Direct Preparation of *Z*-1,3-Enyne Systems with a TMS-Propargylic Sulfone: Application of a One-Pot Julia Olefination

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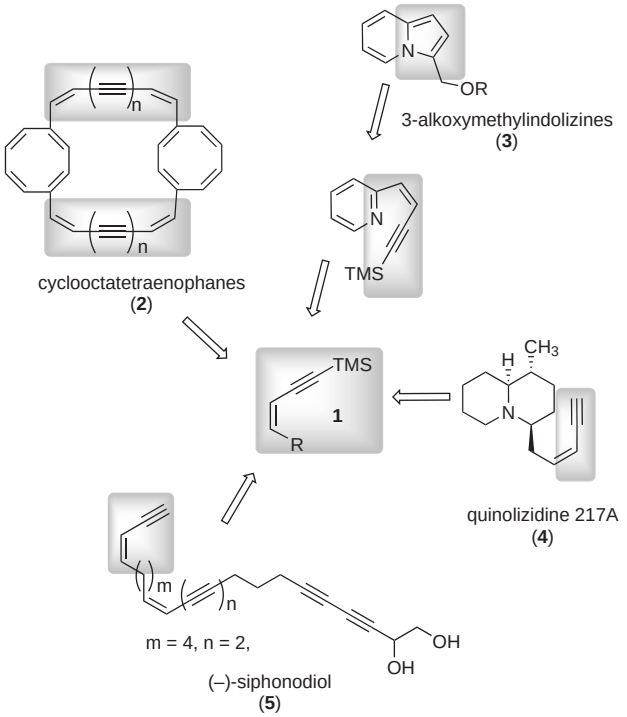
Abstract: A benzothiazolyl TMS-propargylic sulfone was subjected to one-pot Julia olefinations with a variety of aliphatic and aromatic aldehydes. Predominant *Z*-selectivity up to 98:2 and good chemical yields were obtained in a facile route to the desired *Z*-1,3-enyne moieties.

Key words: enynes, olefination, aldehydes, propargylic sulfones, natural products

Vinylacetylenes are important and direct precursors of conjugated π-systems, including dienic, diacetylenic and aromatic compounds which are common features in natural products.[1] Frameworks like **1** (Scheme 1) are frequently used in multistep syntheses of polyunsaturated compounds, suitable for subsequent coupling reactions after silyl deprotection. For example, the *Z*-1,3-enyne system is used in the preparation of cyclooctatetraenophanes (**2**)[2] and of 3-alkoxymethylindolizines (**3**),[3] the latter are potential new calcium entry blockers, chemotherapeutics and cardiovascular agents. The same moiety **1** is the key intermediate in several total syntheses of natural bioactive compounds like the alkaloid quinolizidine 217A (**4**)[4] and the (–)-siphonodiol (**5**),[5] an antifungal and antibacterial polyacetylene.

As part of our ongoing projects on natural product syntheses we are interested in the development of an efficient method for the construction of such *Z*-1,3-enyne system starting from an appropriate acetylenic compound, and in the subsequent stereocontrolled formation of the conjugated double bond. For highly regio- and stereoselective double-bond formation, compatible with multifunctionalized compounds, the most generally applicable methods involve the direct olefination of carbonyl compounds as in the Wittig,[6] Peterson,[7] Johnson,[8] classical Julia[9] and one-pot Julia[10] reactions, or the more recently developed olefin metathesis[11] and transition-metal-catalyzed cross-coupling[12] reactions.

Together with the seminal work on modified Julia olefination,[10c] we have found only a recent report[13] on the preparation of such enyne systems via one-pot reaction of propargylic sulfones with α,β-unsaturated aldehydes, but no applications in total syntheses. Moreover, the reported



Scheme 1

propargylic sulfones are alkyl-substituted at the end of the acetylenic bond (*n*-Bu and Me, respectively).

We have recently developed a simple and highly efficient procedure for the preparation of different propargylic sulfones starting from the corresponding propargylic alcohols.[14] We have chosen the TMS-propargylic sulfone for a general application of the one-pot Julia reaction. With both benzothiazoyl (BT) sulfones and phenyltetrazoyl (PT) sulfones in hand, we have attempted the olefination with benzaldehyde (Table 1), which was not used with propargylic sulfones in the previously reported olefinations.[10,13]

In the first attempts, olefination of sulfone **6a** was conducted at –55 °C in THF using KHMDS, according to the premetallated[15] or Barbier procedure.[16] Reactions afforded the required enyne **7** in 50% and 80% yields, with *Z*/*E* ratios of 87:13 and 96:4, respectively (Table 1, entries 1 and 2).

The same *Z*-selectivity was obtained in the olefination of sulfone **6a** with benzaldehyde using DME as solvent (31% yield, 98:2 *Z*/*E* ratio, entry 3 in Table 1). When

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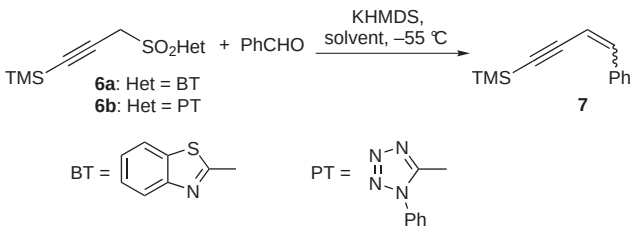
Table 1 Yields and *Z*/*E* Ratios for the One-Pot Julia Olefination of **6a**,**b** with PhCHO



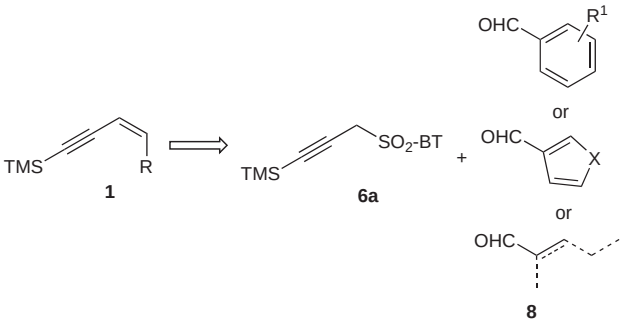
Entry	Sulfone	Solvent	Method **A**[a] or **B**[b]	Ratio *Z*/*E*[c]	Yields (%) of **7**[d]
1	**6a**	THF	**A**	87:13	50
2	**6a**	THF	**B**	**96:4**	**80**
3	**6a**	DME	**A**	98:2	31
4	**6b**	THF	**B**	98:2	38

[a] Method **A**: premetallated conditions: base added to sulfone, aldehyde added thereafter.
[b] Method **B**: Barbier conditions: base added to sulfone and aldehyde.
[c] The ratios were determined by GC-MS analysis.
[d] Yields (%) after chromatographic purification on silica gel.

PT-sulfone **6b** was used under the Barbier conditions in THF, enyne **7** was obtained in 38% yield and 98:2 *Z*/*E* ratio (entry 4).

Considering the results obtained in this preliminary study, we decided to utilize the more suitable sulfone **6a**[17] with different aldehydes.

In Scheme 2 we report our general strategy for the construction of *Z*-1,3-enyne systems like **1**, using aromatic, α,β-unsaturated and linear or branched alkyl aldehydes of type **8**.



Scheme 2 One-pot Julia olefination with propargylic BT-sulfone **6a**

Table 2 shows the results of the one-pot Julia olefination of a variety of aldehydes (1.5–1.6 equiv) using sulfone **6a** (1 equiv). Aromatic and α,β-unsaturated[18] aldehydes **8a**–**c** (entries 1–3), under both premetallated and Barbier conditions, led to enynes **1a**–**c** in 41–46% yields, in good to high *Z*-selectivities.

We then examined the reaction of **6a** with the linear and branched aliphatic aldehydes **8d**–**f** (entries 4–6, Table 2). Aldehyde **8d**, under Barbier conditions, afforded olefin **1d** in 23–44% yield with excellent *Z*-selectivity (*Z*/*E* = 93:7 ratio) and with a significant amount of self-condensation product.

Subsequently, in order to introduce chiral centers upon the enyne system, attempts were also made using functionalized enantiopure aldehydes like the known compounds **8e**[19] and **8f**,[20] which we had prepared for the stereoselective synthesis of natural products.

Using only method A, the same stereochemical trend was observed (entries 5 and 6 in Table 2): the obtained yields remained good and the *Z*-selectivity was still very high (56–76% in yields, >99:1 and 86:14 in *Z*/*E* ratios, for **1e** and **1f**, respectively).[21]

The moderate yields obtained in our protocols, although superior to the previously reported yields with similar substrates, are probably due to the formation of several by-products. Since the BT-sulfones particularly susceptible to nucleophilic attack at C2,[10] self-condensation and side reaction of the sulfone **6a** are likely. In fact, the unreacted aldehydes were recovered, while the sulfone disappeared completely. This was further demonstrated when **6a** and the base reacted under the typical conditions and resulted in volatile compounds and by-products. Moreover, under Barbier conditions utilized in many cases to improve the yields and to avoid side reactions, we obtained olefins **1a**–**d** with excellent *Z*/*E* ratios (from 93:7 to only *Z* isomer), without a general improvement in yields.

The stereochemical outcome of the one-pot Julia olefination is generally substrate-dependent (in this reaction, sulfone and aldehyde) and influenced by the reaction conditions. However, in our case, the reaction appeared to be controlled mainly by the propargylic sulfone **6**, and almost not influenced by the reacting aldehydes and by the reaction conditions.

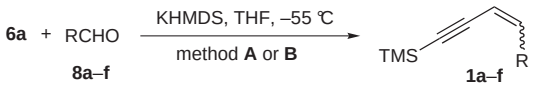
Remarkably, compound **1b**, recently prepared by a different protocol,[22] was obtained with our direct procedure in higher yield and stereoselectivity.

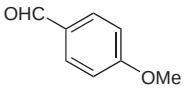
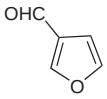
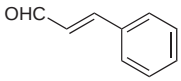
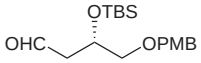
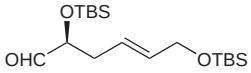
In summary, we have applied a direct and highly stereospecific methodology for the synthesis of *Z*-1,3-enynes, via a general one-pot Julia olefination of aldehydes. Different substituents in the aldehydes are also tolerated in the construction of the 1,3-enyne moieties, and a net increase in chemical yields has been observed with respect to previous reports.[10c,13]

Typical Premetallated Procedure

A solution of sulfone **6a** (1 equiv, 0.13 mmol) in THF (3 mL) at –55 °C was treated dropwise with KHMDS (0.5 M in toluene 1.2 equiv, 0.32 mL). The resulting brown solution was stirred at –55 °C for 30 min, and then aldehydes **8a**–**f** (1.5 equiv, 0.20 mmol) were slowly introduced. The mixture was stirred at –55 °C for 2–3 h, allowed to warm to r.t. for 1 h, and then diluted with Et_2O and washed with H_2O. The aqueous solution was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product by column chromatography on silica gel (PE–Et_2O, 95:5) gave olefins **1a**–**f** as yellow oils.

Table 2 Yields and *Z*/*E* Ratios for the One-Pot Julia Olefination of **6a** with Aldehydes **8a–f**



Entry	Aldehyde **8**	Product **1**	**A** or **B**	Ratio *Z*/*E*[a]	Yields (%)[b]
1	 **8a**	**1a**	**A** **B**	78:22 97:3	51 43
2	 **8b**	**1b**	**A** **B**	95:5 Only *Z*	50 41
3	 **8c**	**1c**	**A** **B**	66:43 94:6	42 46
4	$OHC(CH_2)_4OBn$ **8d**	**1d**	**A** **B**	79:21 93:7	44 23[c]
5	 **8e**	**1e**	**A**	Only *Z*	56
6	 **8f**	**1f**	**A**	86:14	76

[a] The ratios were determined by GC-MS analysis.
[b] Yields (%) after chromatographic purification on silica gel.
[c] A considerable amount of self-condensation product of the aldehyde was isolated after purification.

Typical Barbier Procedure

To a stirred solution of sulfone **6a** (1 equiv, 0.07 mmol) and aldehyde **8a**–**d** (1.6 equiv, 0.08 mmol) in THF (2 mL) at –55 °C KHMDS 0.5 M in toluene (1.2 equiv, 0.12 ml) was dropwise added. The resultant yellow solution was stirred at –55 °C for 4 h and allowed to warm to r.t. for 1 h. The mixture was then diluted with Et_2O and washed with H_2O. The aqueous solution was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product by column chromatography on silica gel (PE–Et_2O, 95:5) gave olefins **1a**–**d** as yellow oils.

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(15) Premetallated conditions*:* base added to sulfone, then aldehyde added.
(16) Barbier conditions*:* base added to the mixture of sulfone and aldehyde.
(17) Pent-2-ynyl BT-sulfone, reacting with benzaldehyde according to method A, afforded the corresponding enyne in only 18% yield but with 94:6 *Z*/*E* ratio.
(18) For other examples with high *cis*-selectivity during the one-pot Julia olefination of allyl benzothiazolyl sulfones with α,β-unsaturated aldehydes, see: (a) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1023. (b) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949. (c) Ref. 13. (d) Vaz, B.; Alvarez, R.; Souto, J. A.; de Lera, A. R. *Synlett* **2005**, 294. (e) Vaz, B.; Alvarez, R.; Brückner, R.; de Lera, A. R. *Org. Lett.* **2005**, *7*, 545.
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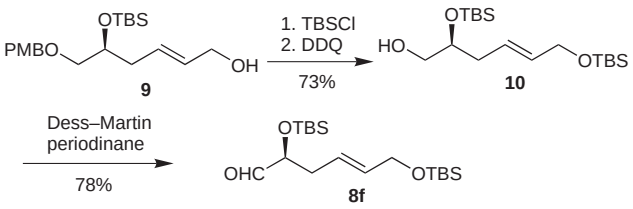
(20) Preparation of aldehyde **8f**, starting from the alcohol **9** (Scheme 3). Alcohol **9** was prepared according to: Bonini, C.; Chiummiento, L.; Videtta, V.; Colobert, F.; Solladié, G., *manuscript in preparation.*



Scheme 3

(21) No β-elimination product was observed for aldehyde **8e**. Moreover, the optical rotation for the unreacted aldehyde **8f** shows the same the value of the starting aldehyde, thus indicating that no epimerization reaction occurs.
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