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A Brønsted Acid Mediated Cascade Enone Synthesis from Aldehydes Containing a Tethered Propargylsilane

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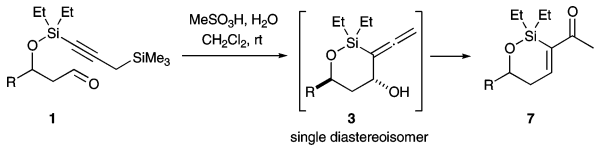
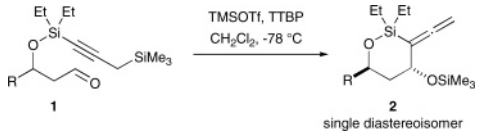
Received October 31, 2007



$MeSO_3H$ effects the intramolecular allenylation of a series of aldehydes **1** to provide allenyl alcohol product **3** as a single diastereoisomer. Cyclization proceeds rapidly at −78 °C. However, when the reaction is performed at room temperature, aldehyde **1** provides enone product **7** instead. A mechanism for the formation of this product is proposed in which the initially formed allenyl alcohol **3** undergoes dehydration to provide an allyl carbocation, which is trapped with water, thereby installing the enone.

Forming a tether between two reacting partners allows a subsequent reaction to proceed in an intramolecular fashion and benefit from the advantages associated with unimolecular processes. However, if the tether is then cleaved, the product obtained is the result of a net intermolecular reaction.[1] We[2] and others[3−8] have demonstrated that temporary silicon tethers provide a powerful strategy for intramolecular nucleophile delivery. For example, we recently used a temporary silicon connection to tether a propargylsilane nucleophile to a range of β-hydroxy aldehyde electrophiles.[2d] Treatment of the resulting aldehyde **1** with TMSOTf in the presence of the Brønsted acid scavenger tri-*tert*-butylpyrimidine (TTBP)[9] led to the formation of a single allenylsilane diastereoisomer **2** in good to very good yield (Scheme 1).[2d]

SCHEME 1. Stereoselective Intramolecular Allenylation



While the reaction of silicon nucleophiles, such as allylsilanes, propargylsilanes and related systems, with aldehydes is most commonly effected by Lewis acids,[10] Brønsted acids provide a potentially attractive alternative activation source.[11] For our purposes, using a Brønsted acid in place of TMSOTf would provide an operationally more simple cyclization method and remove the need to employ expensive acid scavengers. Reaction would also generate an alcohol, rather than a silyl ether product, which is primed for further manipulation and potential use as a directing group for the diasteroselective functionalization of the proximal allene.[12] From a practical viewpoint, a more polar alcohol product would also facilitate product purification through its more straightforward separation from the apolar silyl byproducts and pyrimidine acid scavenger, which we employed in our Lewis acid mediated intramolecular allenylation studies. For these reasons, we were keen to investigate whether Brønsted acids could also mediate our intramolecular allenylation reaction.

To this end, aldehyde **1a**, containing a propargylsilane tethered through a β-silyl ether connection, was prepared using our established protocol.[2d] Although silicon nucleophiles are

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(2) (a) Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, *5*, 4231−4234. (b) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971−3974. (c) Beignet, J.; Tiernan, J.; Woo, C. H.; Kariuki, B. M.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341−6356. (d) Ramalho, R.; Beignet, J.; Humphries, A. C.; Cox, L. R. *Synthesis* **2005**, 3389−3397.

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(7) For applications in intramolecular aglycon delivery: (a) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248. (b) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. (c) Bols, M.; Hansen, H. C. *Chem. Lett.* **1994**, 1049−1052. (d) Bols, M. *Acta Chem. Scand.* **1993**, *47*, 829−834. (e) Bols, M. *Tetrahedron* **1993**, *49*, 10049−10060.

(8) See also: (a) Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Lett.* **2004**, *45*, 8647−8651. (b) Robertson, J.; Hall, M. J.; Stafford, P. M.; Green, S. P. *Org. Biomol. Chem.* **2003**, *1*, 3758−3767. (c) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915−2917.

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(10) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* (*N.Y.*) **1989**, *37*, 57−575.

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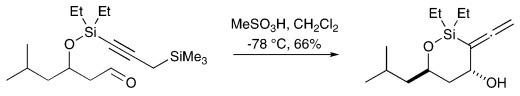
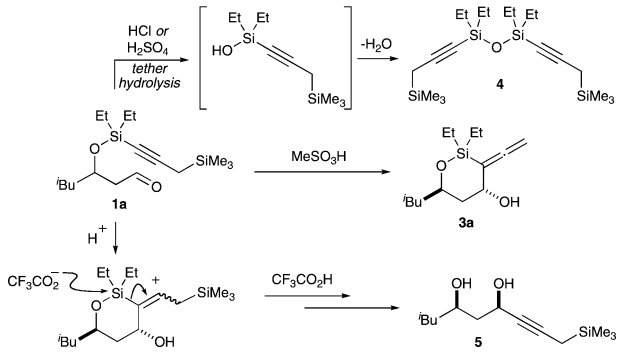
10.1021/jo702351s CCC: $40.75
Published on Web 01/16/2008

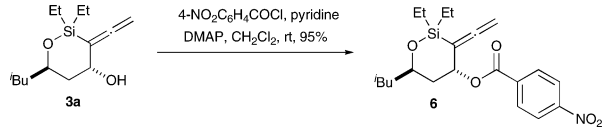
SCHEME 2. Brønsted Acid Mediated Intramolecular Allenylation



SCHEME 3. Of Brønsted Acids Screened, $MeSO_3H$ Was Most Effective for Accessing Desired Allenyl Oxasilacycle 3a



SCHEME 4. Relative Stereochemistry in Allenyl Alcohol Cyclization Product 3a Confirmed by Derivatization



susceptible to protodesilylation in the presence of Brønsted acids,[13] in related work we recently successfully carried out intramolecular allylation reactions involving allylsilanes using methanesulfonic acid without such competing processes being a problem.[11] We were therefore pleased to observe that treating a solution of **1a** in CH_2Cl_2 with this same Brønsted acid also led to rapid consumption of starting material at −78 °C and the formation of a single oxasilacyclic allenyl alcohol, **3a**, in 66% yield (Scheme 2). Performing the reaction in the more polar solvent MeCN led to a complex mixture of products.

We examined a small range of other Brønsted acid activators in this reaction, although none offered any improvement: siloxane **4** was the only isolable product when the reaction was carried out in the presence of the mineral acids hydrochloric acid and sulfuric acid. This product results from preferential hydrolysis of the silyl ether connection in the starting material. When trifluoroacetic acid was employed, the desired allenyl oxasilacycle **3a** was again obtained, albeit in reduced yield (26%), along with small amounts of siloxane **4** and propargyl silane **5** (25%). The formation of the latter compound can again be rationalized by premature cleavage of the silyl ether connection (Scheme 3).[14]

The stereochemistry in the allenyl alcohol product **3a** was initially assigned by analogy with similar silyl ether products obtained from our previous studies employing TMSOTf as the activator;[2d] however, confirmation of our stereochemical assignment came from an X-ray structure of the 4-nitrobenzoate derivative **6**, which was prepared from alcohol **3a** under standard conditions (Scheme 4, Figure 1).

(13) (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761−786 and references therein. (b) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153−4156.

(14) It is not clear why this product was not observed when $MeSO_3H$ was employed as the activator.

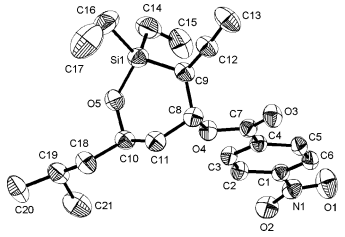


FIGURE 1. ORTEP plot of the 4-nitrobenzoate derivative of **3a** confirming the relative stereochemistry in the cyclization product. Atomic displacement parameters at 293 K are drawn at the 30% probability level.

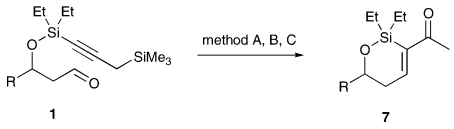
TABLE 1. Brønsted Acid Mediated Intramolecular Allenylation Provides an Alternative Cyclization Method to Our Lewis Acid Mediated Approach

entry	aldehyde	R	isolated yield **3** (%)	% yield of analogous TMS ether **2** obtained using TMSOTf activation (where available)[2d]
1	**1a**	*i*Bu	66	83
2	**1b**	(*E*)-styryl	57	73
3	**1c**	TIPS-alkynyl	60	85
4	**1d**	Ph-alkynyl	42	
5	**1e**	Ph	61	80

A small selection of aldehydes, each containing a propargylsilane tethered through a β-silyl ether connection, were reacted under our optimized conditions. The results suggest this method is fairly general and provides a useful alternative to our Lewis acid mediated intramolecular allenylation protocol. In all cases, the cyclization product is obtained as a single diastereoisomer; however, in comparison to the yields we generally obtain with our TMSOTf-mediated cyclizations, the yields of the allenyl alcohol products **3** are always slightly depressed owing to the formation of a second, less polar product (vide infra) (Table 1).

The best yields of allenyl alcohol **3** were obtained by carrying out the reaction with equimolar quantities of $MeSO_3H$ in CH_2Cl_2 at −78 °C. When the temperature of the reaction mixture was allowed to increase, the yield of allenyl alcohol **3** was further reduced owing to the formation of more of the second product, which was identified as the enone **7** in which the conjugated alkene can also be considered as a vinylsilane owing to the product's retention of the silyl ether connection. Careful monitoring of the reaction by TLC revealed allenyl alcohol **3** to be an intermediate en route to this novel cyclic enone. We now focused on optimizing the reaction conditions for accessing this interesting product. The best yields of enone were obtained by adding 1 equiv of $MeSO_3H$ to a solution of the starting aldehyde **1** in CH_2Cl_2 in the presence of 4 equiv of water at ambient temperature and, after 2−3 h, adding a further 1 equiv of the Brønsted acid to drive the reaction to completion. Using this procedure, enone **7a** was isolated in 78% yield. To probe the scope of this cascade process, a series of aldehydes **1** was exposed to our optimized reaction conditions. In most cases (entries 1, 4−6), the enone products were isolated in very good

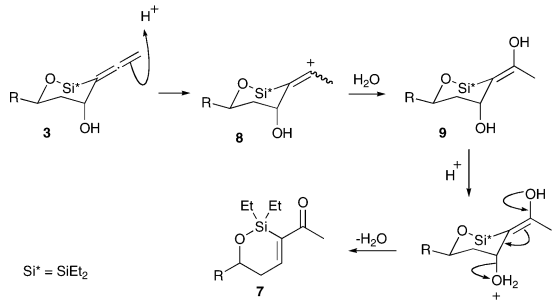
TABLE 2. Enone Synthesis



entry	aldehyde	R	method	isolated yield **7** (%)
1	**1a**	^{i}Bu	A[a]	78
2	**1b**	(*E*)-styryl	B[b]	42[d]
3	**1d**	Ph-alkynyl	B[b]	29[d]
4	**1e**	Ph	A[a]	73
5	**1f**	^{n}Bu	A[a]	78
6	**1g**	BnOCH$_2$CH$_2$	A[a]	71
7	**1h**	Me	C[c]	46[d]

[a] 2 equiv of $MeSO_3H$, 4 equiv of H_2O, CH_2Cl_2, rt. [b] (a) 1 equiv of $MeSO_3H$, CH_2Cl_2, −78 °C; (b) 2 equiv of $MeSO_3H$, 4 equiv of H_2O, CH_2Cl_2, rt. [c] (a) 1 equiv of Me_3SiOTf, TTBP, CH_2Cl_2, −78 °C; (b) 2 equiv of $MeSO_3H$, 4 equiv of H_2O, CH_2Cl_2, rt. [d] Isolated yield of enone over two steps.

SCHEME 5. Possible Mechanism for Formation of Enone 7

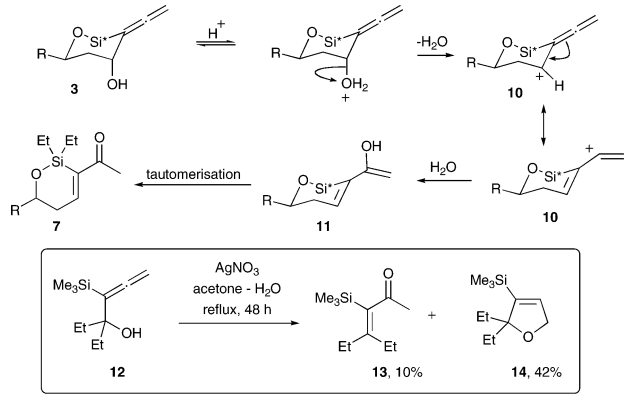


yield. In other cases (entries 2, 3, 7), improved yields of enone product were obtained by performing the transformation in two stages, i.e., first carrying out the intramolecular allenylation under Brønsted acid or Lewis acid conditions and then treating the product from this reaction with $MeSO_3H$ to effect enone formation. The results are summarized in Table 2.

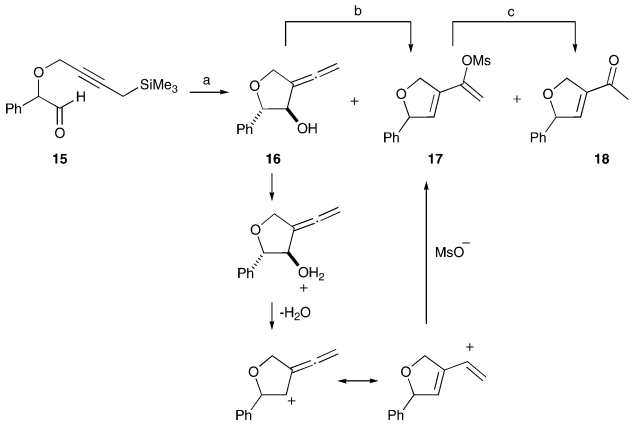
The conversion of aldehyde **1** into enone **7** represents an interesting cascade process involving a number of bond-forming and bond-breaking events. The fact that treatment of the first cyclization product, namely, allenyl alcohol **3** (or its trimethylsilyl ether **2h** (see entry 7, Table 2)), with acid also leads through to the enone confirms its intermediacy in the reaction. From here, a number of possible reaction pathways can be envisaged, which essentially differ in the order in which the keto group and olefin functionality of the enone are introduced (Schemes 5 and 6). Allenylsilanes have been shown to react with Brønsted acids through an S_E2' mechanism.[13b] If this happens in our system, reaction of the allenylsilane embedded within oxasilacycle **3** with acid would generate the carbocationic intermediate **8**, which can then be trapped with water (the reaction is far more effective when additional water is added) to provide enol **9** and thence enone **7** on dehydration.

Alternatively, protonation of the alcohol functionality in the first cyclization product **3**, followed by ionization, would generate allyl carbocation **10**. Trapping with water at the exocyclic terminus would afford enol **11** and enone **3** on tautomerization (Scheme 6). Wang and co-workers have reported that the reaction of trimethylsilyl-substituted α-allenyl alcohol **12** with aqueous silver(I) nitrate provides an enone **13** in addition to the desired 3-trimethylsilyl-2,5-dihydrofuran product **14** (Scheme 6).[15,16] Although they provide no evidence, they suggest a plausible mechanism in which Lewis acid

SCHEME 6. Alternative Mechanism for Formation of Enone 7, Similar to That Proposed by Wang and Co-workers



SCHEME 7. Reaction Time Affects Product Distribution When Aldehyde 15 Is Exposed to $MeSO_3H$[a]



[a] Reagents and conditions: (a) 1 equiv of $MeSO_3H$, $CHCl_3$, −60 °C, 5 min, **16** (55%), **17** (30%), **18** (trace); 15 min, **16** (trace), **17** (81%), **18** (10%); 30 min, **16** (trace), **17** (trace), **18** (88%); (b) 1 equiv of $MeSO_3H$, $CHCl_3$, −60 °C, 10 min, 90%; (c) 1 equiv of $MeSO_3H$, $CHCl_3$, −60 °C, 15 min, 91%.

mediated ionization of the alcohol affords a tertiary carbocation, which is subsequently trapped with water at the allylic position to provide an enol product and thence enone **13** on tautomerization.

Results from a related study within our group shed more light on the reaction mechanism.[17] We have found that the reaction of aldehyde **15**,[18] which contains a propargylsilane nucleophile tethered through an ether linkage to the electrophilic component, with $MeSO_3H$ in $CHCl_3$ at −60 °C provides a range of products depending on the reaction time (Scheme 7). When the reaction is quenched after 5 min, the allenyl alcohol cyclization product **16** is produced with excellent stereoselectivity (>20:1)[19] in 55% isolated yield,[20] along with enol mesylate **17** in 30% yield and

(15) Nikam, S. S.; Chu, K.-H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745−747.

(16) Yokozawa has also reported enone byproducts from the reaction of certain allenylsilanes with aldehydes and methoxytrimethylsilane in the presence of a Lewis acid; however, since these products contain two molecules of the aldehyde, they are formed by a pathway that is not operating in our system: Niimi, L.; Hiraoka, S.; Yokozawa, T. *Tetrahedron* **2002**, *58*, 245−252.

(17) See also: Clive, D. L. J.; He, X.; Postema, M. H. D.; Mashimbye, M. J. *J. Org. Chem.* **1999**, *64*, 4397−4410.

(18) Readily prepared from ethyl mandelate; see Supporting Information.

a trace of enone **18**. If the reaction is left for 15 min, enol mesylate **17** can be isolated in 81% yield, along with enone **18** in 10% yield; extending the reaction time to 30 min provides a good route to enone **18**, which can be isolated under these conditions in 88% yield. Allenyl alcohol **16** can be converted separately into enol mesylate **17**, and enol mesylate **17** into enone **18** (Scheme 7), which confirms the intermediacy of **16** and **17** en route to enone **18**. The formation of enol mesylate **17** provides good evidence for dehydration preceding keto formation; were reaction to proceed by initial protonation on the allene, enol mesylate **17** would not be expected. External trapping of the intermediate carbocation by the methanesulfonate conjugate base also rules out the possibility, at least in this system, that the OH functionality within the allenyl alcohol traps the cationic intermediate intramolecularly.

In summary, we have shown that a Brønsted acid can be used to effect the intramolecular allenylation of aldehyde **1** to provide the corresponding allenyl alcohol oxasilacycle **3** as a single diastereoisomer, whose relative stereochemistry has been confirmed by X-ray crystallography. The best results are obtained by employing short reaction times and low temperatures. When the reaction is performed at elevated temperatures and with an excess of acid, the allenyl alcohol cyclization product reacts further to provide a cyclic enone **7** in which the conjugated alkene can also be considered as a vinylsilane. Possible mechanisms to rationalize the outcome of this cascade process have been proposed. The isolation of an enol mesylate from a similar reaction on a related substrate supports a mechanism in which dehydration and installation of the vinylsilane precede ketone formation. It is noteworthy that all possible mechanisms involve cationic intermediates, which possess a β-C−Si bond. Such species are potentially susceptible to olefination pathways via cleavage of the C−Si bond; however, the fact that a product in which the C−Si bond is retained can be rationalized by poor orbital overlap between the C−Si bond and the leaving group/positively charged intermediates disfavoring these reaction pathways. The conversion of aldehyde **1** into enone **7** represents an unusual cascade process. The enone product is ripe for further elaboration and a useful starting point for diversity-oriented synthesis. Future work will investigate the reactivity of the enone with this in mind.

(19) Although it is not significant for the present study, we have assigned the major diastereoisomer as the *anti* product by comparison with related work: Jervis, P. J.; Cox, L. R. Unpublished results (see Supporting Information).

(20) The yield of this product can be improved to 84% by performing the reaction in CH_2Cl_2 at −78 °C for 2 min.

Experimental Section

General Procedure for the Synthesis of Enone 7 from Aldehyde 1. $MeSO_3H$ (65 μL, 1.0 mmol) was added dropwise over 5 min to a solution of aldehyde **1** (1.0 mmol) in CH_2Cl_2 (10 mL) and H_2O (72 μL, 4.0 mmol) at room temperature. TLC monitoring of the reaction generally showed consumption of the starting material after 5−20 min and full conversion of the intermediate allenyl alcohol **3** to the desired enone product within 2 h. If necessary, more $MeSO_3H$ (65 μL, 1.0 mmol) was then added. After a further 2 h, the reaction mixture was cooled to 0 °C and quenched by the addition of $NaHCO_3$ solution (10 mL), and the biphasic mixture was allowed to warm to room temperature. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography (eluent, EtOAc in hexane) afforded enone **7** as a colorless oil.

Acknowledgment. We thank Merck, Sharp & Dohme and the University of Birmingham for a studentship (to R.R.) and the Engineering and Physical Sciences Research Council and University of Birmingham for a studentship (to P.J.J.).

Supporting Information Available: General experimental details, experimental procedures and complete compound characterization data for all new compounds, scanned ^{1}H NMR and ^{13}C NMR spectra for all new compounds, and a CIF file for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702351S