New and Stereospecific Synthesis of Allenes in a Single Step from Propargylic Alcohols

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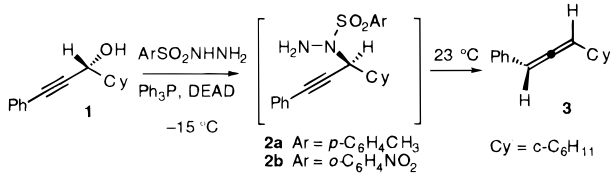
There are few reliable methods for the stereodefined construction of allenes, despite their growing importance in organic synthesis.[1] As part of an earlier study, we developed a three-step procedure for the synthesis of allenes from readily available propargylic alcohols involving (1) mesylate formation, (2) displacement with excess hydrazine, and (3) oxidation with an azodicarboxylate reagent to produce a propargylic diazene intermediate that evolves dinitrogen in a sigmatropic elimination process (e.g., **1** → **3** below).[2] Although this method did provide a stereospecific preparation of allenes, it was lengthy, unsuccessful in the preparation of the important (trimethylsilyl)-substituted allenes,[3] and proceeded in 48−81% yield. We describe herein a new and stereospecific method for the synthesis of allenes from propargylic alcohols that proceeds in a single operation, is efficient, and provides access to a wide range of stereodefined, substituted allenes, to include (trimethylsilyl)-allenes.

The new methodology evolved from the speculation that the sulfonamide group of arenesulfonylhydrazines would function as the nucleophilic component in a Mitsunobu inversion reaction (e.g., **1** → **2**).[4,5] In addition, results from a study of the fragmentation of 1-(trialkylsilyl)-1-tosylhydrazines[6] suggested that a 1-alkyl-1-arenesulfonylhydrazine (e.g., **2**) might fragment under much milder conditions than suggested by prior work.[7] Initial experiments were conducted with tosylhydrazine. Addition of a solution of diethyl azodicarboxylate (DEAD, 3.0 equiv) in benzene to a solution of alcohol **1** (1 equiv), triphenylphosphine (3.0 equiv), and tosylhydrazine (2.0 equiv) in benzene at 5−8 °C led to the formation of the crystalline 1-alkyl-1-tosylhydrazine derivative **2a** (mp 115−116 °C, dec) in 62% yield after purification by chromatography on silica gel. As anticipated, **2a** fragmented under exceedingly mild conditions; stirring a solution of **2a** in methanol at 23 °C for 16 h brought about the spontaneous elimination of *p*-toluenesulfinic acid and dinitrogen to form the allene **3** in 79% yield. Allene formation could also be conducted without isolation of the intermediate **2a**, by replacing the solvent benzene with methanol after the inversion step (67% yield of **3** from **1**). The elimination reaction proceeded at a comparable rate when trifluoroethanol was employed as solvent but was considerably slower in ethanol. The use of a base, such as triethylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene, had no apparent affect on the rate of the elimination reaction, and the presence of acetic acid in the reaction proved deleterious, with multiple products being formed (cf. ref 7).



On the basis of these observations, we hypothesized that the elimination reaction proceeded by a unimolecular, polar transition state. We felt that the overall process could benefit substantially by the modification of the arenesulfonyl group so as to accelerate the elimination reaction, potentially reducing the entire sequence to a single operation. Hünig et al. have documented that electron-withdrawing arene substituents accelerate the thermal decomposition of arenesulfonylhydrazines.[8] In addition, it was anticipated that the greater acidity of electron-withdrawing arenesulfonylhydrazine derivatives would improve the efficiency of the Mitsunobu reaction. After a survey of several candidates, *o*-nitrobenzenesulfonylhydrazine (NBSH) was determined to be the reagent of choice for the one-step conversion of propargylic alcohols to allenes. NBSH, a known compound,[9] is efficiently prepared from *o*-nitrobenzenesulfonyl chloride and anhydrous hydrazine in tetrahydrofuran (THF) at −15 °C. NBSH is isolated as a pale yellow, crystalline solid (81−85% yield, mp 97−99 °C, dec, lit mp 101 °C,[9] dec) that can be stored at ambient temperature for several days but should be refrigerated for long-term storage. When we implemented an order of addition sequence typically employed in the Mitsunobu inversion reaction (with carboxylic acids as nucleophiles)[4] for the reaction of **1** with NBSH (Ph_3P, 3 equiv; **1**, 1 equiv; NBSH, 3 equiv; then DEAD, 3 equiv), the major product was not the anticipated allene **3** (yield 12%), but a 1:1.4 mixture of the diastereomeric propargylic sulfinate esters (52%). Further experimentation revealed that NBSH was much more reactive toward the reagent combination Ph_3P·DEAD than was tosylhydrazine and apparently underwent rapid degradation to *o*-nitrobenzenesulfinic acid, which then served as a nucleophile in a Mitsunobu reaction with **1**. By modifying the order of addition, premixing Ph_3P (1.5 equiv) and DEAD (1.5 equiv) in THF at −15 °C and then adding **1** (1 equiv) and finally NBSH (1.5 equiv), the allene **3** was obtained reproducibly in 72−77% yield, in a single operation.

This procedure has proven to be a general method for the synthesis of a wide range of allenes from propargylic alcohols (Table 1).[10] Typically, the Mitsunobu inversion reaction of a propargylic alcohol with NBSH occurs within 1−2 h at −15 °C; elimination of the resultant alkylated sulfonylhydrazine is complete within 1−8 h at 23 °C. Thin-layer chromatographic

(1) Reviews: (a) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25. (b) *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980. (c) *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982. (d) Coppola, G. M.; Schuster, H. F. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (e) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. For leading references into the preparation and synthetic utility of the important (trialkylsilyl)allenes, see: (f) Danheiser, R. L.; Tsai, Y.-M.; Fink, D. M. *Org. Synth.* **1988**, *66*, 1. (g) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

(2) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747.

(3) Unpublished results; desilylation is observed.

(4) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(5) Mitsunobu reactions with *N*-alkylsulfonamides as nucleophiles are known: (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, Jr., G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (b) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (c) Bell, K. E.; Knight, D. W.; Gravestock, M. B. *Tetrahedron Lett.* **1995**, *36*, 8681. Reference 5a discusses the fact that primary sulfonamides ($ArSO_2NH_2$) are incompatible with the Mitsunobu reaction.

(6) (a) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208. Prior to this work, Corey et al. had developed a method for reductive allylic transposition based on the air-oxidation of an allylic hydrazine: (b) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.

(7) 1-Allyl-1-sulfonylhydrazines have been prepared by base-promoted alkylation, and their fragmentation has been induced by heating (60 °C) in acetic acid: (a) Sato, T.; Homma, I. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1885. (b) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016. 1-Alkyl-1-sulfonylhydrazines have been prepared and fragmented in situ by the amination of sulfonamides with chloramine in refluxing THF in the presence of hydroxide: (c) Nickon, A.; Hill, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 1152. (d) Guziec, F. S., Jr.; Wei, D. *J. Org. Chem.* **1992**, *57*, 3772.

(8) Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271.

(9) Dann, A. T.; Davies, W. *J. Chem. Soc.* **1929**, 1050.

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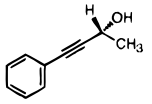
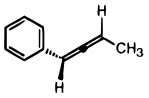
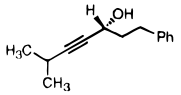
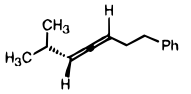
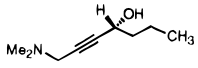
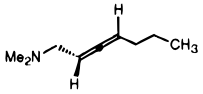
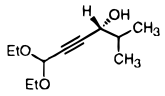
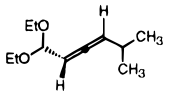
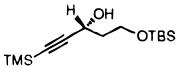
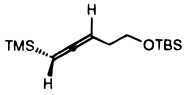
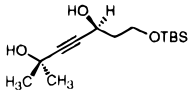
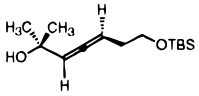
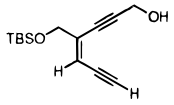
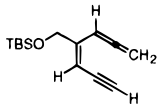
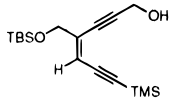
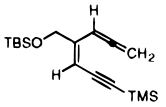
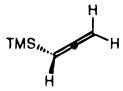
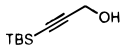
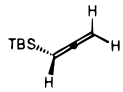
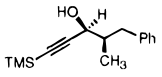
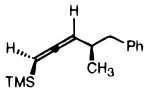
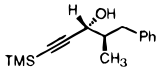
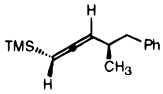
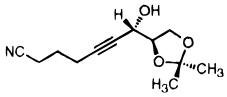
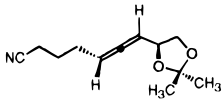
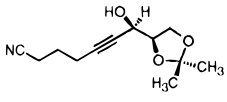
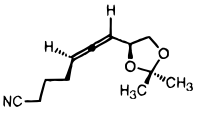
Table 1. Synthesis of Allenes from Propargylic Alcohols

Entry	Substrate	Product	Yield[b]
1			85
2[a]			87
3[a]			83
4[a]			74
5[a]			91
6[a]			85
7			72
8			76
9			53 (88)
10			75
11[c]			77
12[c]			86
13[c]			76
14[c]			70

[a] Racemic substrate. [b] Isolated yield; yield in parentheses was obtained by gas chromatography. [c] The configuration of the products was assigned on the basis of the stereochemistry of the transformation of entry 1.

(TLC) analysis of the reaction mixture at −15 °C reveals the formation of a more polar, unstable intermediate, presumably the alkylated sulfonylhydrazine (e.g., **2b**), which decomposes during elution to form the allene **3**. The allenes of entries 1−12 (Table 1) were obtained using 1.2−1.6 equiv each of Ph_3P, DEAD, and NBSH. More hindered alcohols (entries 13 and 14) required 3.0 equiv of each reagent to complete the Mitsunobu reaction.

As is evident from the examples of Table 1, the method is tolerant of a wide variety of functional groups, to include tertiary amines, tertiary alcohols, acetals and ketals, silyl ethers and nitriles. It is also useful for the preparation of the important (trialkylsilyl)allenes.[1] In particular, (trimethylsilyl)- and (*tert*-butyldimethylsilyl)allene[11] are now easily synthesized in one step from the corresponding C-silylated propargyl alcohol derivatives (entries 9 and 10). The general transformation proceeds with complete stereospecificity. For example, the optically active propargylic alcohol of entry 1 (78 ± 2% ee) produced the (*R*)-allene ($[\alpha]^{21}_D = -184°$, $c = 1.33$, acetone) with 77 ± 2% ee, as determined by ^1H NMR analysis with the chiral shift reagent Ag(fod)−Yb(hfc)$_3$.[2] This demonstrates that the overall process occurs with the stereospecificity implied by structures **1**−**3**. Entries 11−14 further establish the stereospecificity of the process; each substrate produced the corresponding allene without detectable contamination by the alternative diastereomer. The syntheses of the sensitive allene-ene-ynes of entries 7 and 8 are especially noteworthy and represent a considerable advance over previous methodology.[2]

In summary, we have developed an expedient, one-step synthesis of allenes from propargylic alcohols. The success of the method depends critically upon the following ordering of three reaction rates: Mitsunobu inversion (several minutes at −15 °C) > fragmentation of the intermediate 1-alkyl-1-*o*-nitrobenzenesulfonylhydrazine (1−8 h in THF at 23 °C) > spontaneous generation of diimide from NBSH (days to weeks at 23 °C). We have shown that the transformation proceeds with complete stereospecificity and, given the wide availability of optically active propargylic alcohols, should provide access to an equally wide range of optically active allenes.

Acknowledgment. Financial support from American Cyanamid Company is gratefully acknowledged. We express our appreciation to Professor Erick Carreira and Mr. Vincent Tai for a gift of the substrate of entry 6, Table 1.

Supporting Information Available: Listings of analytical data for **2a**, **3**, and new compounds in Table 1 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) A representative experimental procedure, *1-Dimethylamino-2,3-heptadiene* (entry 3, Table 1): DEAD (0.10 mL, 0.65 mmol, 1.3 equiv) was added to a solution of Ph_3P (170 mg, 0.65 mmol, 1.3 equiv) in THF (2 mL) at −15 °C. After 10 min, a solution of 1-dimethylamino-2-heptyn-4-ol (78 mg, 0.50 mmol, 1 equiv) in THF (1.5 mL) was added to the yellow reaction mixture, followed 10 min later by a solution of NBSH (0.14 g, 0.65 mmol, 1.3 equiv) in THF (2.0 mL). The resulting suspension was held at −15 °C for 1 h, after which time TLC analysis indicated complete consumption of the starting alcohol. The reaction mixture was warmed to 23 °C and allowed to stand overnight (8 h). Concentration of the reaction mixture and purification of the residue by chromatography on silica gel afforded the title allene as a colorless oil (57 mg, 83%).

(11) (a) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron*, **1983**, *39*, 935. (b) Hopf, H.; Naujoks, E. *Tetrahedron Lett.* **1988**, *29*, 609.