ORGANIC LETTERS

2005
Vol. 7, No. 5
897−900

Sulfur Dioxide-Mediated Syntheses of Polyfunctional Alkenes and (*E*,*Z*)- and (*E*,*E*)-2,4-Dien-1-ones

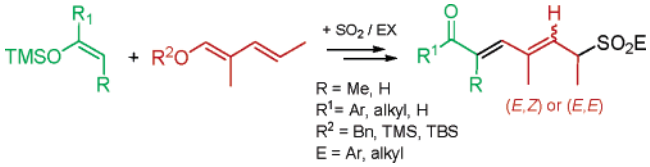
Laure C. Bouchez, Cotinica Craita, and Pierre Vogel*

Laboratoire de Glycochimie et de Synthèse Asymétrique (LGSA), BCH, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

pierre.vogel@epfl.ch

Received January 3, 2005

ABSTRACT

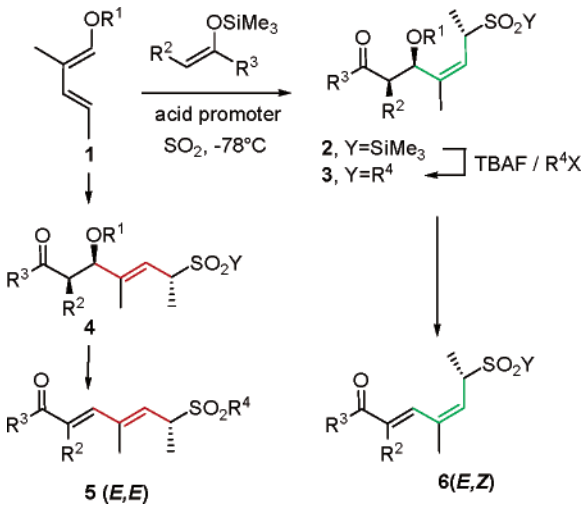


Efficient methods for the stereoselective synthesis of polyfunctional (*E*)- and (*Z*)-alkenes and conjugated (*E*,*E*)- and (*E*,*Z*)-dienones are presented. They rely upon one-pot, four-component processes that condense 1-oxy-1,3-dienes, silyl enol ethers, SO_2, and carbon electrophiles.

The great complexity of biologically active natural products now routinely tackled by total synthesis demands that the methods employed in such endeavors must be not only highly regio- and stereoselective but also compatible with the requisite multifunctional fragments. A variety of fundamentally different approaches to the synthesis of alkenes have been developed; however, none of them provides a universal solution to all the problems faced by synthetic chemists.[1] In earlier reports[2] we demonstrated that electron-rich dienes can be condensed with enoxysilanes in the presence of an excess of SO_2 and a catalytic amount of an acid promoter. This generates β,γ-unsaturated silyl sulfinates **2**[3] that can be alkylated or allylated in situ in the presence of TBAF to provide the corresponding sulfones **3** containing (*Z*)-alkene units exclusively (Scheme 1).

We present here an important extension of this methodology giving rise to polyfunctional sulfones **4** containing (*E*)-alkene units and up to three stereogenic centers. We report also that alkenes **3** and **4** can be converted into conjugated (*E*,*Z*)- and (*E*,*E*)-dienones of types **5** and **6**, respectively.

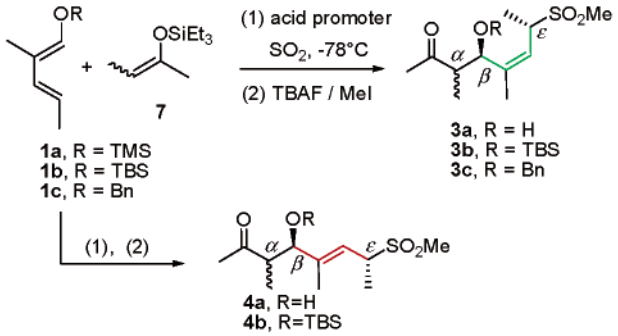
Scheme 1



(1) (a) See for example: Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
(2) (a) Deguin, B.; Roulet, J. M.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 6197. (b) Roulet, J. M.; Puhr, G.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 6202. (c) Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66* (15), 5080. (d) Turks, M.; Murcia, M. C.; Scopelliti, R.; Vogel, P. *Org. Lett.* **2004**, 6, 3031.
(3) Huang, X.; Vogel, P. *Synthesis* **2002**, 232.

10.1021/ol050006z CCC: $30.25
Published on Web 02/09/2005

Table 1



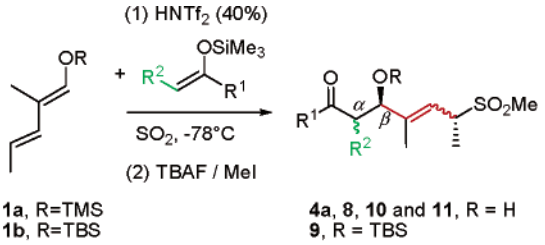
entry	acid	%	*E*/*Z*	product[a]	yield %
1	TBSOTf	12%	*Z*	**3a**	58%
2	$HNTf_2$	5%	*Z*	**3a**	66%
3	$HNTf_2$	45%	*E*	**4a**	71%
4	$TMSNTf_2$	45%	*Z*	**3a**	72%
5	TfOH	3%	*E*	**4a**	79%
6	TfOH	3%	*E*	**4b**	69%
7	TfOH	3%	*Z*	**3c**	62%

[a] Structures of compounds are established by ^{1}H NMR and two-dimensional NOESY ^{1}H NMR experiments. Compounds obtained as 1:1 mixtures of α,*β*-syn and α,*β*-anti diastereoisomeric ketones containing (*Z*)- and/or (*E*)-alkene units.

In a first series of assays, (*E*,*E*)-2-methyl-1-trimethylsilyloxy-1,3-diene (**1a**)[4] was condensed with a 3:2 mixture of (*Z*/*E*)-2-triethylsilyloxy-2-butene (**7**),[5] in the presence of a large excess of SO_2 (100 equiv) and a catalytic amount of an acid promoter. As expected, under standard conditions (12% of TBSOTf), only sulfone containing (*Z*)-alkene ((*Z*)-**3a**) was isolated (entry 1, Table 1). Replacing TBSOTf with $HNTf_2$ (from 5 to 45%; entries 2 and 3, Table 1) led to the formation of (*E*)-alkene ((*E*)-**4a**) instead of (*Z*)-**3a**. Above 50% $HNTf_2$, polymerization became a competitive reaction. Using $TMSNTf_2$ (entry 4, Table 1), prepared by mixing allyltrimethylsilane and $HNTf_2$, as an acid promoter, produced (*Z*)-**3a** as the major product. The same outcome was observed when exchanging (*E*,*E*)-2-methyl-1-trimethylsilyloxy-1,3-diene (**1a**) for (*E*,*E*)-2-methyl-1-{[*tert*(butyl)dimethylsilyl]oxy}-1,3-diene (**1b**)[6] (entry 6, Table 1). However, the reactions of alkoxydienes such as **1c** with acid promoters such as TBSOTf, $HNTf_2$, and TfOH failed to give the desired (*E*)-alkenes selectively (entry 7, Table 1). The best result was obtained using TfOH (3%). This suggests that the nature of the acid (protic, Lewis acid) is responsible for the (*E*)-/(*Z*)-selectivity, not its acidity. Protic acids are required for the selective formation of (*E*)-alkenes, at least when using dienes **1a** and **1b**.

We next explored the scope of the reaction of (*E*,*E*)-silyloxy-2-methylpenta-1,3-pentadienes **1a** and **1b** with different enoxysilanes in the presence of SO_2 and 0.4 equiv of $HNTf_2$. To our surprise, depending on the nature of the enoxysilanes, we found that either (*E*)-alkenes (**4a**, **8,** and **10**) or (*Z*)-alkenes (**9** and **11**) were formed (Table 2). These results suggest that the nature of the enoxysilanes (methyl-substituted or not) also affects the (*E*)-/(*Z*)-selectivity.

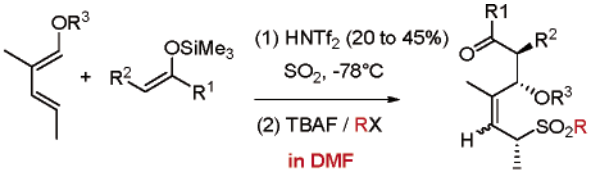
Table 2



entry	R^1	R^2	*E*/*Z*	syn/anti	product yield %
1	Ph	Me	*E*	3:1	**8,** 55%
2	2,4,6-$(MeO)_3C_6H_2$	Me	*E*	6:1	**9,** 90%
3[2c]	Ph	H	*Z*	-	**10,** 68%
4[2c]	Me	Me	*E*	2:1	**4a,** 83%
5	*t*-Bu	H	*Z*	-	**11,** 79%

To develop our methodology further, we examined the reactivity of a variety of electrophiles with our silyl sulfinate intermediates. Under standard conditions (1 M solution of TBAF in THF, CH_2Cl_2, −50 to 25 °C over 8 h), only simple electrophiles such as MeI, allyl-bromide derivatives, and substituted benzyl bromides reacted to provide the corresponding sulfones.[3] We found, however, that the exchange

Table 3



entry	R^1	R^2	R^3	RX (equiv)	*Z*/*E*	product	yield (%)
1[a]	*t*-Bu	H	TMS	**Et**I (2.5)	*Z*	**12**	20
2[a]	*t*-Bu	H	TMS	**Et**I (7)	*Z*	**12**	77
3	*t*-Bu	H	Bn	***n*-Bu**I (5)	*Z*	**13**	81
4[a,b]	Et	Me	TMS	***i*-Pr**I (5)	*Z*	**14**	62
5[b]	Me	Me	Bn	***i*-Pr**I (5)	*Z*	**15**	78
6[a,c]	Ph	H	TMS	**DNP**F (3)	*Z*	**16**	87
7[a]	*t*-Bu	H	TMS	**DNP**F (3)	*Z*	**17**	81
8[a,d]	Et	Me	TMS	**DNP**F (3)	*E*	**18**	76
9[a,d]	-$(CH_2)_4$-		TMS	**DNP**F (3)	*E*	**19**	55

[a] R^3 = H in isolated products, after chromatography. [b]Sulfones **14** and **15** were obtained as a 1:1 mixture of α,*β*-syn/α,*β*-anti diastereoisomers. [c]DNPF = 2,4-dinitrophenyl fluoride. [d]Sulfones **18** and **19** were obtained as 2:1 mixture of α,*β*-syn/α,*β*-anti diastereoisomers.

(4) Makin, S. M.; Kruglikova, R. I.; Shavrygina, O. A.; Chernyshev, A. I.; Popova, T. P.; Nguen Phyong Tung *Zh. Org. Khim.* **1982**, *18* (2), 287.
(5) (a) Ojima, I. *Organometallics* **1982**, *1*, 1390. (b) Ojima, I.; Korgue, T. *Tetrahedron Lett.* **1972**, *49*, 5085. Risk of explosion in the preparation of **7**: see Supporting Information.
(6) (a) Roulet, J.-M.; Puhr, G.; Vogel, P. *Tetrahedron Lett.* **1997**, *38* (35), 6201. (b) For more details about the preparation, see Supporting Information.

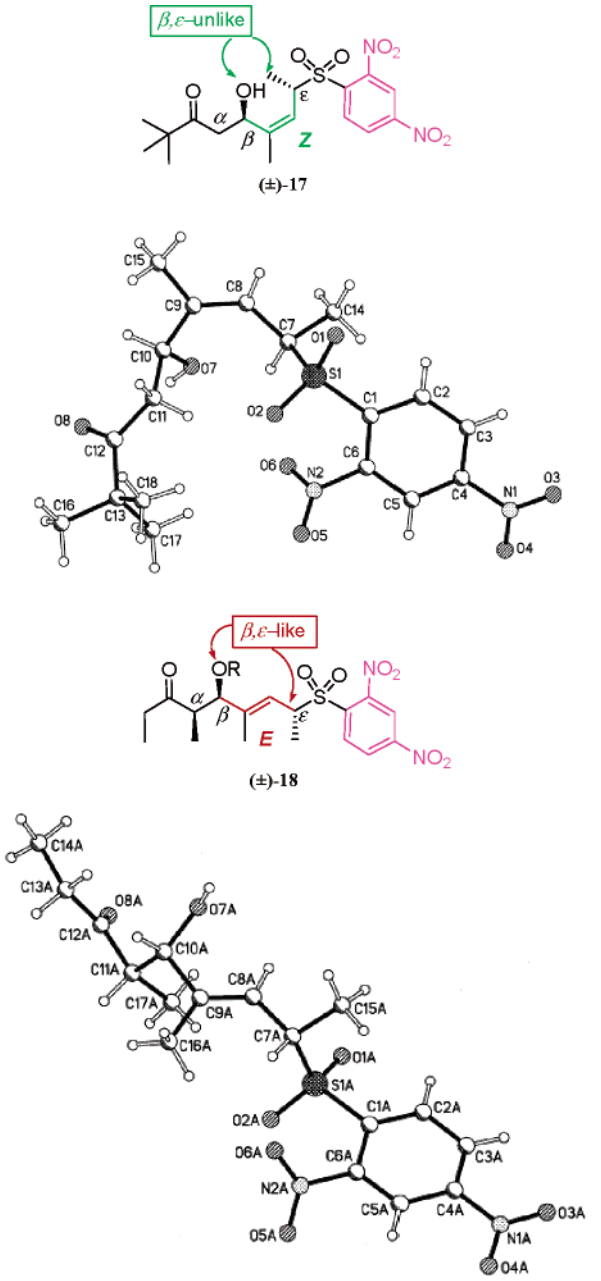
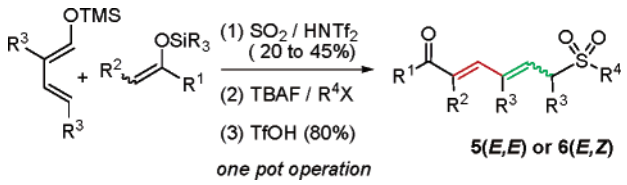


Figure 1.

of CH_2Cl_2 for a polar aprotic solvent (HMPA, DMF, or CH_3CN) allows this limitation to be overcome. To emphasize the flexibility and the reproducibility of these new conditions, dienes **1a** and **1c** were combined with a series of enoxysilanes and of electrophiles in the presence of 0.2 equiv of $HNTf_2$ and an excess of SO_2 (100 equiv). This led to the corresponding sulfones **12**−**19** that were isolated in high yield (Table 3).

To our knowledge, this is the first time that aryl-substituted sulfones of type of **16**−**19** have been prepared from silyl sulfinates. The structures of **12**−**19** were suggested by their spectral data (two-dimensional NOESY ^{1}H NMR). The α,β and β,ϵ relative configurations and alkene configuration of

Table 4



entry	R^1	R^2	R^3	R^4	5*E*/*Z*	product	yield %
1	Me	Me	Me	methallyl	5*Z*	**6b**	75
2	Me	Me	H	*n*-Bu	5*E*	**5a**	52
3	Et	Me	Me	DNP[a]	5*E*	**5b**	62
4	Ph	H	Me	DNP	5*Z*	**6c**	68
5	Me	Me	Me	Me	5*E*	**5c**	59

[a] DNP = 2,4-dinitrophenyl.

products **17** and **18** have been established unambiguously by X-ray crystallography[7] (Figure 1). By analogy, we proposed that the same stereocontrol occurs in all reactions affording (*E*)-alkenes and that it leads to a β,ϵ-like relationship. As for all the related systems reported so far,[8] (*Z*)-alkene **17** shows a β,ϵ-unlike relationship.

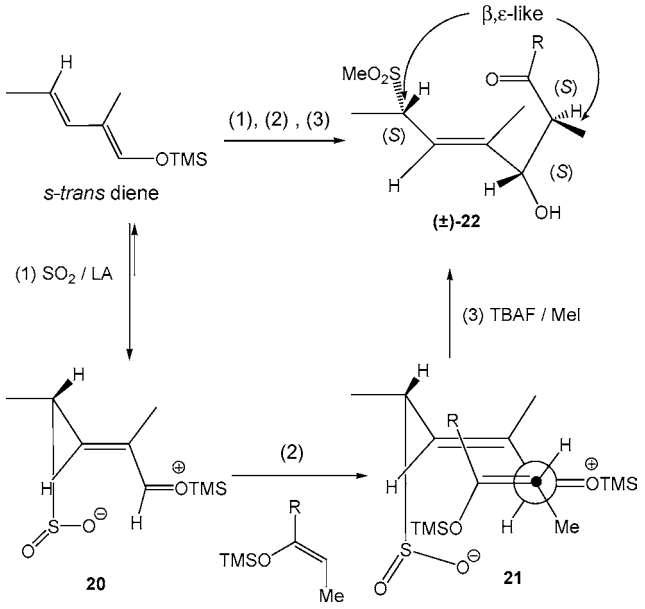
It is important to note that the formation of the (*E*)-alkene follows a different route than the formation of its (*Z*)-isomer and it does not result from its isomerization during the course of the reaction due to the acidity of the SO_2 combined to the acid promoter. Indeed, even after 3 days, when the reaction of (*Z*)-alkene ((*Z*)-**3a**) was performed with SO_2 and TfOH at −78 °C, (*Z*)-alkene ((*Z*)-**3a**) was not isomerized into its (*E*)-isomer. Moreover, after longer reaction time (1 week), only traces of product ((3*E*,5*Z*)-**5a**-diene) were observed. Additionally, the same observations were made with other (*E*)- and (*Z*)-alkenes. A straightforward preparation (one-pot operation, good yields) of the corresponding dienes (3*E*,5*Z*)-**5b**,**c** and (3*E*,5*E*)-**6a**−**c** was possible when TfOH (80%) was added directly after the oxyallylation process (Table 4). Structures of the new compounds were established unambiguously by their ^{1}H NMR and two-dimensional NOESY ^{1}H NMR spectra.

These results demonstrate that the formation of sulfones with (*E*)-alkene units follows a different route than that forming their (*Z*)-isomers. At this stage of the study, it would be too early to give an exact mechanism. However, we must admit that sulfur dioxide, activated by a strong protic acid, adds to the diene faster than the isomerization of the *s-trans*-conformer into the *s-cis*-diene. This leads to the formation of (*E*)-zwitterionic intermediates **20**. The latter add to enoxysilanes (oxyallylation) to give sulfinates **21** that can be alkylated or allylated in situ to provide the corresponding sulfones **22** with (*E*)-alkene units. Moreover, the β,ϵ-like

(7) Crystallographic data for **17** and **18** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-254537 (for **17**) and 254738 (for **18**), respectively.

(8) (a) Megevand, S.; Moore, J.; Schenk, K.; Vogel, P *Tetrahedron Lett.* **2001**, *42*, 673. (b) Narkevitch, V.; Schenk, K.; Vogel, P. *Angew. Chem., Int. Ed.* **2000**, *39* (10), 1806.

Scheme 2



relative configuration observed in this case can be interpreted in terms of the preferred formation of (*E*)-zwitterionic intermediates **20**, followed by addition of the enoxysilanes onto the face anti with respect to that occupied by the sulfinate moiety (Scheme 2).

In summary, our reaction cascade can be applied to generate a variety of open-chain polyfunctional sulfones with (*Z*)- and (*E*)-alkene units and containing up to three new stereogenic centers. Acidic treatment of the latter compounds generates the corresponding (*E*,*Z*)- and (*E*,*E*)-dienones in good yields and with high stereoselectivity.

A large number of enoxysilanes and electrophiles can be engaged, demonstrating the versatility of the method and, thus, adding to the molecular diversity. Further applications of this new methodology in the total synthesis of natural products and analogues will be reported in due course.

Acknowledgment. This work was supported by the Roche Research Foundation, the Swiss National Science Foundation (Grant 200020-100002), and the Office Fédéral de l'Enseignement et de la Recherche (COST D13/010/01). We thank Mr. S. Reddy Dubbaka for HRMS. We wish to thank Dr. Rosario Scopelliti for X-ray diffraction measurements.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050006Z