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OBSERVATIONS REGARDING THE FIRST STEP OF THE JULIA-LYTHGOE OLEFIN SYNTHESIS

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Abstract. *Using DME as a solvent in the addition of metallated sulfones to aldehydes can increase yields in the first step of the Julia-Lythgoe olefin synthesis. The addition of metallated sulfones to ketones is also discussed.* Copyright © 1996 Elsevier Science Ltd

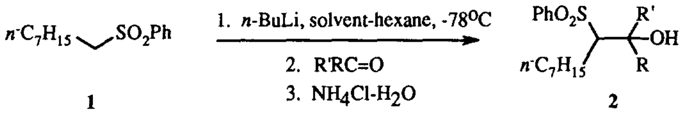
The first step of the Julia-Lythgoe olefin synthesis involves the addition of a metallated sulfone to an aldehyde or ketone.[1,2] Although this process has been widely used it is not without problems. For example, reactions with aldehydes have been complicated enolization and the addition of metallated sulfones to ketones has been regarded to have an unfavorable equilibrium between starting materials and the β-oxidosulfone adduct. During the course of a synthesis of himbacine,[3] we examined solvent effects on this process and made some observations that should extend the scope of the Julia-Lythgoe synthesis. Our results are reported herein.

We have made two potentially useful observations: (1) using 1,2-dimethoxyethane (DME) as the solvent reduces enolization problems in some instances[4-6] and (2) it is possible to add metallated sulfones to ketones in moderate to high yield using fairly standard reaction conditions in either tetrahydrofuran or DME.[7-12]

The results of a series of reactions between a primary and secondary metallated sulfone and a series of aldehydes and ketones are shown in Tables 1 and 2. Table 1 suggests that DME is the solvent of choice for reactions between metallated primary sulfones and unbranched aldehydes (entries 1-4).[13] There is little difference between DME and THF for an α-branched aldehyde (entries 5-6). Finally, ketones are reasonably good substrates for primary sulfones regardless of solvent (entries 7-12). A number of metallated sulfone-ketone addition reactions have been reported,[7-9] but these results came as surprise to us because it had been implied that a close relative of entry 7 was problematic due to the reversible addition issue (*vide supra*).[2a] After completion of our studies, it was reported that a cold trimethylsilyl chloride or benzoyl chloride quench of metallated sulfone-ketone reactions can be used to overcome this problem.[9,10] Our results indicate that such a quench will not always be necessary to achieve good yields of β-hydroxysulfones.

The results shown in Table 2 suggest that DME is only marginally better than THF when metallated secondary sulfones are reacted with aldehydes or ketones (entries 1-10). Once again, however, it appears that ketones will serve moderately well as electrophiles in this process (entries 7-10) although *tert*-butyl methyl ketone does finally appear to be too hindered to serve as a useful electrophile (entries 11-12).

Table 1. Reactions of a Primary Sulfone with Aldehydes and Ketones

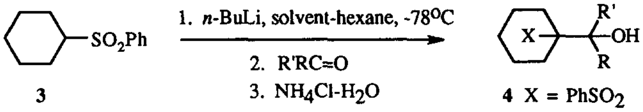


Entry	Electrophile	Solvent[a]	% Yield 2[b, c]	% Recovered 1[b]
1	n-$C_6H_{13}CHO$	DME	95	0
2		THF	45*	45*
3	n-C_2H_5CHO	DME	90	3
4		THF	56*	38*
5	c-$C_6H_{11}CHO$	DME	89	6
6		THF	94	0
7	cyclohexanone	DME	97	0
8		THF	96	0
9	$(MeO)_2CHCH_2COMe$	DME	82	9
10		THF	80	11
11	$(Me)_3CCOMe$	DME	47*	50*
12		THF	53*	34*

(a) Reactions were run as described in the text and stirred at -78°C (dry ice-acetone bath) for either 30 min (entries 1-6) or 60 min (entries 7-12) prior to quenching with aqueous ammonium chloride. Internal reaction temperatures of about -70°C were measured on several occasions (b) Isolated yields with the exception of entries marked with an asterisk, in which case yields are based on integration of ^{1}H-NMR spectra of a purified mixture of the **1** and **2**. (c) Entries 1-10 gave close to an equal mixture of diastereomers. Entries 11-12 gave a 6:1 mixture of diastereomers.

A typical reaction procedure follows (entry 9 in Table 1): To a solution of 508 mg (2.0 mmol) of *n*-octyl phenyl sulfone in 4.0 mL of DME at -70°C (internal temperature) was added via syringe 1.3 mL (2.08 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred for 30 min followed by addition via syringe of 260 mg (2.0 mmol) of 4,4-dimethoxy-2-butanone in 1.5 mL of DME. The mixture was stirred at -70°C for 60 min and 30 mL of saturated aqueous ammonium chloride was added. The resulting mixture was extracted with three 30-mL portions of diethyl ether. The combined extracts were washed with 30 mL of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with 6% ethyl acetate in hexane gradually increased to 20% ethyl acetate in hexane) to give 46 mg (9%) of recovered sulfone and 632 mg (82%) of a mixture of diastereomeric adducts (55:45) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 0.77 (two overlapping triplets, 3H, CH_3), 0.9-1.3 (m, 10H), 1.4 and 1.55 (two s, 3H, CH_3), 1.6-1.9 (m, 2H), 1.95 (m, 1H, CH_2C of one isomer), 2.1 and 2.5 (two dd, 1H, CH_2C of other isomer), 3.1 and 3.3 (t and dd, 1H, CHS), 3.33, 3.34 and 3.41, 3.41 (four s, 6H, OCH_3), 4.3 and 4.4 (two s, 1H, OH), 4.7 and 4.8 (two t, 1H, OCH), 7.6 (m, 3H, ArH), 7.9 (d, 2H, ArH); exact mass calcd for $C_{19}H_{31}O_5S$ (M^+-OCH_3) *m/z* 371.1893, found *m/z* 371.1896.

Table 2. Reactions of a Secondary Sulfone with Aldehydes and Ketones



3

4 X = PhSO$_2$

Entry	Electrophile	Solvent[a]	% Yield 4[b]	% Recovered 3[b]
1	*n*-$C_6H_{13}CHO$	DME	26*	72*
2		THF	17*	81*
3	*n*-C_2H_5CHO	DME	65	27
4		THF	56*	40*
5	*c*-$C_6H_{11}CHO$	DME	89	11
6		THF	76*	19*
7	cyclohexanone	DME	64*	32*
8		THF	56*	40*
9	$(MeO)_2CHCH_2COMe$	DME	40	52
10		THF	31	61
11	$(Me)_3CCOMe$	DME	0*	96*
12		THF	0*	95*

(a) Reactions were run as described in the text and stirred at -78°C (dry ice-acetone bath) for either 30 min (entries 1-6) or 60 min (entries 7-12) prior to quenching with aqueous ammonium chloride. Internal reaction temperatures of about -70°C were measured on several occasions (b) Isolated yields with the exception of entries marked with an asterisk, in which case yields are based on integration of ^{1}H-NMR spectra of a purified mixture of the 3 and 4.

In summary, it has been discovered that DME may be the solvent of choice for conducting metallated sulfone-carbonyl addition reactions. It is also hoped that the results reported herein, in conjunction with a recent report by Marko,[9] Shechter,[10] and others[14] will encourage use of the Julia-Lythgoe procedure for the synthesis of trisubstituted olefins.

Acknowledgements. We thank the National Institutes of Health for generous support.

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