JOC Article

Sulfur Dioxide Mediated One-Pot, Three- and Four-Component Syntheses of Polyfunctional Sulfonamides and Sulfonic Esters: Study of the Stereoselectivity of the Ene Reaction of Sulfur Dioxide

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The ene reaction of sulfur dioxide with enoxysilanes or with allylsilanes generates silyl sulfinates that can be brominated (Br_2 or NBS) or chlorinated (NCS or Cl_2) to produce the corresponding sulfonyl halides. They react with primary and secondary amines or alcohols to give the corresponding sulfonamides and sulfonic esters, respectively. The hetero-Diels−Alder addition of sulfur dioxide to 1-oxy- or 1,3-dioxy-1,3-dienes generates zwitterions that add to enoxysilanes or allylsilanes giving silyl sulfinates that can be converted in situ into polyfunctional sulfonamides or sulfonic esters. This realizes quick access to libraries of complicated sulfonamides and sulfonic esters applying one-pot, three- and four-component methods.

Introduction

The sulfonamides constitute an important class of drugs (the sulfa drugs), with several types of pharmacological agents possessing antibacterial, anticarbonic anhydrase, diuretic hypoglycemic antithyroid, antihypertensive, antiinflammatory, and antiviral properties.[1,2] Recently, structurally novel sulfonamide derivatives have shown substantial antitumor activities,[3,4] or are caspase-1[5] inhibitors.[6] The majority of sulfonamides are prepared from the reaction of sulfonyl chlorides with ammonia and primary or secondary amines.[7] Arenesulfonyl chlorides are prepared from arenes by electrophilic substitution with $ClSO_3H$ or from arenesulfonic acids by reaction with PCl_5,[8] $POCl_3$,[9] or $COCl_2$.[10] Other methods imply the reactions of arenediazonium salts with $SO_2/CuCl_2$,[11] the oxidation of thioesters[12] or sulfenyl chlorides,[13] or the reaction of organolithium[14] or organomagnesium[15] reagents with SO_2Cl_2 or $SO_2 + Cl_2$. Alkanesulfonyl chlorides can be obtained by reaction of the corresponding

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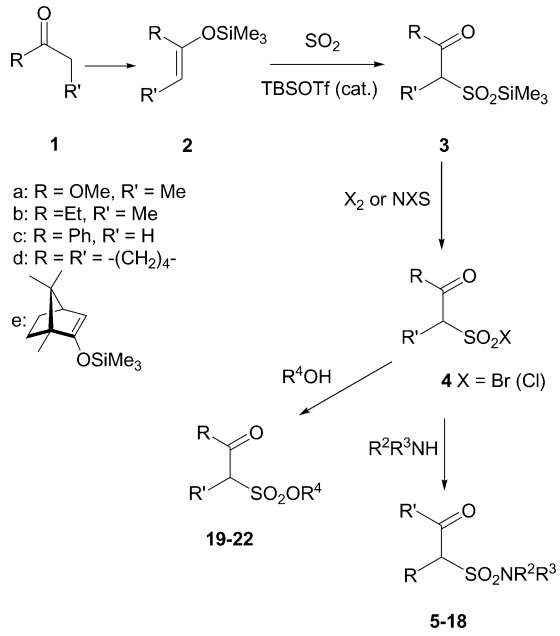
alkane with SO_2 and Cl_2 under radical conditions.[16] All these methods[17] are relatively harsh (acidic, basic) and cannot be applied to polyfunctional substrates. Recently the direct synthesis of sulfonamides and sulfonic esters from sulfonic acids[18] and a one-pot synthesis of sulfonamides from Grignard reagents and SO_2[18,19] has been reported. Both procedures are amenable to aromatic and heteroaromatic sulfonamides.

We disclose here unprecedented one-pot three- and four-component synthesis of sulfonamides and sulfonic esters that allow the easy preparation of polyfunctional derivatives that can contain keto β-alkoxyketone, allylic ether, alkenyl ester moieties, or/and β,γ-unsaturation and up to three stereogenic centers. The methods rely on recently discovered ene reactions of SO_2 with allylsilanes and enoxysilanes, on one hand,[20] and on our reaction cascade combining electron-rich 1,3-dienes and alkenes with sulfur dioxide, on the other hand.[21−23] Sulfonamides with the functional and stereochemical complexities of those described in this work would require multistep procedures applying available methods.[24]

Results and Disscusion

One-Pot, Three-Component Synthesis. In 1975, Grieco et al.[25] reported the ene reaction of sulfur dioxide with enoxysilanes derived from carboxylic esters. We have found that silyl enol ethers derived from acylic and cyclic ketones also undergo the ene reaction with SO_2 under the promotion of Lewis acids with the generation of the corresponding silyl β-oxoalkanesulfinates **3** (Scheme 1). As for trialkyltin sulfinates that can be oxidized into the corresponding sulfonyl halides by halogenosis by (Cl_2, Br_2, or I_2)[26,27] we found that silyl sulfinates **3** are readily converted into the corresponding sulfonyl chlorides **4** either by chlorination (Cl_2) or by treatment with *N*-chlorosuccinimide (NCS). The corresponding sulfonyl bromides can also be prepared by treatment of silyl sulfinates **3** by bromine (Br_2) or *N*-bromosuccinimide (NBS). Without purification, the crude sulfonyl halides react with primary and secondary amines in the presence of Et_3N or pyridine to give the corresponding sulfonamides **5**−**18** (entries 1−14, Table 1).

SCHEME 1. Preparation of Sulfonamides and Sulfonic Esters



To illustrate the method we reacted the trimethylsilyl enol ethers of methyl propanoate,[28] pentan-3-one,[28] acetophenone, cyclohexanone[29] and camphor[30] with an excess of SO_2 containing 5 mol % of (*t*-Bu)$Me_2SiOSO_2CF_3$, as acid promoter, in CH_2Cl_2 at −78 °C. Under these conditions only acyclic compounds **2a** and **2b** were converted into **3a** and **3b** in a few hours at −78 °C. With cyclic enol ethers **2d** and **2e**, ene reactions with SO_2 were only possible at higher temperatures such as 40 °C but with low yield due to decomposition of starting materials. We found that changing CH_2Cl_2 for CH_3CN dramatically enhanced the rates of the reaction. In the case of enoxysilanes **2d** and **2e** reactions were converted after a few hours at −78 °C. A mixture of SO_2/CH_3CN/*t*-Bu)Me_2-

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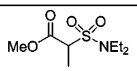
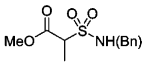
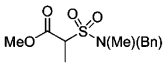
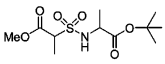
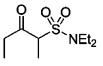
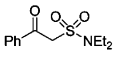
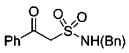
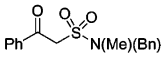
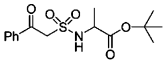
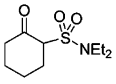
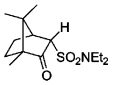
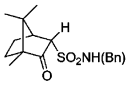
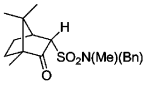
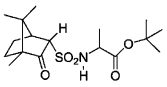
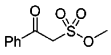
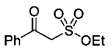
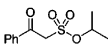
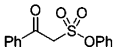
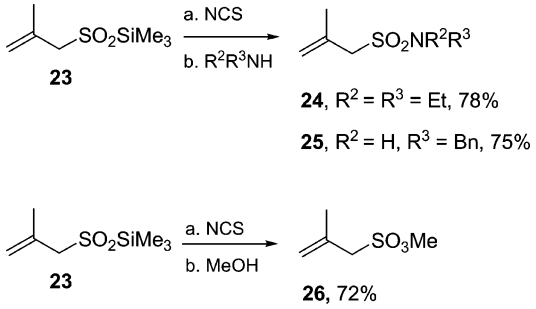
TABLE 1. One-Pot, Three-Component Synthesis of Sulfonamides 5−18 and Sulfonic Esters 19−22

entry	enoxysilanes	products	product No	yield
1	**2a**		**5**	65
2	**2a**		**6**	70
3	**2a**		**7**	65
4	**2a**		**8**	61
5	**2b**		**9**	88
6	**2c**		**10**	67
7	**2c**		**11**	65
8	**2c**		**12**	72
9	**2c**		**13**	57
10	**2d**		**14**	traces (67)[a]
11	**2e**		**15**	69
12	**2e**		**16**	60
13	**2e**		**17**	75
14	**2e**		**18**	58
15	**2c**		**19**	68[b]
16	**2c**		**20**	65
17	**2c**		**21**	30
18	**2c**		**22**	35

[a] Pyridine as base. [b] Without base.

SCHEME 2. One-Pot, Three-Component Syntheses of Allyl Sulfonamides and Allyl Sulfonic Esters



$SiOSO_2CF_3$ does not freeze at −78 °C. The excess of SO_2 and the solvent were evaporated from −78 °C to room temperature in vacuo before the oxidative workup at −20 °C with Cl_2 (or NCS) or Br_2 (or NBS) and subsequently treated with primary and secondary amines such as Et_2NH, $BnNH_2$, Bn(Me)NH, and *L*-*t*-BuOOC−CH(Me)NH_2 to give the corresponding sulfonamides **14**−**18** (entries 10−14, Table 1),[31] or with alcohols such as MeOH, EtOH, *i*-PrOH, or phenol to provide sulfonic esters **19**−**22** (entries 15−18, Table 1).

Product from the ene reaction of SO_2 with (2-methylpropen-1yl)trimethylsilane[20] **23** also underwent halogenolysis with NCS and subsequent reaction with Et_2NH, $BnNH_2$ to give the corresponding sulfonamides **24** and **25** (Scheme 2), or with alcohols such as MeOH to give the methyl sulfonate **26** (Scheme 2).

The structures of compounds **5**−**26** in Table 1 and Scheme 2 were established by their spectral data (see Supporting Information).

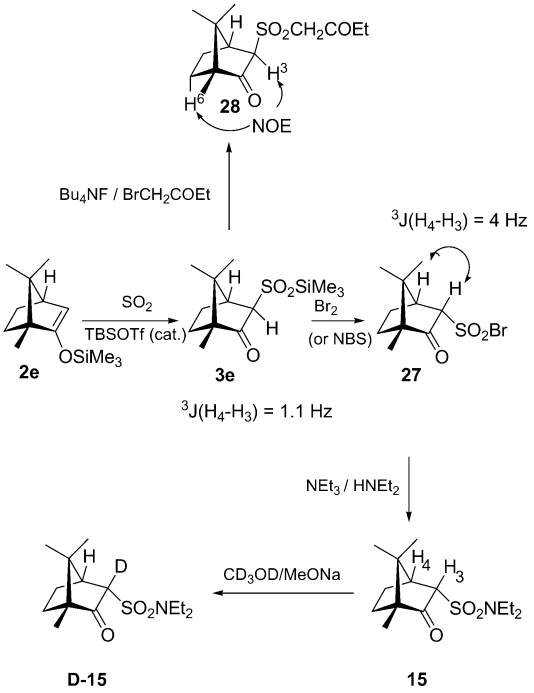
In the case of the camphor-derived sulfonamide **15**, its ^{1}H NMR spectra confirmed the endo configuration of the sulfonamide moiety as it showed relatively large vicinal coupling constants ^3J(H-3,H-4) = 4.0 Hz[32] as well as ^4J(H-3,H-5*exo*) = 1.4 Hz.[32] In the presence of MeONa in CD_3-OD, sulfonamide **15** was rapidly equilibrated with the deuterated **D-15** (Scheme 3). Subsequent addition of H_2O to the above CD_3OD/CD_3ONa solution of **D-15** led to the recovery of **15** showing that the exchange occurs without epimerization and that the endo configuration of the sulfonamide corresponds to the product of thermodynamic control. Thus, steric repulsions between the Me-C(7) and the *exo*-$SO_2NR^2R^3$ group make the exo sulfonamides less stable than their endo stereomers.

Interestingly, when running the ene reaction SO_2 + **2e** in a NMR tube, the ^{1}H NMR spectrum of the intermediate silyl sulfinate **3e** showed ^3J(H-3,H-4) = 1.1 Hz consistent with an exo configurated[32] sulfinic ester (Scheme 3). Halogenation of **3e** with either Br_2 or NBS gave **27**, the ^{1}H NMR spectrum of which showed ^3J (H-

(31) For other approaches to the synthesis of *N*-alkyl-2-oxo-alkanesulfonamides see: (a) Leclerc, M.; Brienne, M.-J. *Tetrahedron Lett.* **1990**, *31*, 3875. (b) Vega, J. A.; Molina, R.; Alajarin, R.; Vaguero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1992**, *33*, 3677. (c) Vega, J. A.; Alajarin, R.; Vaguero, J. J.; Alvarez-Builla, J. *Tetrahedron* **1998**, *54*, 3589. (d) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1970**, *5*, 345. (e) Truce, W. E.; Veiesen, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 2525. (f) Bender, A.; Günther, D.; Willims, L.; Winger, R. *Synthesis* **1985**, 66. (g) Bender, A.; Günther, D.; Winger, R. *Liebigs Ann. Chem.* **1985**, 579. (h) Thompson, M. E. *Synth. Commun.* **1988**, 733.

(32) Joela, H. *Org. Magn. Reson.* **1977**, *9*, 338 and references cited therein.

SCHEME 3. Kinetic versus Thermodynamic Control



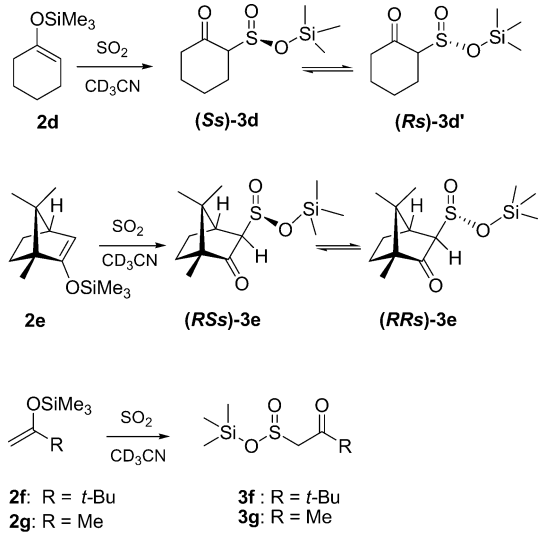
4, H-3) = 4.0 Hz. This demonstrates that the SO_2Br moiety in **27** occupies the endo position. The acidity of the reaction medium is thus capable of inducing exo → endo isomerization of the sulfonyl moiety. To confirm the exo configuration of silyl sulfinate **3e**, we treated it with Bu_4NF. This generated the corresponding tetrabutylammonium sulfinate, which was then reacted with 1-bromobutan-2-one giving the exo sulfone **28**. This compound was isolated in 92% yield and was fully characterized by its spectral data, including 2D NOESY ^1H NMR.

The formation of the exo silyl sulfinate **3e** demonstrates that the exo face of enoxysilane **2e** is preferred for the ene-reaction although the exo silyl sulfinate **3e** must be destabilized by steric factors as for the corresponding sulfonyl bromide and sulfonamides. We attribute the kinetic exo selectivity of the ene reaction of **2e** to the nonplanarity of the bicyclo[2.2.1]hept-2-ene alkene moiety that polarizes its π-electrons toward the exo face.[33]

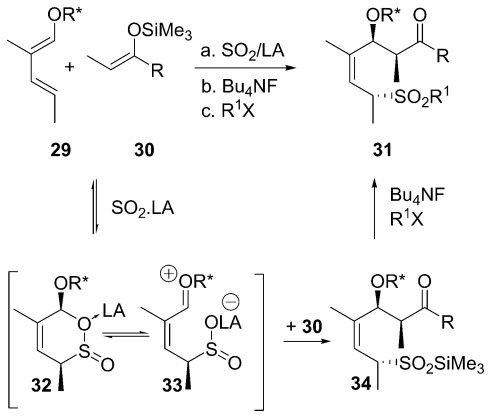
Diastereoselectivity of the Ene Reaction of Sulfur Dioxide. In the case of enoxysilane **2d**, the formation of the cyclohexanone-derived sulfinate **3d** was monitored by ^1H and ^{13}C NMR. When running the reaction in CD_3CN in the presence of a catalytical amount of the acid promoter (TBSOTf, 0.05 equiv) and an excess of SO_2 (15 equiv), the corresponding sulfinate **3d** was formed after 1 h at −60 °C and, to our surprise, only one single diastereoisomer was observed.

We decided to perform a second experiment in which the Lewis acid was suppressed and SO_2 was used as cosolvent (3:1, SO_2/CD_3CN). In this case, after 2 h at −40 °C, 75% of the starting material had been converted into a 6:4 mixture of two diastereoisomers. After 36 h at room temperature, the reaction was complete and the ratio of

SCHEME 4. Diastereoselectivity of the Ene Reaction of SO_2 with Enoxysilanes



SCHEME 5. C−C Bond Formation through Umpolung with Sulfur Dioxide: Four-Component Synthesis of Sulfones

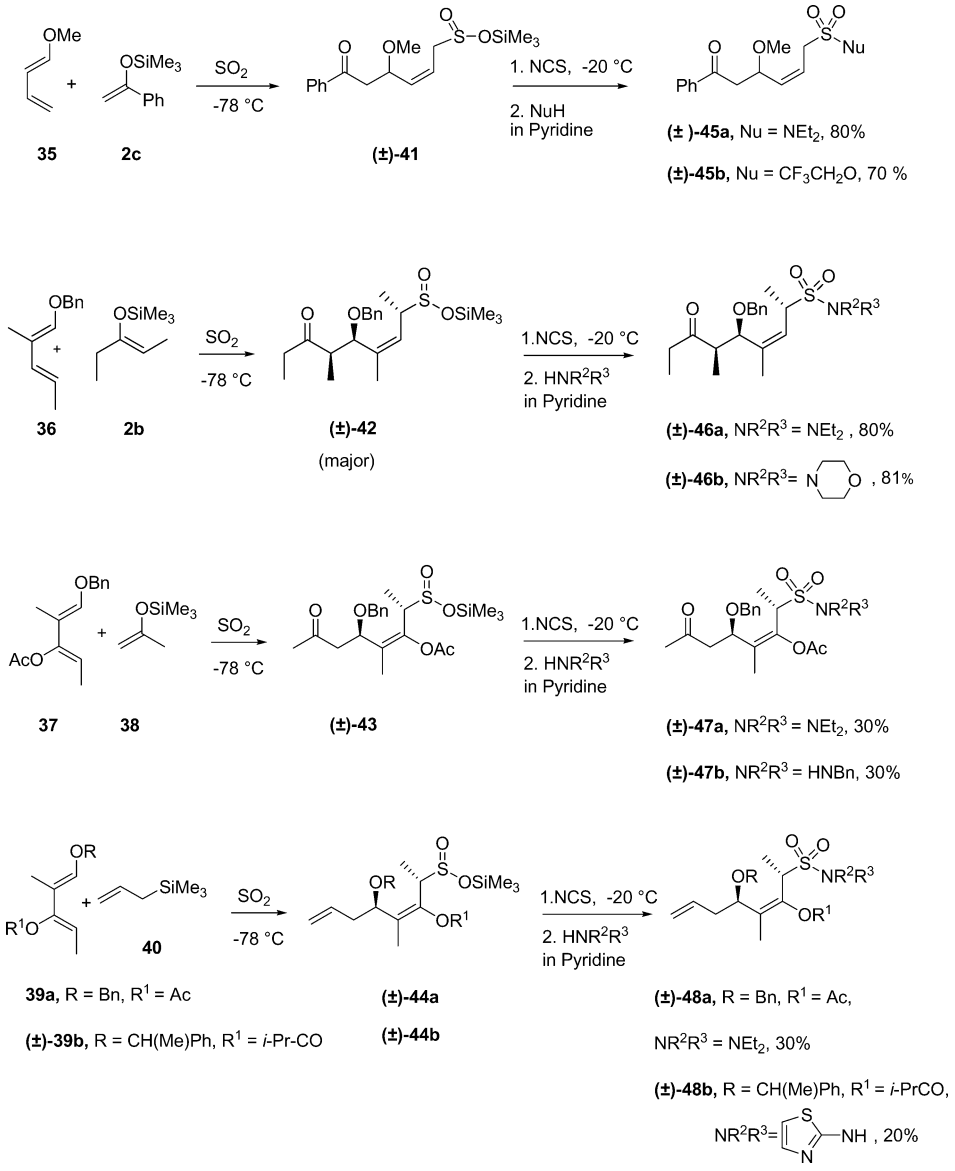


the two diastereoisomeric sulfinates was ca. 5:4. This experiment demonstrates that in acetonitrile, even if it takes a longer time, the ene reaction of SO_2 may occur without promotion by a strong (and destructive) Lewis acid. To exemplify this feature, we performed the ene reaction of SO_2 with enoxysilanes **2f** and **2g** without Lewis acid.

In addition, the same observations were made with the camphor-derived enoxysilane **2e**. When running the reaction in CD_3CN, in the presence of a catalytical amount of Lewis acid (TBSOTf, 0.05 equiv) and an excess of SO_2 (15 equiv), the formation of the corresponding sulfinate **3e** was complete after 20 min at −78 °C and a 95:5 mixture of two diastereoisomeric sulfinates ((*RSs*))-**3e** and (*RRs*)-**3e**) was obtained. The 95:5 product ratio did not change on longer standing at −78 °C or on increasing the temperature (decomposition above 20 °C). A second experiment without TBSOTf was performed with SO_2 + **2e**. After 2 h at −40 °C, **2e** was fully converted into a 95:5 mixture of two diastereoisomeric sulfinates. The product ratio changed from 95:5 to 75:25 after 6 h at −40 °C and finally reached 1:1 after 12 h at this same temperature and stayed unchanged after staying longer at −40 °C. Obviously, in both cases, **2d** and **2e**, the

(33) Jones, G. R.; Caldarelli, S.; Vogel, P. *Helv. Chim. Acta* **1997**, *80*, 59 and references therein.

SCHEME 6. Example of One-Pot, Four-Component Syntheses of Sulfonamides and Sulfonic Esters



diastereoisomers of **3d** and **3e** arise from the chirality of the sulfur atom in the silyl sulfinates (Scheme 4).

Our experiments demonstrate that the ene reaction of SO_2 with **2e** occurs under kinetic control giving a major silyl sulfinate. It then equilibrates with the thermodynamic diastereoisomeric sulfinate ((*RSs*))-**3e** ↔ (*RRs*)-**3e**). Both diastereoisomers (*RSs*)-**3e** and (*RRs*)-**3e** have *exo*-SO_2SiMe_3 groups. This isomerization probably implies the migration of the silyl group from one oxygen to the other of the SO_2SiMe_3 moiety. The same hypotheses can be retained for the reaction of SO_2 with monocyclic enol ether **2d**. Distinction between diastereomeric sulfinate pairs (*Ss*))-**3d** and (*Rs*)-**3d**, and (*RSs*))-**3e** and (*RRs*)-**3e** cannot be possible (Scheme 4). The relative structures of sulfinates **3d** and **3e** were deduced from their spectral data (see Supporting Information).

One-Pot, Four-Component Synthesis of Sulfonamides and Sulfonic Esters. Recently we reported[21,22] a new C−C bond-forming reaction **29** + **30** → **31** (Scheme 5), involving a cascade of reactions starting with the hetero-Diels−Alder addition of SO_2 to 1,3-dienyl ether **29**, giving the corresponding sultine **32**.[34] The latter is ionized into zwitterionic intermediate **33**, which then adds to enoxysilanes (oxyallylation) to give silyl sulfinate **34** that can be alkylated or allylated in situ providing the corresponding sulfones.[21,22] We have extended this reaction cascade to allylsilanes and to 1,3-dioxydienes.[23] We show now that the silyl sulfinates **34** and analogues obtained as intermediates in those reactions can be converted, as the simpler silyl sulfinates **3** and **23**, into polyfunctional sulfonamides or sulfonic esters.

As an illustration of the method we have combined (*E*)-1-methoxybutadiene (**35**) with enoxysilane **2c**, (*E*,*E*)-1-benzyloxy-2-methylpenta-1,3-diene (**36**) with enoxysilane

(34) (a) Roversi, E.; Scoppelliti; R.; Solari, E.; Estoppey, R.; Vogel, P.; Braña, P.; Menendez, B.; Sordo, J. A. *Chem. Eur. J.* **2002**, *8*, 1336. (b) Markovic, D.; Roversi, E.; Scoppelliti, R.; Vogel, P.; Meana, R.; Sordo, J. A. *Chem. Eur. J.* **2003**, *9*, 4911.

2b, (*E*,*E*)-1-benzyloxy-2-methylpenta-1,3-dien-3-yl acetate (**37**) with the trimethylsilyl enol ether of acetone (**38**), and racemic 1,3-dioxydienes **39a** and **39b** with allyltrimethylsilane (**40**) [23] in the presence of Lewis acid (LA). All the intermediate trimethylsilyl sulfinates (**41**−**44**) obtained in this way were converted into the corresponding sulfonyl chlorides by treatment with NCS at −20 °C in CH_2Cl_2 and, without isolation, they were reacted by representative amines in pyridine at −20 °C giving sulfonamides (**45a**, **46a**,**b**, **47a**,**b**, **48a**,**b**). Alternatively, quenching with alcohol/pyridine mixtures provided the corresponding sulfonic esters, as exemplified with **45b** (Scheme 6).

Conclusion

This work discloses efficient one-pot, three-component and four-component syntheses of sulfonamides and sulfonic esters. Polyfunctional systems are obtained under smooth reaction conditions and a high molecular diversity can be reached. Some of the keto-sulfonamides obtained can be seen as peptidomimetics. We have demonstrated also that the ene reaction of sulfur dioxide with enoxysilanes can be stereoselective as the hetero-Diels−Alder addition under conditions of kinetic control. Moreover, this kinetic selectivity is not controlled by the relative stability (Dimroth principle) of the two isomeric silyl sulfinate products of the pericyclic reaction. Investigations aiming at a further expansion of this new chemistry are actively pursued in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures, unknown compounds characterization, and references to known compounds as well as all spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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