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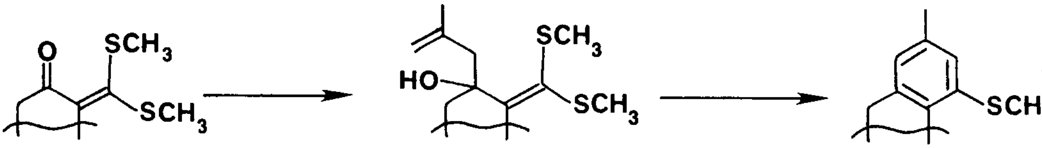
SYNTHESIS OF ARYL METHYLTHIO ETHERS EMPLOYING α-OXOKETENE DITHIOACETALS

R. Karl Dieter* and Yawares Jenkitkasemwong Lin

Department of Chemistry, Boston University, Boston, Massachusetts 02215

Abstract: Reaction of α-oxoketene dithioacetals with methallyl magnesium chloride followed by acid treatment affords simple and annulated aryl methylthio ethers. The methylthio substituent can be easily removed with Raney Ni, undergo a Ni catalyzed substitution reaction with Grignard reagents, or serve as a directing and protecting group in Friedel-Crafts acylation reactions.

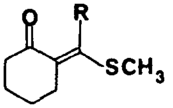
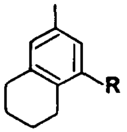
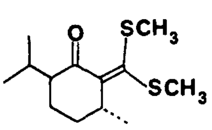
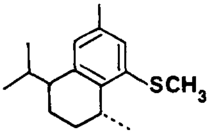
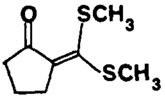
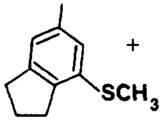
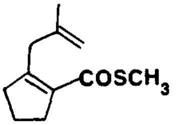
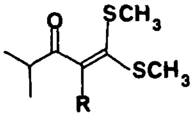
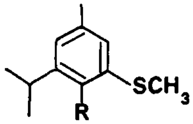
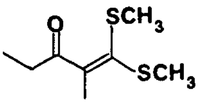
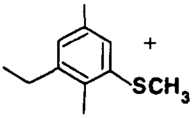
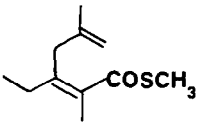
We have, over the past few years, demonstrated that α-oxoketene dithioacetals[1] are versatile substrates for the sequential regioselective construction of new carbon-carbon bonds via a cascade of 1,2 and/or 1,4-nucleophilic addition reactions.[2,3] In the course of developing a 1,3-carbonyl transposition sequence employing α-oxoketene dithioacetals it was discovered that 1,2-nucleophilic addition of methallyl magnesium chloride to **1**, followed by treatment with aqueous HBF_4, led not to a rearranged α,β-unsaturated thiol ester, but to an annulated aryl methylthio ether[3b]. This transformation provides a direct synthetic route to simple and annulated benzenoid aromatic compounds with complete control of the alkyl substitution pattern (eq. 1).



eq. 1

In recent years, several annulation and cyclization approaches[4] to substituted aromatic compounds have been developed as an alternative to aromatic substitution strategies[5] which generally require protecting/deprotecting sequences. The present method, although similar to a recently reported aromatic annulation procedure employing vinylogous silyl esters[4d], affords an aryl methylthio ether in which the easily removed alkylthio substituent can be utilized in additional carbon-carbon bond forming reactions and serve as a protecting and/or a directing substituent[6].

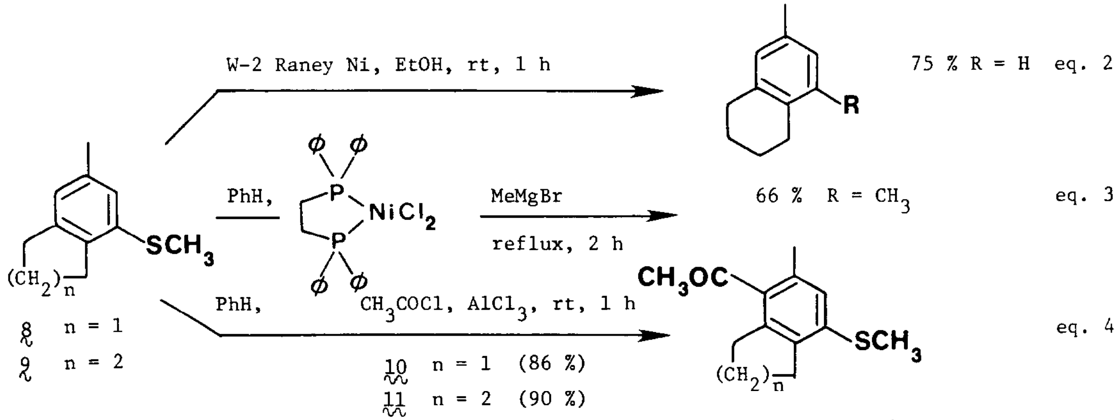
Table 1. Synthesis of Aryl Methylthio Ethers and an Aromatic Hydrocarbon.

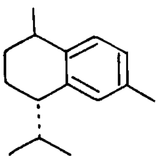
Entry	Substrate	Alcohol (% Yield)^a	Cyclization conditions^b	Product(s) (% Yield)^a	
					
1	1 R = SCH_3	92^c	A	87	
2			B	64	
3	2 R = CH_3	43	C	22	
4			D	28	
					
5	3	89	D	88	
				 +	
6	4	85^c	A	55	15
7			B	62	
					
8	5 R = H		D	43	
9	6 R = CH_3	80	F	47	
				 +	
10	7	60^c	E	37	12
11			B	47	
12			D	52	
13			C	29	

[a] Yields are based upon products purified by column chromatography (silical gel, petroleum ether) unless otherwise noted. [b] Procedure. A = THF, H_2O (4:1), 10% (v/v) HBF_4 (1 part). B = $HgCl_2$, 60 - 70°C, CH_3CN, 1h. C = $BF_3 \cdot Et_2O$, CS_2, 0°C (1.5h) to room temperature (1.5h). D = $BF_3 \cdot Et_2O$, CH_3NO_2, 0°C, 1h. E = $HgCl_2$, 60 - 70°C, aq CH_3CN. F = $AlCl_3$, CH_3NO_2, 0°C, 1h. [c] Based upon crude product and determined by NMR.

The synthesis of aryl methylthio ethers and an aromatic hydrocarbon from α-oxoketene dithioacetals 1, 3-7 and vinylogous thiol ester 2, respectively, are listed in Table 1. Several points are noteworthy. First, the six membered ring α-oxoketene dithioacetals 1 and 3 afford excellent yields (entries 1,5) of aryl methylthio ethers which decrease to moderate yields (43-62%) for the five membered ring and acyclic substrates 4-7 (entries 7,8,9,12). Second, for each substrate the yield of aromatic product is dependent upon the acid/solvent couple employed. α-Oxoketene dithioacetal 1 afforded an excellent yield of aromatic product even under aqueous acidic conditions whereas α-oxoketene dithioacetals 4 and 7 afforded significant quantities of the rearranged α,β-unsaturated thiol esters (entries 1,6,10). For the latter substrates anhydrous $HgCl_2/CH_3CN$, $BF_3 \cdot Et_2O/CH_3NO_2$, or $AlCl_3/CH_3NO_2$ proved more effective (entries 7-9,11-12).

Vinyl sulfide 2 could only be converted to the aromatic hydrocarbon in low yields (entries 3-4) which was consistent with an earlier unsuccessful attempt to use vinyl sulfides in an aromatic annulation process[4d]. The higher yields obtained with α-oxoketene dithioacetals presumably reflects the greater facility for aromatization via methanethiol elimination from an intermediate cyclohexadiene dithioacetal than from the corresponding intermediate sulfide. Treatment of aryl methylthio ether 9 with W-2 Raney Ni cleanly effected reductive cleavage of the methylthio substituent (eq. 2). Consequently, the ketene dithioacetal of ℓ-menthone [80 %, $[\alpha]_D$ -195° (c 2.6, hexane)] was converted to the thioether (entry 5) which afforded a mixture[7] of trans-(-)/cis-(+)-calamenenes[8] 12 and 13 [94%, $[\alpha]_D$ -71° (c 0.2, hexane)] upon Raney Ni (W-2) desulfurization. The alkylthio group can also be removed after serving as a protecting and directing substituent for the Friedel-Crafts acylation reaction (eq. 4). Here Raney Ni desulfurization is, however, complicated by reduction of the carbonyl and the yield of ketones





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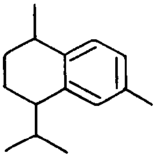

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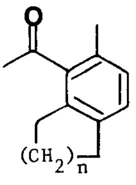
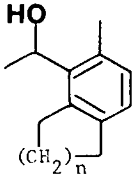


14

a n = 1
b n = 2



15

14 a-b and alcohols **15** a-b is dependent upon the substrate structure. Treatment of 0.31 mmol of **10** with 1.0 g of Raney Ni (EtOH, rt, 0.5 h) yielded **14**a (13%) and **15**a (65%) while reduction of **11** (0.28 mmol, 2.0 g Raney Ni, EtOH, 1 day) afforded a good yield of ketone **14**b (59%) and only a trace of the alcohol **15**b (4%). Pyridinium chlorochromate oxidation (CH_2Cl_2, rt, 7 h) of **15**a afforded **14**a in 83% yield providing a solution to the over reduction problem.

Finally, reaction of thioether **9** with methyl magnesium bromide in the presence of dichloro [1,2-bis(diphenylphosphino)ethane] nickel(II)[9] under reflux affords the aromatic hydrocarbon in 66% yield (eq. 3). This reaction provides an alternative to the use of substituted vinyl sulfides for the synthesis of regiospecifically substituted aromatic hydrocarbons.

In summary, α-oxoketene dithioacetals can be converted to simple and annulated aryl methylthio ethers in good yields. The substitution[3b] and nucleophilicity of the participating olefin will limit the generality of the cyclization step and a vinyl group may not cyclize. The methylthio substituent of the aromatic products can be exploited in carbon-carbon bond forming processes involving either direct or electrophilic aromatic substitution reactions.

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