)-1,3-butadiene (3) in the presence of 3-hydroxyquinuclidine (HQD) to afford adducts 4. The *E*-isomers of the products cyclized to the corresponding functionalized piperidines 8 under base-catalyzed conditions. Simultaneous equilibration of (*E*)-4 and (*Z*)-4 was effected by photoisomerization to improve the efficiency of the cyclization.

The Morita−Baylis−Hillman reaction[1] has been widely investigated as an effective carbon−carbon bond-forming method.[2] In its original and most common variation, an alkene containing an electron-withdrawing group (EWG) undergoes a conjugate addition of a tertiary phosphine[1a] or amine[1b] catalyst and the resulting zwitterion adds to the carbonyl group of an aldehyde. Elimination of the amine then regenerates the alkene double bond, resulting in the formation of the corresponding adduct **1**, as shown in Scheme 1.

More recent studies have resulted in numerous variations of this useful process. For example, chalcogenides in the presence of Lewis acids have proved to be effective replacements for tertiary phosphines or amines as nucleophilic catalysts.[3] Furthermore, several reports have indicated that imines[4] can be employed in lieu of aldehydes in Scheme 1. Although diverse types of electron-deficient alkenes have been used in the Morita−Baylis−Hillman reaction, there are only a few reports of vinyl sulfones[5] in this context.

Scheme 1. Morita−Baylis−Hillman Reaction[a]



[a] EWG = electron-withdrawing group; Y = P or N.

(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. *Ger. Offen.* 2,155,113, 1972; *Chem. Abstr*. **1972**, *77*, 34174q.

(2) For recent reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052. (e) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670.

(3) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45−58.

(4) For examples of the use of imines with carbonyl compounds or nitriles in Morita−Baylis−Hillman reactions, see: (a) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951−5952. (b) Campi, E. M.; Holmes, A.; Perlmutter, P.; Teo, C. C. *Aust. J. Chem.* **1995**, *48*, 1535−1540. (c) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731−2732. (d) Kündig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413−414. (e) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 319−321. (f) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869−8882. (g) Cyrener, J.; Burger, K. *Monatsh. Chem.* **1995**, *126*, 319−331. (h) Shi, M.; Xu, Y.-M. *J. Org. Chem.* **2003**, *68*, 4784−4790.

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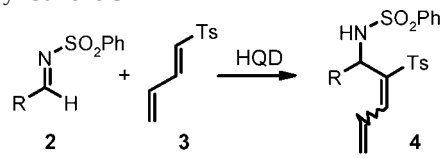
As part of our general interest in the chemistry of unsaturated sulfones,[6,7] we decided to investigate Morita−Baylis−Hillman reactions between aldimines **2** and the conjugated dienyl sulfone **3**. To our knowledge, the Morita−Baylis−Hillman chemistry of dienyl sulfones, or other similarly activated dienes, has not yet been explored, and the anticipated products **4** comprise potentially useful functionalized allylic amine derivatives. Moreover, the regenerated dienyl sulfone moiety provides possibilities for further transformations.

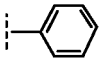
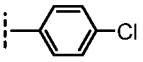
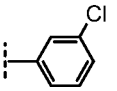
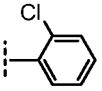
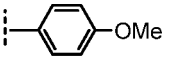
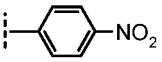
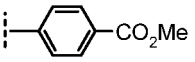
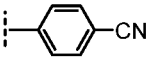
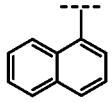
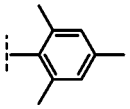
A series of imines **2** were prepared from the corresponding aldehydes by a standard procedure,[8] and 1-(*p*-toluenesulfonyl)-1,3-butadiene (**3**) was obtained by a literature method.[9] To optimize the conditions for the Morita−Baylis−Hillman reaction, the imine **2a** (R = Ph) was treated with **3** in the presence of DBU, DABCO, DMAP, triethylamine, triphenylphosphine, and 3-hydroxyquinuclidine (HQD) in a variety of solvents. The best results were typically obtained in the presence of 25 mol % HQD[10] in DMF at room temperature for ca. 5 h. These conditions were then similarly applied to imines **2b**−**j**, and the results are shown in Table 1. In some cases the imine **2** was employed in excess over the sulfone **3** to compensate for its partial hydrolysis during the reaction. However, equimolar amounts of **2** and **3** afforded comparable yields of **4** if rigorously anhydrous conditions were maintained. Although the dienyl sulfone **3** was prepared as the *E*-isomer, the adducts **4** were obtained as *E*/*Z* mixtures, presumably because of free rotation prior to elimination of HQD in the product-forming step. The method is compatible with both electron-withdrawing and -donating substituents on the aryl moiety of the imine. Exceptions were observed with the nitro- and cyano-substituted derivatives **2f** and **2h**, respectively, which reacted very rapidly in DMF to afford complex mixtures of products, and with the more hindered mesityl derivative **2j**, which failed to react under all attempted conditions. The additions to **2f** and **2h** were achieved in THF, in which the reaction proceeded at a significantly slower rate compared to DMF.

Table 1. Morita−Baylis−Hillman Reactions of Aldimines **2** with Dienyl Sulfone **3**[a,b]



2 **3** **4**

(Ts = *p*-toluenesulfonyl)

product	R	yield (%)	*E*/*Z* ratio
4a		86	70/30
4b		73	70/30
4c		63	70/30
4d		46	50/50
4e		46	60/40
4f		31	70/30
4g		70	70/30
4h		75	75/25
4i		61	65/35
4j		–	

[a] All reactions were performed in DMF at room temperature for 4−6 h, except the preparations of **4f** and **4h**, which were carried out in THF for 16 and 20 h, respectively. [b] All reactions were performed in the presence of 25 mol % HQD except in the case of **4e**, where 50 mol % was used.

The major product in each successful example in Table 1 proved to be the corresponding *E*-isomer. This was established unequivocally for **4a** by NMR experiments. Thus, when a D_2O exchange was performed, the doublet at δ 5.91 ppm collapsed to a singlet, establishing it as the benzylic proton α to the sulfonamide moiety. This signal showed a strong NOE (16%) when the multiplet at δ 6.64, assigned to the proton γ to the sulfone group in the diene moiety,

(5) For examples of the reaction of vinyl sulfones with aldehydes in Morita−Baylis−Hillman reactions, see: (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5095−5098. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095−6106. (c) Hoffmann, H. M. R.; Weichert, A.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1990**, *46*, 5591−5602. (d) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098−4112.

(6) (a) For an overview of sulfone chemistry, see: Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) For a review of vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951−6984. (c) For a review of acetylenic and allenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, *57*, 5263−5301. (d) For a review of dienyl sulfones, see: Bäckvall, J. E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291−2312.

(7) For recent examples, see: (a) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566−6571. (b) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261−264. (c) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552. (d) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779−1781. (e) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223−2233. (f) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389−9393. (g) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967−972.

(8) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203-210.

(9) Barluenga, J.; Martínez-Gallo, J. M.; Nájera, C.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2605−2609.

(10) It is possible that the particular efficacy of HQD in this process is due to stabilization of the zwitterion formed by its addition to the 2-position of **3** through hydrogen-bonding between the HQD hydroxyl group and a sulfone oxygen atom. Similar hydrogen-bonding effects have been postulated in the additions of HQD to other activated alkenes. (a) Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495−500. (b) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565−1572.

was irradiated, and vice versa (14%). This established that the vinyl substituent and the α-aminobenzyl side chain are cis oriented. The similarity of the NMR signals of the diene moieties and of the benzylic protons in the major isomers of the other products in Table 1 when compared to (*E*)-**4a** indicates that they too possess the *E*-configuration. In each example in Table 1, the yield refers to the total of both geometrical isomers. However, careful flash chromatography of the mixtures permitted the isolation of the pure, less polar *E*-isomers, while the *Z*-isomers generally could not be obtained completely free from the corresponding *E*-isomers. The identities and amounts of the *Z*-isomers were inferred from the NMR spectra of the unseparated *E*/*Z* mixtures.

Attempts to employ the more sterically hindered methyl-substituted dienyl sulfones **5**,[9] **6**,[11] or **7**[9] (Figure 1) in place of **3** with imine **2a** (R = Ph) failed under similar conditions.

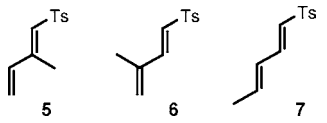
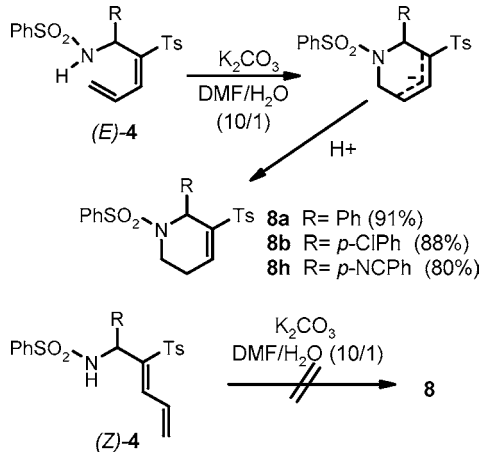


Figure 1. Substituted dienyl sulfones **5**−**7**.

When the pure *E*-isomers of the representative Morita−Baylis−Hillman adducts **4a**, **4b**, and **4h** were dissolved in DMF−water (10/1) containing K_2CO_3 at room temperature, intramolecular conjugate additions of the sulfonamide functionalities to the terminal positions of the diene substituents occurred to afford the corresponding piperidine derivatives **8a**, **8b**, and **8h**, respectively, in high yield (Scheme 2). Not

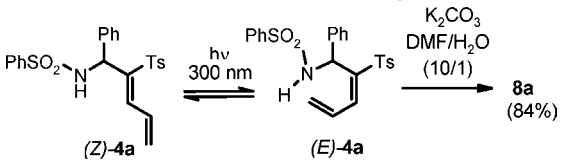
Scheme 2. Cyclization of Morita−Baylis−Hillman Adducts **4**



surprisingly, treatment of the corresponding *Z*-isomers under similar conditions failed to afford significant amounts of the cyclized products. The difference in behavior between the geometrical isomers is attributed to the inability of the *Z*-isomers to adopt a conformation compatible with the 6-centered transition state required for the cyclization.

We also attempted to cyclize the unseparated *E*/*Z* mixture of **4a** to **8a** under conditions designed to promote the in situ equilibration of the geometrical isomers, thereby allowing the otherwise inert *Z*-isomer to cyclize via its *E*-counterpart. First, we observed in separate experiments that pure (*E*)-**4a** and a 40/60 mixture of (*E*)- and (*Z*)-**4a** afforded identical 70/30 mixtures of the two geometrical isomers when irradiated with 300 nm UV light. This experiment established that photoisomerization of **4a** is possible and that the 70/30 *E*/*Z* ratio represents the mixture at equilibrium. Attempts at equilibration in the presence of the HQD catalyst for extended periods or at elevated temperatures gave less satisfactory results. Finally, an unseparated 65/35 mixture of (*E*)- and (*Z*)-**4a** was treated under the usual cyclization conditions (K_2CO_3, DMF−H_2O) while being irradiated with UV light at 300 nm, affording **8a** in 84% yield (Scheme 3),

Scheme 3. Photoisomerization and Cyclization of **4a**



comparable to what had been obtained earlier by cyclization of the pure *E*-isomer. This demonstrates the feasibility of a one-pot photoisomerization and cyclization protocol for the conversion of both isomers to the final cyclized product.

Attempts to perform [4 + 2]-cycloadditions of **2a** with **3** to afford **8a** in one step by heating in various solvents or in the presence of Lewis acids (e.g., BF_3·OEt_2, $TiCl_4$) have so far proved to be fruitless.

These experiments demonstrate that aldimines **2** undergo relatively facile Morita−Baylis−Hillman reaction with dienyl sulfone **3** in the presence of HQD to afford *E*/*Z* mixtures of the adducts **4**. Moreover, the dominant *E*-isomers of **4** can be cyclized to the corresponding 2-substituted piperidines **8**. Alternatively, cyclization of a mixture of both geometrical isomers can be effected by photoisomerization that permits their in situ equilibration. The presence of the vinyl sulfone moiety in the products **8** offers potential for further useful transformations.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of compounds **4a**−**i**, **8a**, **8b**, and **8h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Bordwell, F. G.; Mecca, T. G. *J. Am. Chem. Soc.* **1972**, *94*, 4, 5829−5837.