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Efficient Synthesis of Substituted Vinyl Ethers Using the Julia Olefination

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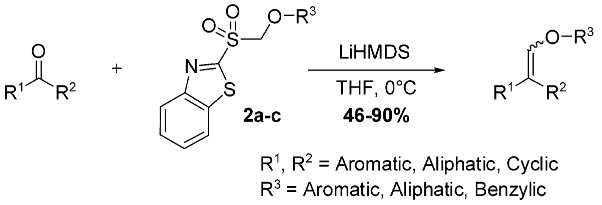
ABSTRACT

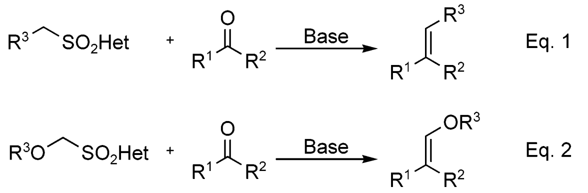


Julia olefination between α-alkoxy sulfones 2a–c and a wide variety of ketones or aldehydes afforded substituted vinyl ethers in 46–90% yields. Sulfones 2a–c were readily prepared in two steps from commercially available reagents in 68–80% yields. Optimization revealed that the nature of the base, the solvent, and the temperature were crucial to obtaining the desired vinyl ethers.

Vinyl ethers[1] have received considerable attention for their utility in many useful organic reactions such as Diels−Alder reaction,[2] Claisen rearrangement,[3] and aldehyde homologation,[4] as well as for their applications in the synthesis of polymers[5] and surfactants.[6] Formation of vinyl ethers through olefination of carbonyl compounds may suffer from low yields, the high temperature required, and the phosphine oxide formation, which may be difficult to remove from the desired products.[7,8] Alkoxymethyltriphenylphosphorane ylides are reportedly unstable and afford low yields of vinyl ethers with enolizable substrates.[7b,9] As part of our medicinal chemistry efforts, we were seeking an efficient method to prepare substituted vinyl ethers from ketones and aldehydes. We decided to explore the possibility of using α-alkoxy heteroaryl sulfones in a Julia olefination reaction as a potentially new way to synthesize vinyl ethers from enolizable carbonyl compounds.

The S. Julia olefination was used extensively in the last decade for the construction of alkenes present in many natural products (Scheme 1, eq 1).[10−11] However, to our knowledge, no such olefination has been achieved with an α-alkoxy substituent on the sulfone moiety. In this paper, we wish to

Scheme 1. Extension of the Modified Julia Olefination



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[1] (a) Maercker, A. *Org. React.* **1965**, *14*, 270. (b) See enol ethers and vinyl ethers in *Comprehensive Organic Synthesis*; Trost B. M.; Fleming I., Eds; Pergamon: Oxford, 1991; Vol. 9, Cumulative Indexes.

[2] (a) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537. (b) Pindur, U.; Gundula, L.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Part 4.1, pp 315.

[3] (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Part 7.2, pp 827. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

[4] Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.

[5] (a) Reyntjens, W. G. S.; Goethals, E. J. *Polym. Adv. Technol.* **2001**, *12*, 107−122. (b) Müller, H. W. J. *Vinyl Ethers Polymers*, 2nd ed.; Marcel Dekker: New York, 2001.

[6] Jong-Mok, K.; Thomson, D. H. *Dispersion Sci. Technol.* **2001**, *22*, 399.

[7] For Wittig olefination see: (a) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Böll, W.; Krück, K.-H. *Chem. Ber.* **1962**, *95*, 2514. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (d) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1. (e) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost B. M.; Fleming I., Eds; Pergamon: Oxford, 1991; Vol. 1, Part 3.1, pp 729.

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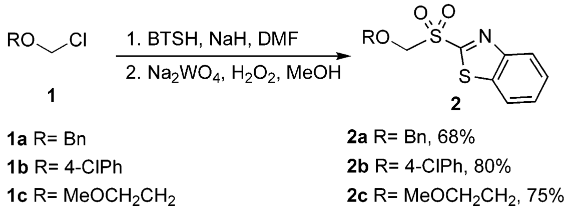
report the first examples of a modified Julia olefination using α-alkoxyheteroaryl sulfones to yield vinyl ethers (Scheme 1, eq 2).

Syntheses of the starting sulfone substrates were accomplished employing a two-step process from commercially available reagents. Three electronically and sterically different alkylating agents such as BOMCl, α,4-dichloroanisole, and MEMCl were coupled first with 2-mercaptobenzothiazole (BTSH) to afford the corresponding α-alkoxy-substituted thioethers in quantitative yields (Scheme 2).[12]

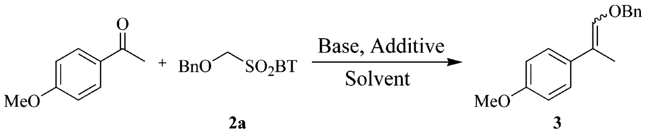
Scheme 2. Synthesis of α-Alkoxysulfones **2a−c**



Oxidation of these thioethers proceeded smoothly with a catalytic amount of sodium tungstate[13] in the presence of hydrogen peroxide to afford the desired α-alkoxysubstituted sulfones **2a−c** in 68−80% yields.

We first explored the coupling between sulfone **2a** and 4′-methoxyacetophenone (Table 1). The desired vinyl ether **3** was obtained in low yield with moderate *E*:*Z* selectivity by using KHMDS or NaHMDS (entries 1−4). Addition of HMPA to the reaction mixture increased the yield to 52% with a decrease in *E*:*Z* selectivity (entry 5). We were pleased to obtain the corresponding vinyl ether **3** in 87% yields by simply changing the base to LiHMDS (entry 6). Furthermore, we investigated the effect of temperature (−78 to 25 °C); reaction time;[14] amount of sulfone, base, and additive;[15] solvent (DMF, THF, DME, DCM, toluene); and order of addition[16] (Barbier or premetalate) on the vinyl ether formation. The best condition was the addition of LiHMDS to a mixture of sulfone and a carbonyl compound in THF at 0 °C.

Table 1. Exploration of the Reaction Conditions



entry	base[a]	solvent	additive[b]	yield (%)[c]	(*E*:*Z*)[d]
1	KHMDS	DME		13	84:16
2	KHMDS	THF		16	85:15
3	NaHMDS	DCM		39	86:14
4	NaHMDS	THF		21	80:20
5	NaHMDS	THF	HMPA	52	58:42
6	LiHMDS	THF		87	50:50
7	LiHMDS	THF		70[e]	50:50
8	LiHMDS	THF		84[f]	50:50
9	LiHMDS	THF	12-C-4	61	50:50
10	LiHMDS	THF	DMPU	35	42:58
11	LiHMDS	THF	HMPA	86	37:63
12	LiHMDS	THF	TMEDA	74	50:50
13	LiHMDS	THF		75[g]	58:42
14	LiHMDS	DMF		44	42:58
15	LDA	THF		44	50:50

[a] Base was added to a solution of ketone and sulfone **2a** at 0 °C. [b] Additive was added in the reaction mixture prior to base. [c] Isolated yields after purification. [d] *E*:*Z* ratio determined by ^{1}H NMR spectroscopy. [e] Performed with 1.5 equiv of base. [f] LiHMDS (1 M)/hexanes was used. [g] Reaction was run at −78 °C.

To evaluate the scope and limitations of this method, we performed the modified Julia olefination between sulfone **2a** and a variety of carbonyl compounds under the optimized reaction conditions (Table 2).

Enolizable carbonyl compounds bearing electron-donating and electron-withdrawing substituents afforded vinyl ethers **3−7** in 75−90% yields (entries 1−5).[17] Trifluoroacetophenone also underwent olefination in 82% yield (entry 6). Furthermore, a variety of enolizable aliphatic ketones, including a functionalized cyclopentanone and cyclohexanone, were successfully employed in this Julia

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(8) For Horner−Emmons−Wadsworth olefination, see: (a) Kluge, A. F. *Tetrahedron Lett.* **1978**, *19*, 3629. (b) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.

(9) See ref 4 and: Ferwanah, A.; Pressler, W.; Reichardt, C. *Tetrahedron Lett.* **1973**, 3979.

(10) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.

(11) For an excellent review on the modified Julia olefination, see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, *23*, 2563.

(12) Other heterocycles have been used. For PT, see: (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285. For PYR, see: Charette, A. B.; Berthelette, C.; St-Martin, D. *Tetrahedron Lett.* **2001**, *42*, 5149 and 6619. For TBT, see: Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365.

(13) (a) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140. (b) Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672.

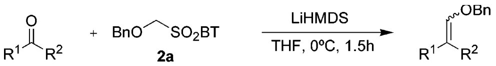
(14) Progress of the reaction was followed using a React-IR instrument, and all the reactions were completed between 15 and 90 min.

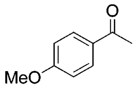
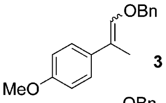
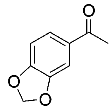
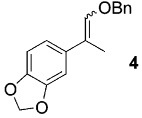
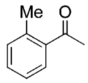
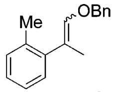
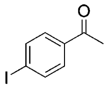
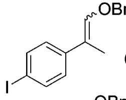
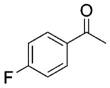
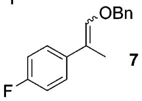
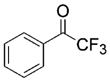
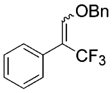
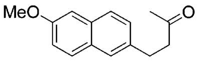
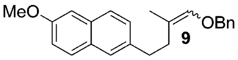
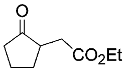
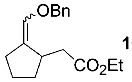
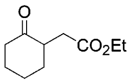
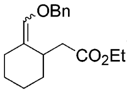
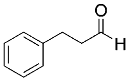
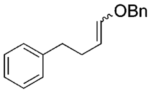
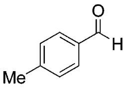
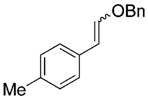
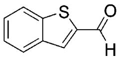
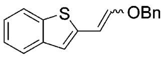
(15) Addition of 12-C-4, TMEDA, and DMPU failed to improve the yields and the *E*:*Z* selectivity.

(16) Barbier = base added to a mixture of sulfone and carbonyl; premetalate = base added to sulfone and then carbonyl added. Addition of base using a syringe pump over 30 min did not increase the yield or the *E*:*Z* ratio of vinyl ether **3**.

(17) **Representative Procedure for the Synthesis of Vinyl Ether 3.** To a solution of sulfone **2a** (498 mg, 1.56 mmol, 1.2 equiv) and 4′methoxyacetophenone (195 mg, 1.3 mmol, 1.0 equiv) in THF (15 mL, 0.085M) at 0 °C was added LiHMDS (3.1 mL, 3.1 mmol, 2.4 equiv, 1 M in THF) dropwise over 2 min. The reaction was stirred at 0 °C for 90 min, quenched with 20 mL of saturated NH_4Cl, extracted three times with 50 mL of EtOAc, washed with 20 mL of brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (0−20% EtOAc/Hex) to give vinyl ether **3** (287 mg, 87% yield) as a 1:1 *E*:*Z* mixture. ^{1}H NMR (500 MHz, acetone-d_6): δ (trans) 7.42−7.34 (m, 5H), 7.23 (d, $J = 7.2$ Hz, 2H), 6.84 (m, 2H), 6.66 (s, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 1.96 (s, 3H); δ (cis) 7.63 (d, $J = 7.3$ Hz, 2H), 7.42−7.29 (m, 5H), 6.84 (m, 2H), 6.33 (s, 1H), 4.91 (s, 2H), 3.76 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ (mixture of cis and trans) 153.03, 158.68, 143.69, 143.19, 139.06, 138.90, 133.72, 131.77, 129.39, 128.25, 128.59, 128.31, 128.23, 126.59, 114.49, 113.90, 110.88, 74.86, 74.39, 55.40, 55.33, 18.46, 12.93. HRMS (FAB) calcd for $C_{17}H_{19}O_2$ 255.1385, found 255.1385.

Table 2. Synthesis of Vinyl Ethers Using Sulfones **2a**

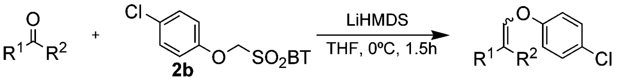


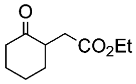
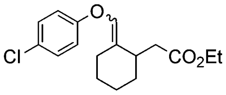
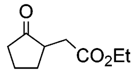
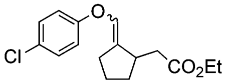
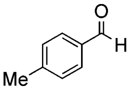
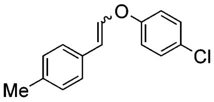
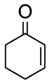
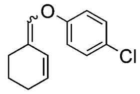
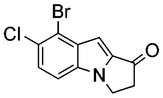
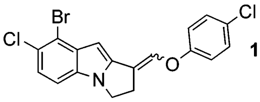
entry	carbonyl	product	yield (%)^a	(E:Z)^b
1		 **3**	87	50:50
2		 **4**	86	50:50
3		 **5**	79	68:32
4		 **6**	75	50:50
5		 **7**	90	52:48
6		 **8**	82	64:36
7		 **9**	86	60:40
8		 **10**	70	50:50
9		 **11**	71	67:33
10		 **12**	46	52:48
11		 **13**	73	50:50
12		 **14**	71	67:33

[a] Isolated yields after purification, average of two runs. [b] *E*:*Z* ratio determined by ^{1}H NMR spectroscopy.

olefination to afford vinyl ethers **10** and **11** in 70 and 71% yields, respectively (entries 8 and 9). In our hands, conventional methods using phosphonate or phosphorane reagents gave only low yields (10−40%) for the synthesis of vinyl ethers from cyclopentanone substrates. Finally, aliphatic and aromatic aldehydes gave vinyl ethers **12**−**14** in 46−73% yields (entries 10−12).[18]

Table 3. Steric and Electronic Effects of Sulfone **2b** for the Formation of Vinyl Ethers



entry	carbonyl	product	yield (%)^a	(E:Z)^b
1		 **15**	76	67:33
2		 **16**	75	50:50
3		 **17**	83	55:45
4		 **18**	71	57:43
5		 **19**	65	74:26

[a] Isolated yields after purification, average of two runs. [b] *E*:*Z* ratio determined by ^{1}H NMR spectroscopy.

We then turned our attention to a phenol substituent on the sulfone moiety in order to explore electronic and steric effects on the olefination reaction (Table 3).

Sulfone **2b** was first reacted with ethyl (2-oxocyclohexyl) acetate to afford vinyl ether **15** in 76% yield (entry 1). Similarly, the cyclopentanone analogue gave vinyl ether **16** in 75% yield (entry 2). Vinyl ether **17** was obtained in 83% yield from the corresponding 4-methylbenzaldehyde (entry 3). Furthermore, an α,*β*-unsaturated cyclohexenone was converted smoothly to vinyl ether **18** in 71% yield (entry 4). Finally, we explored the Julia olefination with an indolone and were pleased to form the corresponding vinyl ether **19** in 65% yield with an *E*:*Z* ratio of 74:26 (entry 5). All attempts to form vinyl ethers from indolones using conventional methods (Wittig or Horner−Emmons−Wadsworth) gave only low yields in our hands. The electronic and steric nature of the sulfone **2b** did not affect the yield or the selectivity of the Julia olefination.

It was reported that substituted vinyl ethers could be generated in moderate yields (38−63%) from the coupling of ketones with a MEM-phosphorane.[8] Therefore, we then decided to compare these results with our modified Julia olefination using sulfone **2c** (Table 4). Reaction of sulfone **2c** with acetophenone afforded the desired vinyl ether **20** in 86% yield (entry 1). This represents an improvement over the reported 37% using the MEM-phosphorane. Again,

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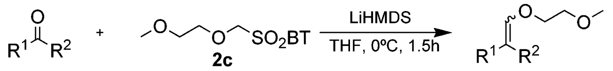
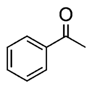
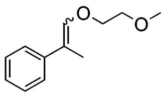
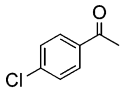
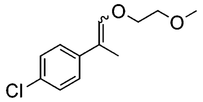
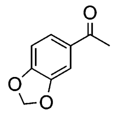
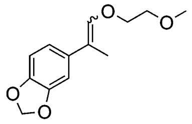
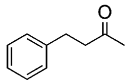
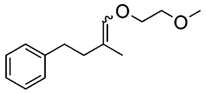
(18) Purification of vinyl ethers from aldehydes was conducted with Et_3N-treated silica gel to avoid decomposition to the homologated aldehydes.

Table 4. Effect of a MEM Substituent on the Sulfone Moiety



2c

entry	carbonyl	product		yield (%)[a]	(E:Z)[b]
1			**20**	86	57:43
2			**21**	87	62:38
3			**22**	76	57:43
4			**23**	83	57:43

[a] Isolated yields after purification. [b] *E*:*Z* ratio determined by ^{1}H NMR spectroscopy.

electron-rich or electron-poor acetophenone reacted well to afford the desired vinyl ethers **21** and **22** in 87 and 76% yield, respectively (entries 2−3). The reaction with aliphatic ketone afforded product **23** in 83% yield (entry 4).

In summary, we have demonstrated that substituted vinyl ethers are readily available from enolizable and nonenolizable carbonyl compounds in moderate to good yields (46−90%). We are currently extending this methodology to include other heterocycles on the sulfone moiety as well as attempting to improve the *E*:*Z* selectivity of this transformation.

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Supporting Information Available: Experimental procedure and characterization data for all new compounds (^{1}H, ^{13}C, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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