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ATTEMPTED SIMMONS-SMITH REACTION ON α-OXOKETENE DITHIOACETALS: A NEW GENERAL ROUTE TO 3,4-SUBSTITUTED AND ANNELATED THIOPHENES[1]

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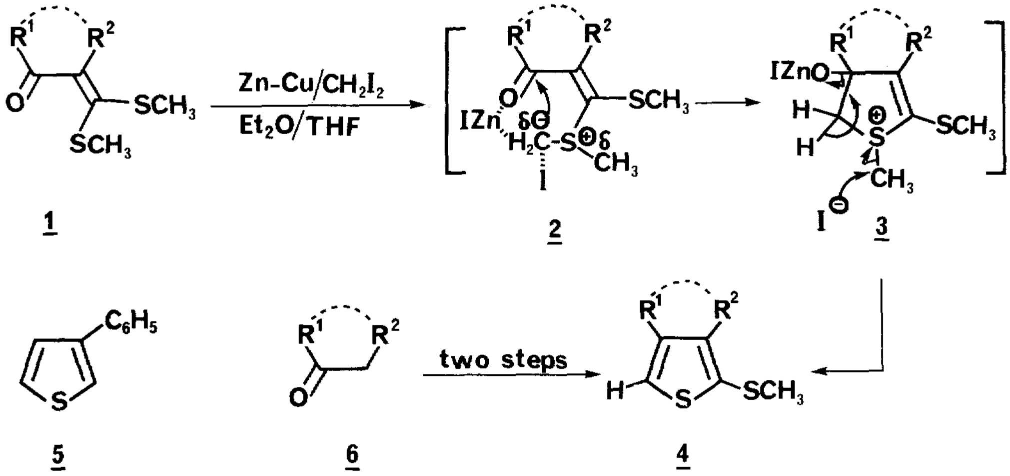
Summary: A new general method for 3,4-substituted and annelated thiophenes through intramolecular cyclocondensation of a sulphonium ylid intermediate under Simmons-Smith reaction conditions on α-oxoketene dithioacetals has been reported.

Although ketene O,O-acetals, vinylethers, and enamines have been reported to undergo cyclopropanation under Simmons-Smith reaction conditions[2], vinylsulfone appears to be the only example of sulphur compounds studied for cyclopropanation under these conditions[2,3]. Neither vinyl sulphides nor ketene S,S-acetals have been investigated under these reaction conditions[3,4]. It was therefore considered of interest to attempt cyclopropanation on α-oxoketene dithioacetals under Simmons-Smith reaction conditions. However, when 1 were treated with methylene iodide in the presence of zinc-copper couple, the envisaged cyclopropanes were not formed and the product analysis revealed that they are 3- or 3,4-disubstituted-5-methylthiothiophenes formed in good yields. We herein report a new general synthesis of the title thiophenes from 1 under Simmons-Smith reaction conditions involving an unusual intramolecular cyclocondensation of a sulphonium ylid intermediate formed through methylene insertion.

The overall transformation is depicted in the Scheme. The open-chain acetals 1a-g smoothly reacted with methylene iodide in the presence of zinc-copper couple in refluxing ether[5] to give the corresponding thiophenes 4a-g[6] in 58-64% overall yields. The regiochemistry in 4a-g was confirmed by independent synthesis[7] of 4b by reported procedure and also by Raney Nickel desulphurization of 4b to the known thiophene[8] 5, thus confirming the structural assignment. The presence of an additional double bond as illustrated in the entry 8, did not interfere in the thiophene formation suggesting the regiospecific nature of the carbenoid addition. The method was found to be general when extended to cyclic acetals 1i-l (entries 9-12), which afforded the corresponding 3,4-annelated thiophenes 4i-l under similar reaction conditions in good yields[6].

The probable mechanism of the described transformation apparently involves the carbenoid methylene addition to one of the sulfur atoms of 1 to yield the initially formed ylid[9] 2, which on intramolecular aldol type condensation, assisted by coordination of zinc with carbonyl oxygen lone pair followed by demethylation of S-methylthiophenium salt 3 affords the thiophenes 4.

The overall transformation provides a facile two step entry to not easily accessible



Scheme

3-or 3,4-substituted thiophenes from abundantly available active methylene ketones. From the literature survey, it was revealed that Marino and Kostusyk[7] have reported the synthesis of some of these thiophenes from 1 in low yields. Thus 1b on treatment with LDA in the presence of HMPA underwent thiomethyl group deprotonation and subsequent intramolecular aldol type condensation to yield the corresponding thiophene 4b in 30% yield. Only in one case (R^1=C$_6$H$_5$; R^2=Et), the yield of thiophene was recorded 55%, while in all other cases, an average of 22-42% overall yields were obtained. Besides, the method failed to yield the expected thiophenes, when R^1 is alkyl and R^2 is methyl group. The present thiophene synthesis involving the conversion of 1 under Simmons-Smith reaction conditions in high yields and free from described limitations would certainly be a method of choice. The method distinguishes itself from other thiophene synthesis[10] as it involves an unusual facile intramolecular aldol type condensation of a sulphonium ylid[11] resulting in ring closure. Although carbenes are known to add to the sulfides to give sulfur ylids, to our knowledge, this is the first report on their formation under Simmons-Smith reaction conditions. Further work to probe into the mechanism of thiophene formation and its extension to β-alkylthio-β-substituted α,β-enones and α-oxoketene O,S-acetals is in progress.

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References and Notes

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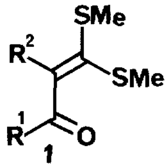
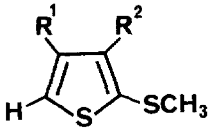
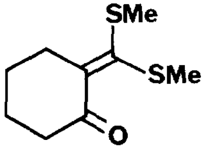
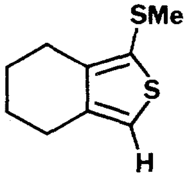
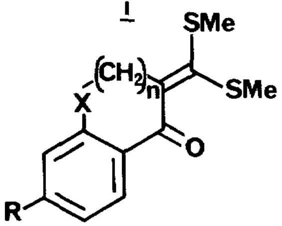
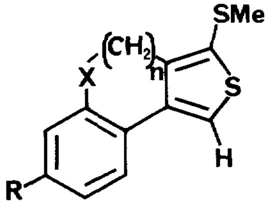
Table

Entry	Dithioacetal	Product	yield(%)
	 1	 4	
1	1, 4 a R^1= 4-MeC_6H_4 ; R^2= H		64
2	b R^1=C_6H_5 ; R^2=H		61
3	c R^1= 2-furyl ; R^2= H		58
4	d R^1= 2-thienyl ; R^2= H		63
5	e R^1= C_6H_5 ; R^2= n-C_3H_7		60
6	f R^1=R^2=Me		59
7	g R^1=Me ; R^2= n-C_4H_9		62
8	h R^1=C_6H_5CH=CH ; R^2= H		58
9	 i		65
			
10	j X=CH_2 ; n = 1 ; R= H		62
11	k X=O ; n=2 ; R= H		61
12	l X= S ; n=2 ; R=Me		63

S.S.; Scharf, D.J.; Tosi, G. J. Am. Chem. Soc. **1970**, 92, 7428. (c) Kuehne, M.E.; King, J.C. J. Org. Chem. **1973**, 38, 304. (d) Nishimura, J.; Furukawa, J.; Kawabata, N.; Kitayama, M. Tetrahedron, **1971**, 27, 1799, (e) Conia, J.M.; Girard, C. Tetrahedron Lett. **1973**, 2767.

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(4) Attempted Simmons-Smith cyclopropanation of bis(phenylthio)ketene acetals was found to be unsuccessful: Braun, M.; Seebach, D. Chem. Ber. **1976**, 109, 669.

(5) General Procedure for 4a: To a well stirred suspension of zinc-copper couple (4.0g) in dry ether (25ml) under nitrogen atmosphere, a small crystal of iodine and CH_2I_2 (6.70g,25 mmol) are added and the reaction mixture is refluxed for 45 min. A solution of 1a (2.4g, 10 mmol) in dry THF (15 ml) is added and the reaction mixture is further refluxed with stirring for 8 hr (monitored by TLC). The solvent is removed under reduced pressure and the residue is diluted with water (200 ml) followed by addition of $CHCl_3$(150 ml). The reaction mixture is filtered, the residue washed with chloroform and the combined organic layer is washed with satd. NH_4Cl solution and water, dried (Na_2SO_4) and evaporated to give crude 4a, which is purified by column chromatography over silica gel using hexane as eluent; yield 1.4g,(64%); m.p. 60-61°C; ν_{max}(KBr): 1500, 1413, 1305, 1198, 1000, 813, 752 cm^{-1}; δ_H($CDCl_3$)(400 MHz); 2.30 (3H,s,CH_3); 2.46(3H,s,SCH_3): 7.13(2H,d,J=8.5Hz,arom); 7.27(1H,d,J=1.5Hz,H-4); 7.30 (1H,d,J=1.5Hz,H-2); 7.39(2H,d,J=8.5Hz,arom); δ_C($CDCl_3$): 21.49(CH_3); 21.95(SCH_3); 122.09(2-CH); 130.26(4-CH); 126.41, 129.76(CH,arom); 132.76, 136.85(C-1' and C-4' of aryl): 138.14(C-5); 142.58(C-3); m/z 220(M^+,100%); Anal. Calcd. for $C_{12}H_{12}S_2$: C,65.41; H,5.49. Found: C,65.30; H,5.35%.

(6) All thiophenes 4b-l gave satisfactory spectral and analytical data.

(7) Marino, J.P., Kostusyk, J.L. Tetrahedron Lett. **1979**, 2493. The reported m.p. of 4b in this paper is 92°C, however our product showed m.p. 42°C; while its i.r., n.m.r. and mass spectra were superimposable with the product obtained by Marino's method.

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