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An expedient approach to *E,Z*-dienes using the Julia olefination

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Abstract—New reaction conditions were developed for the synthesis of *E,Z*-dienes from α,β-unsaturated aldehydes and heteroarylsulfones using the Julia reaction. In most cases under optimal conditions, the selectivity of the olefination reaction is better than 88:12 when a pyridylsulfone was used as the precursor. In addition, novel reaction conditions for the chemoselective oxidation of heteroarylthioethers that are compatible with alkenes and dienes are also reported.

The stereoselective synthesis of alkenes has represented one of the long-standing challenges in organic synthesis. Traditionally, the Wittig, Julia and other related olefination processes have played prominent roles in natural product synthesis containing *E*- or *Z*-alkenes.[1] Recently, olefin metathesis[2] and the transition metal-catalyzed cross coupling reactions[3] have been extensively used to generate stereodefined alkenes. Extension

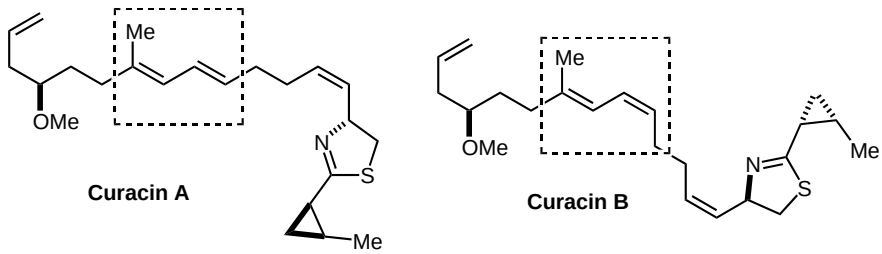
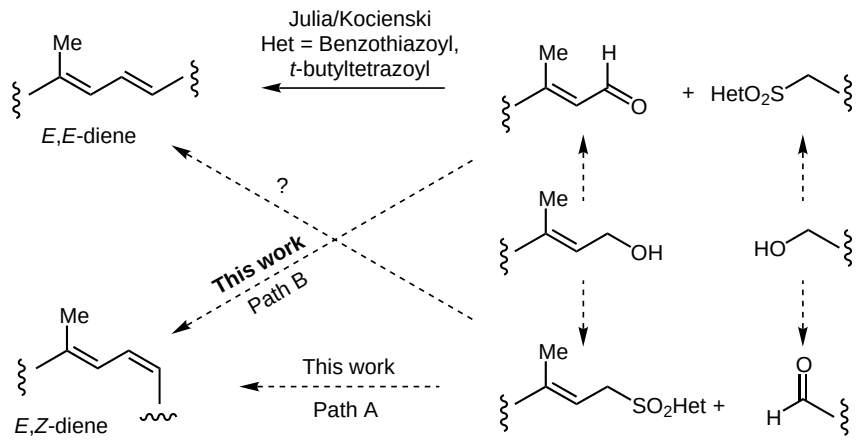


Figure 1. Structures of curacin A and B.



Scheme 1.

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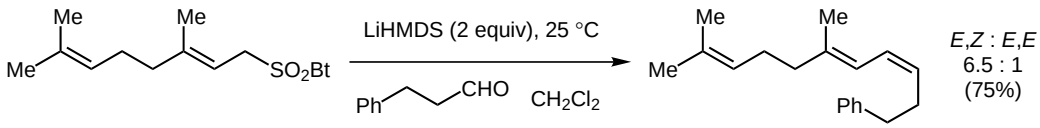
of these methodologies to the synthesis of *E*,*E*-dienes has also been quite successful. Conversely, the synthesis of *E*,*Z*-dienes by a C=C bond forming process is not that common.[4] Our interest in natural product synthesis containing *E*,*Z*-dienes prompted us to develop an alternative methodology for the synthesis of these subunits. Our strategy relies on the possible application of the novel Julia one-pot olefination reaction[5] or the Kocienski's modification[6] to the synthesis of *E*,*Z*-dienes. These methods have become quite versatile to synthesize either *E*-alkenes[7] as well as *E*,*E*-dienes.[8] These findings and our interest in synthesizing the structurally related curacin A[9] and B[10] from a common synthetic precursor prompted us to develop a new method to access to the *E*,*Z*-isomers based on the Julia/Kocienski one-pot olefination reaction (Fig. 1). In this paper, we have examined the possibility of accessing *E*,*Z*-dienes either by the coupling of an aldehyde with an allylic sulfone (Scheme 1, path A) or by the coupling of an α,β-unsaturated aldehyde with an alkylsulfone (Scheme 1, path B). Furthermore, we also disclose an efficient chemoselective oxidation protocol to prepare the starting sulfones that is compatible with alkenes and dienes.

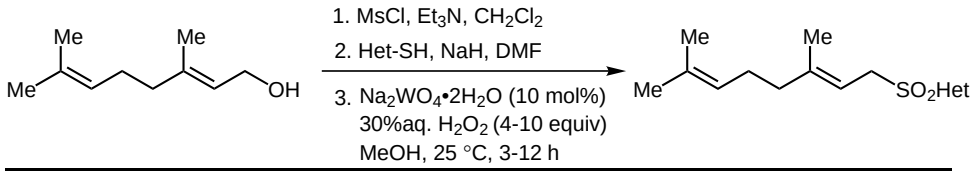
Preparation of heteroarylsulfones: oxidation of thioethers with H_2O_2/Na_2WO_4. The Julia precursors have been typically prepared by displacement of an halide or of an arylsulfonate by the arylthioxide followed by oxidation of the thioether to the sulfone. Although in some cases, MoOPh has been used as the oxidizing agent, MCPBA, ammonium molybdate[11] or oxone have been the reagents of choice. These reagents could sometimes lead to undesired side reactions when the oxidation is carried out in the presence of alkenes or dienes. For example, the oxidation of the benzothiazoyl ether derived from geraniol proceeded in very low yields when these reagents were used partially due to the competing oxidation of the alkenes or of the nitrogen-containing heterocyclic unit. After an extensive survey of the different reagents available to oxidize heteroarylthioethers, we observed that H_2O_2/Na_2WO_4[12] is a very effective combination for the chemoselective oxidation of heteroarylthioethers in the presence of alkenes. The oxidation reaction proceeded quantitatively with the benzothiazoyl- (Bt), pyridyl- (Pyr), and benzoimidazoyl- (Bi) thioethers and in good yields with the pyrimidyl- (Pym) and *N*-methylbenzoimidazoyl (Mbi) thioethers. Unfortunately, these conditions did not allow smooth oxidation of the *N*-phenyltetrazoylthioether (Pt) (Table 1, entry 6).

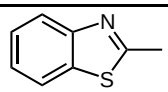
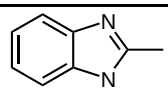
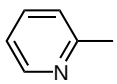
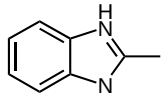
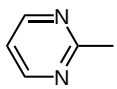
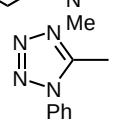
Coupling of allylic heteroarylsulfones with linear aldehydes (Scheme 1, path A). A wide range of different reaction conditions were tested to optimize the stereoselective coupling of allylic heteroarylsufones with 3-phenylpropanal. The best results obtained are complementary to those reported by Julia in that the best selectivity was observed when the reaction was carried out using the benzothiazoylsulfone and LHMDS in CH_2Cl_2 (Eq. (1)).[13] An extensive study of the different bases, solvent and temperature showed that these selectivities could not be increased with this substrate combination. Therefore, the alternative mode of coupling involving α,β-unsaturated aldehydes and alkylsulfones was investigated.



(1)

Table 1. Oxidation of thioethers to sulfones



Entry	Het	Thioether formation	Oxidation	Entry	Het	Thioether formation	Oxidation
1		84%	>95%	4		63%	>95%
2		71%	>95%	5		*a*	70%
3		77%	79%	6		90%	*b*

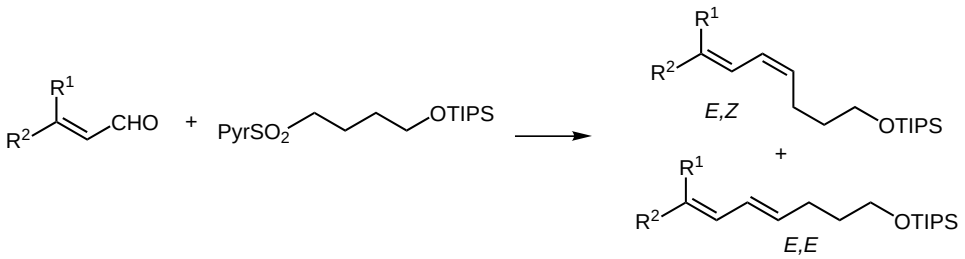
[a] The thioether was prepared by methylation (NaH, MeI) of the thioether prepared in entry 4.

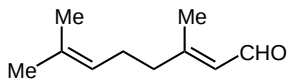
[b] In this case, the oxidation was more efficiently carried out in with MoOOPh (see Ref. 6a).

Coupling of heteroarylsulfones with α,β-unsaturated aldehydes (Scheme 1, path B). The coupling reactions of the various heteroarylsulfones (Het = Bt, Pyr, Pym, Bi, MBi, Pt) with α,β-unsaturated aldehydes were tested in different solvents, temperatures and using different bases. Extensive optimization indicated that the use of the 2-pyridyl sulfone was optimal to obtain high *E,Z*:*E,E* selectivities when NaHMDS or KHMDS was used as the base (Table 2). Another important feature of the 2-pyridyl sulfone unit is that unlike its benzothiazoyl- or its tetrazoyl-counterpart, the deprotonation can be accomplished with KHMDS in the absence of the aldehyde and the anion is stable at room temperature for at least 5 min.[5,6] Quite interestingly, the *E,Z*:*E,E* selectivities were higher if the coupling process was carried out at room temperature (entries 1–3). NaHMDS is also quite effective as the base but the isolated yields were slightly lower in some cases (entry 5). These conditions were quite effective with several aldehydes producing the *E,Z* isomer with excellent selectivities (88:12 to 91:9). Additional applications of this methodology to natural product synthesis will be reported in due course.

General procedure for the oxidation of heteroaromatic sulfones (Table 1, entry 2). To a solution of 2-[(2*E*)-3,7-dimethyl-2,6-octadienyl]sulfanylpyridine (510 mg, 2.05 mmol) in methanol (10 mL) at 0°C was added sodium tungstate dihydrate (68 mg, 0.51 mmol) followed by 30% aqueous H_2O_2 (2.1 mL, 20.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was then diluted with CH_2Cl_2 (10 mL) and a solution of 10% aqueous $NaHSO_3$ was added. The biphasic mixture was stirred for 15 min and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2×25 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 15% EtOAc/hexanes and filtered through a small pad of silica gel. Evaporation of the solvent afforded the pure sulfone as a colorless oil (570 mg, 99%): R_f 0.38 (15% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (dq, J=4.8, 1.0 Hz, 1H, C*H*), 7.91 (dt, J=7.8, 1.0 Hz, 1H, C*H*), 7.86 (td, J=7.6, 1.6 Hz, 1H, C*H*), 7.47 (dd, J=4.7, 1.2 Hz, 1H, C*H*), 5.05 (t, J=8.0 Hz, 1H, C*H*-CH_2SR), 4.85 (m, 1H, C*H*-CH_2R), 4.02 (d, J=8.0 Hz, 2H, CH_2SR), 1.86 (m, 4H, CH_2CH_2), 1.54 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.46 (*C*=N), 149.93 (*C*H), 146.33 (*C*q), 137.64 (*C*H), 131.48 (*C*q), 127.07 (*C*H), 123.02 (*C*H), 122.57 (*C*H), 109.11 (*C*H), 51.78 (*C*H_2), 39.28 (*C*H_2), 25.82 (*C*H_2), 25.32 (*C*H_3), 17.31 (*C*H_3), 16.16 (*C*H_3); IR (film): 3000, 2920, 1665, 1580, 1450, 1315, 1165, 1110, 1080, 990, 755 cm^{-1}; HRMS calcd for $C_{15}H_{22}NO_2S$ $(M+H)^+$: 280.1371. Found: 280.1364; Anal. calcd for $C_{15}H_{22}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.47. Found: C, 64.15; H, 7.62; N, 4.78; S, 11.49.

Table 2. Reaction of pyridylsulfones and α,β-unsaturated aldehydes



Entry	Aldehyde R^1	Aldehyde R^2	Conditions (base, solvent, temp.)	Yield [a] (%)	Ratio (*E,Z* : *E,E*) [b]
1	Me	H	KHMDS, toluene, -78 °C	35	84:16
2	Me	H	KHMDS, toluene, 0 °C	53	90:10
3	Me	H	KHMDS, toluene, 25 °C	67	91:9
4	Me	H	KHMDS, toluene, 25 °C	44 [c]	91:9
5	Me	H	NaHMDS, toluene, 25 °C	54	91:9
6	Pr	H	KHMDS, toluene, 25 °C	64	90:10
7	Ph	H	KHMDS, toluene, 25 °C	70	92:8
8			KHMDS, toluene, 25 °C	64	88:12
9			NaHMDS, toluene, 25 °C	73	83:17

[a] Isolated yield of analytically pure (^{1}H, ^{13}C, HRMS and/or elemental analysis) diene. [b] The ratio was determined by ^{1}H NMR or by capillary GC analysis. [c] In this entry, the base was added to a mixture of the aldehyde and sulfone.

General procedure for the *E,Z*-selective olefination. To a solution of 2-pyridyl sulfone **1** (120 mg, 0.323 mmol) in toluene (12 mL) was added dropwise a 0.5 M solution of KHMDS in toluene (1.29 mL, 0.646 mmol). The clear orange solution was stirred for 3 min and a toluene solution of crotonaldehyde (23 mg, 0.323 mmol in 500 μL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature. The solution was diluted with Et_2O and with saturated aqueous NH_4Cl. The layers were separated and the organic layer was washed with saturated, aqueous $NaHCO_3$, with brine and then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. An aliquot was analyzed by GC to determine the isomeric ratio of *E,Z*:*E,E* of 91:9. The crude was purified by silica gel column using 100% hexanes as eluent to produce the desired diene as a colorless oil (61 mg, 67%): R_f 0.19 (hexanes); IR (film): 3020, 2942, 2866, 1463, 1382, 1107, 983, 882, 680 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 6.56 (dd, $J_1=J_2=13.2$ Hz, 1H, Me-CH=C*H*=), 6.15 (dd, $J_1=J_2=10.8$ Hz, 1H, Me-CH=CH=C*H*=), 5.63 (dq, $J_1=14.8$, $J_2=6.7$ Hz, 1H, Me-C*H*=), 5.30 (dt, $J_1=10.6$, $J_2=8.0$ Hz, 1H, =C*H*-CH_2-CH_2-), 3.68 (t, $J=6.1$ Hz, 2H, CH_2-O-), 2.27 (dt, $J_1=J_2=7.3$ Hz, 2H, =CH-CH_2-CH_2-), 1.68 (approx. quintet, $J=6.4$ Hz, 2H, -CH_2-CH_2-CH_2-), 1.16 (m, 24H, C*H* (TIPS), CH_3 (TIPS), CH_3-CH=); ^{13}C NMR (100 MHz, C_6D_6): δ 126.92, 126.30, 125.25, 124.86, 59.98, 30.56, 21.50, 15.45, 9.50. Anal. Calcd for $C_{17}H_{34}OSi$: C, 72.27; H, 12.13. Found: C, 72.66; H, 12.53.

Acknowledgements

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11. See also Refs. 5–8 for specific examples illustrating the efficiency of various oxidizing agents. Julia (Ref. 5) has used ammonium molybdate to oxidize thioethers in the presence of alkenes.
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13. Julia has reported one example of the reaction between an allylic 2-pyridylsulfone and heptaldehyde that provided a 92:8 *E*,*Z*:*E*,*E* mixture of isomers when LDA and LiBr were used in THF (Ref. 5).