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A DIRECT SYNTHESIS OF SUBSTITUTED THIOPHENES *VIA* α-OXOKETENE DITHIOACETALS. II.[1]

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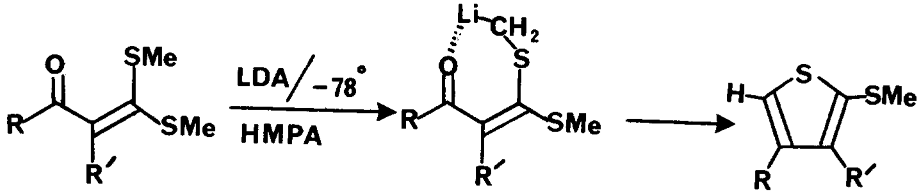
The regioselective deprotonation of S,S-dimethyl-α-oxoketene dithioacetal at the (Z)-S-methyl group leads to a direct synthesis of 2-S-methyl-3,4-disubstituted thiophenes.

In the accompanying communication,[2] we reported on some regioselective deprotonations of α-oxoketene dithioacetals. During the course of this study, we uncovered an interesting and novel synthesis of 2-thiomethyl-2,3-disubstituted thiophenes of general structure **II**. Since the α-substitution of thiophenes *via* metallation reactions is an efficient process, the regiospecific introduction of substituents in the 3,4-positions poses the greater synthetic challenge.[3] The chemistry described in this paper allows for the construction of a trisubstituted thiophene from a ketone, aldehyde or ester and carbon disulfide.

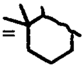
The α-oxoketene dithioacetals (**1**-**7**) were prepared by the condensation of the corresponding enolates with carbon disulfide, followed by the methylation of the intermediate dithiolate species.[4] When a solution of the dithioacetal in hexamethylphosphorotriamide (HPMA)[5] was added to a THF solution of one equivalent of lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LTMP) at -78°, the reaction mixture turned deep red in color. After one hour at -78°, the reaction mixture was quenched with a saturated ammonium chloride solution or with methyl iodide. After three hours at ambient temperatures, the reaction mixture was worked up by a conventional ether extraction procedure. The thiophenes were isolated by simple column chromatography with silica gel and were characterized spectroscopically.[6]



I

II

TABLE 1

Compound		mp/bp	Base		% Yield **II**	UV^+ λ_{max}
1	R=Ph	144-150°	LDA	8	55 (68)	233 nm
	R'=Et	(.75 mm)	LTMP		55 (68)	(ε 16000)
2	R=Ph	92-93°	LDA	9	30 (50)	252 nm
	R'=H		LTMP		30 (50)	(ε 21400)
3	R=pOMePh	102-103°	LDA	10	30 (50)	259 nm
	R'=H					(ε 24400)
4	R=Ph	124-130°	LDA	11	42 (60)	235 nm
	R'=MeO	(.4 mm)				(ε 18500)
5	R,R'= 	113-114°	LDA	12	26 (50)	230 nm
		(.15 mm)	LTMP		26 (50)	(ε 7000)
6	R=H	52°	LDA	13	22 (35)	233 nm
	R'=Ph		LTMP		45 (65)	(ε 13200)
7	R=EtO	125-127°	LDA	14	38 (55)	250 nm
	R'=Ph	(.75 mm)	LTMP	R=MeO	38 (55)	(ε 12500)

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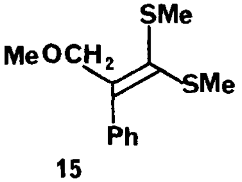
[*] All yields are isolated yields by chromatography. Yields in parentheses are based on recovered starting material.

[+] All UV spectra were taken in absolute ethanol with a Cary 14 spectrometer.

There are several important structural requirements for the success of the cyclization process, which we believe to occur from the dipole-stabilized anion I. The R group of the α-oxoketene dithioacetal cannot contain any acidic hydrogens, while the S-methyl dithioacetals are the only derivatives which undergo the thiophene-forming reaction. The S-ethyl analogues of compounds 1 and 2 do not yield any thiophene under the stated reaction conditions. However, this last structural requirement is not a limiting one since the 5-position of the thiophenes II could be metallated and subsequently substituted.[3]

The kinetic deprotonation of the S-methyl group *cis* to the carbonyl oxygen is also competitive with other deprotonations. The dithioacetal with R=Ph and R'=Me only undergoes allylic anion formation with no thiophene detected.[2] Compounds 2 and 3 undergo deprotonation of the vinyl hydrogen to the same extent as thiophene formation. While all of the reactions listed yielded significant amounts of starting material, use of two equivalents of base did not increase the yield of thiophene. Although the thiophene reactions were quenched with methyl iodide, no incorporation of methyl groups into anion I or its equivalent was observed.

The use of the more hindered base LTMP in place of LDA had no significant effect on yields except for one notable case, compound 6. Recent reports[7] have revealed that LDA can affect reductions of carbonyl groups *via* hydride transfers from the isopropyl group of LDA. In fact, careful chromatography of the reaction mixture yielded a reduced product 15 (20%). The methyl ether was isolated because of the methyl iodide quench of the reaction mixture. Since LTMP does not contain a hydrogen on carbon α to the nitrogen, there was an increase in the yield of the thiophene 13, and 15 was not observed.



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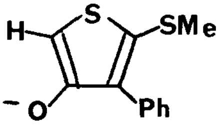

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The conversion of ester 7 into the methoxythiophene 14 proceeded through the methylation of the anion of 4-hydroxythiophene 16. The successful generation of anion 16 opens the way for the preparation of other 4-hydroxythiophenes from esters.

Further improvements in the regioselective generation of intermediates such as I should lead to a more more general approach to thiophenes than the classical Fiesselmann reaction.[8] Various recent modifications of the Fiesselmann reaction have been used to prepare thiophenes from ketones, but these cases have involved several steps and usually do not lead to 5-unsubstituted thiophenes.[9] Thus, the novel deprotonation of α-oxoketene dithioacetals provides for new substitution patterns in thiophenes and offers a more direct route to this class of heterocycles.

References

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3. S. Gronowitz in Chapt. 6, p. 263, Organic Compounds of Sulfur, Selenium and Tellurium, Vol. 4, The Chemical Society of London, Burlington House, London, England, 1977.
4. I. Shahok and Y. Sasson, Tetrahedron Lett., 4207 (1973).
5. Thiophenes were only produced when HMPA was used as a cosolvent. Routinely, the ratio of HMPA to base was 3, while the solvent composition was 10% by volume HMPA in THF.
6. All new compounds (1,4-14) had IR, NMR, UV, C-13 and elemental analyses (±0.2%) consistent with the assigned structures.
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