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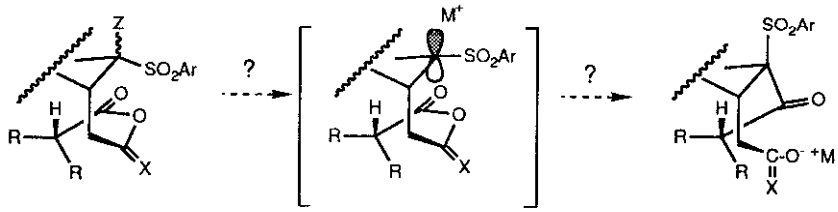
Intramolecular Acylation of an α-Sulfonyl Anion Generated via Halogen-metal Exchange of an α-Halosulfone Bearing an Unsymmetrical Anhydride[1]

M. B. Anderson, M. Lamothe, P. L. Fuchs*
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Abstract: *Summary:* α–Halosulfones are useful for the in situ preparation of α–sulfonyl anions in the presence of acylating agents bearing enolizable protons. Inter- and intramolecular acylations can be effected by halogen-metal exchange at low temperature.

In conjunction with our synthetic program, we wished to effect the intramolecular transacylation of an α-sulfonyl anion (**2**→**3**). The problem was exacerbated because of steric constraints and because the acyl group would bear an acidic proton alpha to the carbonyl group. A solution to this problem ***required the generation of the α-sulfonyl anion in the presence of the reactive acylating agent.*** Our previous findings with α-silyl and α-stannyl sulfones as latent sulfonyl anions[2] suggested that conversion of **1** (Z=R_3Si or R_3Sn) to intermediate **2** would meet with insurmountable chemospecificity problems. We therefore elected to investigate the halogen-metal exchange chemistry of α-halosulfones (**1** Z=Br, I), since reaction of bromides and iodides with alkyl lithium reagents is faster than most other reactions.[3]

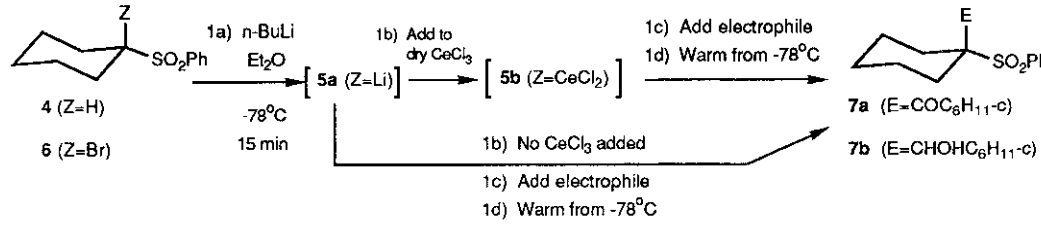


1A (X=O)
1E (X=H_2)

2A,E

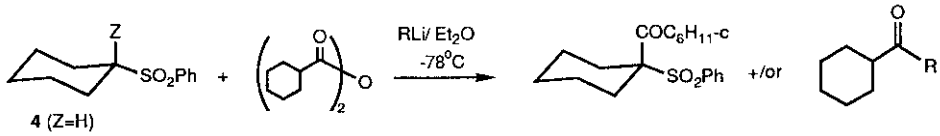
3A,E

Model α–bromo sulfone **6** was prepared from cyclohexyl phenyl sulfone **4**[2] by quenching lithium anion **5a** with either excess carbon tetrabromide[4] or methyl bromo Meldrum's acid[5] (75% and 92% yield, respectively).[6] Direct metalation of sulfone **4** and halogen-metal exchange of α-bromosulfone **6** was essentially instantaneous at -78°C providing anion **5a** which was treated with the cyclohexyl carbonyl electrophiles shown in the table below. The data suggests that anion **5a** suffers partial protonation due to the presence of the enolizable center; this problem being obviated by conversion to the organocerium derivative **5b**.[7]



Starting material	Electrophile (1.5 equiv) (step 1c)	Product[8]	Ratio **4**:**7** (from **5a**)	Ratio **4**:**7** (from **5b**)
4	$(c\text{-}C_6H_{11}\text{-}CO)_2O$	**7a**	10:90	9:91
4	$c\text{-}C_6H_{11}\text{-}CHO$	**7b**	25:75	0:100
6	$(c\text{-}C_6H_{11}\text{-}CO)_2O$	**7a**	7:93	1:99

In order to access the relative rates of metalation, halogen-metal exchange, and nucleophilic addition to the anhydride carbonyl moiety, a 1:1 mixture of dicyclohexyl anhydride and the three sulfones **4, 6,** and **8** were separately treated at -78°C with 1.0 equivalent of alkyllithium and the yield of sulfone acylation versus aklyllithium acylation was measured. As can be readily seen in the table below, n-butyl lithium exclusively adds to the carbonyl in preference to metalation of **4**, while the α-iodosulfone undergoes halogen-metal exchange with n-butyl lithium more rapidly than it adds to the carbonyl of the model anhydride.

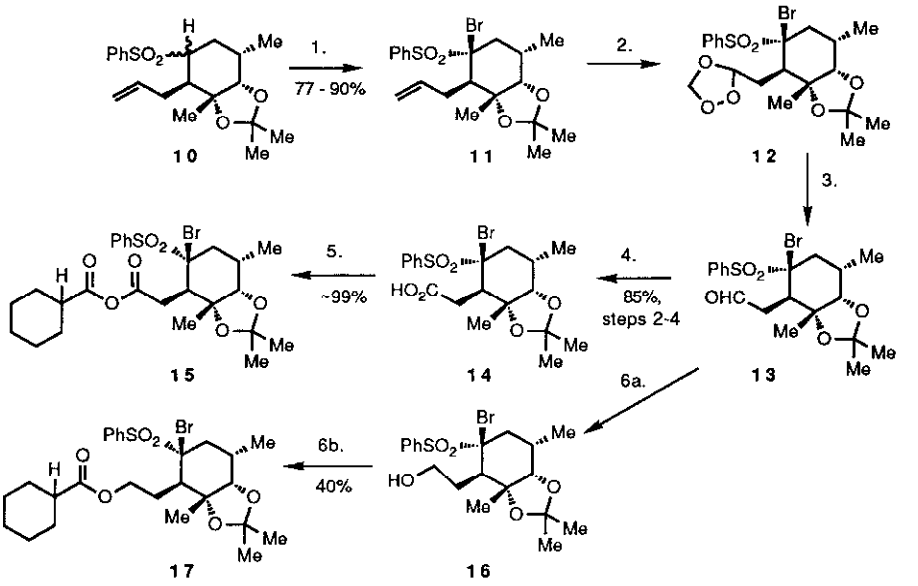


SM	R = (# eq)	Yield **4**§	Yield **7a**	Yield **9***	Recov halide
4	n-Bu (1.0)	97%	0%	**9a** 68%	NA‡
6	n-Bu (1.0)	18 %	43 %	**9a** 37 %	37%
6	t-Bu (1.0)	10 %	15 %	**9b** trace	66 %
6	t-Bu (2.0)	17 %	40%	**9b** 35%	32%
8†	n-Bu (1.0)	25 %	70 %	**9a** < 1 %	<1 %

*Assay of these reactions reveals no detectable amount of dibutyl cyclohexyl carbinol. ‡ Not Applicable. † mp 108-9°C; prepared in 74% yield by reaction of **5a** with 1-chloro-2-iodo-ethane.[9] §The greater amount of **4** in these experiments relative to those in the table above is due to the use of 1.0 equiv of the anhydride.

Treatment of **10** [10,11] with 1.1 equiv of n-butyllithium in THF at -78°C for 0.5 h followed by addition of 1.2 equiv of methyl bromo Meldrum's acid provided α-bromosulfone **11** as a single isomer in 90% yield. The stereochemistry was established by X-ray diffraction.[12] Ozonolysis of **11** at -78°C in CH_2Cl_2 afforded a mixture of two inseparable ozonide diastereomers **12**. The

crude mixture of **12** was reductively cleaved in Et_2O using triphenyl phosphine for 18-24 h at ambient temperature. Excess triphenyl phosphine was quickly converted into triphenyl phosphine oxide within 15 min by treatment with equal portions of oxone ($KHSO_5$) and magnesium sulfate with a catalytic amount of water. Carboxylic acid **14** was obtained in 85% overall yield treated from **11** without any intermediate purification. Conversion of **14** to unsymmetrical anhydride **15** can be done by treatment with cyclohexane carbonyl chloride and excess NaH in THF at 25°C for 10 min. Isolation of the moisture-sensitive anhydride **15** was accomplished by fast plug-filtration through silica gel with either THF or Et_2O. Alternatively, aldehyde **13** can be converted to ester **17** as shown in the scheme below.

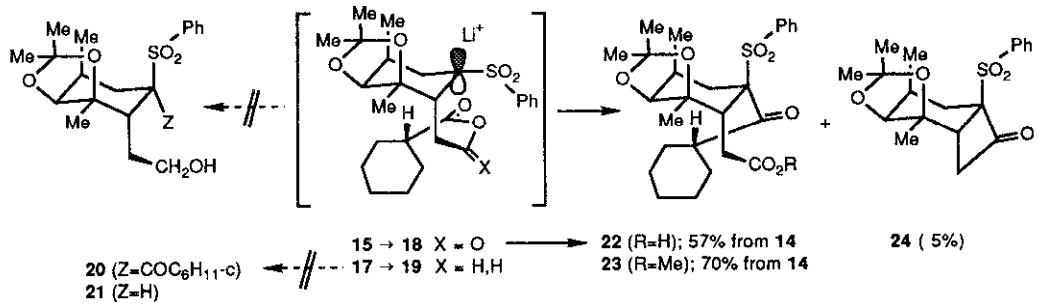


1a) n-BuLi / Et_2O (or THF) - 78°C; 1b) Methylbromo-Meldrum's Acid - 78°C to R.T.; 2a) O_3 / CH_2Cl_2 - 78°C; 2b) aspiration to remove xs O_3; 3) Ph_3P / oxone / $MgSO_4$ / H_2O; 4) $KMnO_4$ / tBu-OH / H_2O / THF / NaH_2PO_4 / RT; 5) c-$C_6H_{11}COCl$, NaH, THF, 25°C; 6) a. THF, BH_3; b. c-$C_6H_{11}COCl$,C_5H_5N, CH_2Cl_2.

Initial attempts to conduct an intramolecular transacylation with ester **17** via low temperature halogen-metal exchange with t-BuLi failed to provide any evidence of the requisite keto alcohol **20.** The only products isolated from this reaction (ca.10%) were debrominated sulfone **21** accompanied by debrominated ester **17.** Apparently the ester moiety is not sufficiently reactive to acylate intermediate α-sulfonyl anion **19.**

Reaction of **15** with 3.0 equiv of *t*-BuLi at -100 to -110°C in THF followed by slow warming, dilution with ether, and ammonium chloride quench provided carboxylic acid **22** in 57% overall yield for the two steps from **14**. A more meaningful estimate of the efficiency of this reaction can be obtained by diazomethane esterification of the crude carboxylic acid **22**. The overall yield of the three-step process is 70% of pure ketone **23**. Further examination of the reaction residues

affords cyclobutanone **24**, which presumably results from acylation of the alternative carbonyl of mixed anhydride **18.** This material is formed in about 5% yield when the reaction is run at -100°C; if the reaction is conducted at -78°C, **24** amounts to about 25-30% of the reaction mixture, with α-ketosulfone **23** being formed in similar quantities.



Acknowledgement. We thank the National Institute of Health (AI 13073, GM 32693) for their generous support of this work. A. Rothwell provided mass spectral data.

Footnotes and References

1 Synthesis via Vinyl Sulfones 41[2]. Cytochalasin support studies 16[2]. For a review on the vinyl sulfone strategy, see: Fuchs, P. L.; Braish, T. F. *Chem Rev.* **1986**, *86*, 903.

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6 Alpha-bromosulfones are also useful intermediates for Ramberg-Bäcklund ring contractions and for radical cyclizations. (See: Block, E. *Reactions of Organosulfur Compounds*, **1978**, *37*, 75; Ibid, *37*, 196. Academic Press Inc. 111 Fifth Avenue, N. Y., New York, 10003; Uneo, Y.; Khare, R. K.; Okawara, M.; *J. Chem Soc. Perkin Trans I.* **1983**, 2637; Clive, D. L. J.; Boivin. T. L. B. *J. Org. Chem.* **1989**, *54*, 1997.)

7 See reference 2 and citations contained therein for additional examples of the beneficial affect of additions of α-dichlorocerio sulfones to enolizable carbonyl groups.

8 All isolated yields were >90%.

9 Nevill, R. C., Jr., Fuchs, P. L. *Synth. Comm.* **1990**, *20*, 760.

10 Anderson, M. B.; Fuchs, P. L. *J. Org. Chem.* **1989**, *54*, 337.

11 Alpha-bromosulfone **11** was selected as the initial substrate to be tested in the intramolecular acylation because of its anticipated greated stability *vis-a-vis* the iodo analog. Success in this reaction sequence precluded the need to synthesize the corresponding α-iodosulfone.

12 We wish to thank P. Fanwick for the determination of this structure. Parameter tables for **11** can be found in the Ph. D. thesis of MBA, Purdue, 1989.

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