A Facile Preparation of 3-Chloro-4-acyl-3-sulfolenes as Common Intermediates for the Synthesis of Thieno-, Pyrazolo- and Isoxazolo-3-sulfolenes†

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A convenient preparation of 3-chloro-4-acyl-3-sulfolenes and their use in the synthesis of thieno-, pyrazolo- and isoxazolo-3-sulfolenes as equivalents to the heterocyclic *o*-quinodimethanes are described.

Synthesis of heterocycle-fused 3-sulfolenes as stable precursors to the heterocyclic *o*-quinodimethanes has recently drawn increasing attention.[1,2] Two commonly employed methods for the preparation of this class of compounds involved either constructing the sulfolene ring on a heterocycle or building the heteroaromatic ring on a pre-existing cyclic sulfone system. The concise synthesis of thiophene-[3] and furan-fused 3-sulfolenes[4] from 4-bromo-3-chloro-2-sulfolene as well as the pyrazole-fused 3-sulfolenes[5] from 3-(phenylsulfonyl)-3-sulfolene demonstrates that the latter route is more attractive if suitably functionalized 3-sulfolenes are readily available. The substitution α to the sulfone moiety, in addition, provides the versatility of the method for generation of derivatives of heterocyclic *o*-quinodimethanes. However, the use of the above strategy for the synthesis of used 3-sulfolenes with a substituent attached on the heterocyclic ring hitherto has not been examined extensively. Only scattered examples of substituted thiazolo,[6] oxazolo-[2] and pyrazolo-3-sulfolenes[5,7] have been reported in the literature. In a continuation of studies on the synthetic utility of 3-chloro-4-(1-hydroxyalkyl)-2-sulfolenes **1**,[8] we now report that 3-chloro-4-acyl-3-sulfolenes **2** derived from **1** may serve as a new class of common synthetic intermediates for the preparation of thieno-, pyrazolo- and isoxazolo-3-sulfolenes (Scheme 1).

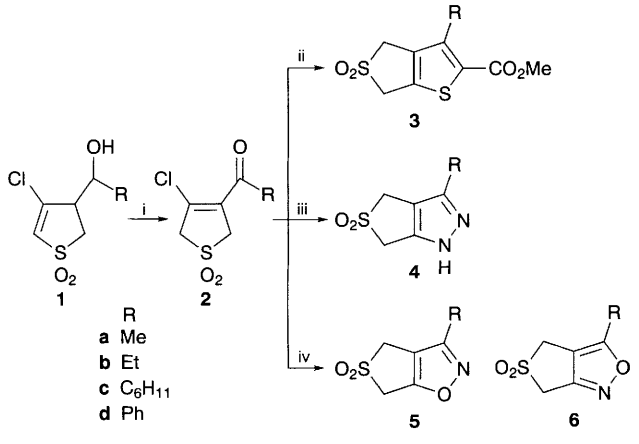
The synthesis of **2** was readily accomplished by simple treatment with pyridinium chlorochromate (PCC, 5 equiv.) and molecular sieves 3 Å of **1** which was readily prepared in high yield by an ultrasound-promoted allylzincation of 4-bromo-3-chloro-2-sulfolene with an aldehyde.[8] The oxidation and the double-bond isomerization occurred in one flask as we reported in a similar system.[9]

Since β-chlorovinyl carbonyl compounds are known to be useful three-carbon annulation units in the synthesis of pyrazole, isoxazole and thiophene,[10,11] we therefore expected that compounds **2**, bearing the same annulation fragment, might be used to establish the heterocycle-fused 3-sulfolenes in a similar manner. Thus the condensation of **2** with methyl thioglycolate was first carried out in NaOMe–MeOH (2 equiv.) at reflux temperature by a Fiesselmann type reaction.[11] Indeed, good yields of 3-substituted 2-methoxycarbonyl-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-dioxides **3a–d** were smoothly obtained (Table 1). Treatment of **2** with hydrazine in refluxing ethanol similarly gave the pyrazolo-3-sulfolenes **4a–d** in high yields (Table 1). The NMR and IR spectral data of product **4a** were identical with those reported.[5] However, when compounds **2a–c** were treated with hydroxylamine hydrochloride (3 equiv.) and NaOMe (4 equiv.) in refluxing methanol, the alkylated isoxazolo-3-sulfolenes **5a–c** were obtained in low yields. The reaction of **2d** with the hydroxylamine hydrochloride salt under the same conditions failed to give the phenyl substituted isoxazole analogue (Table 1). In no case was any regioisomer **6** detected in the reaction mixture.

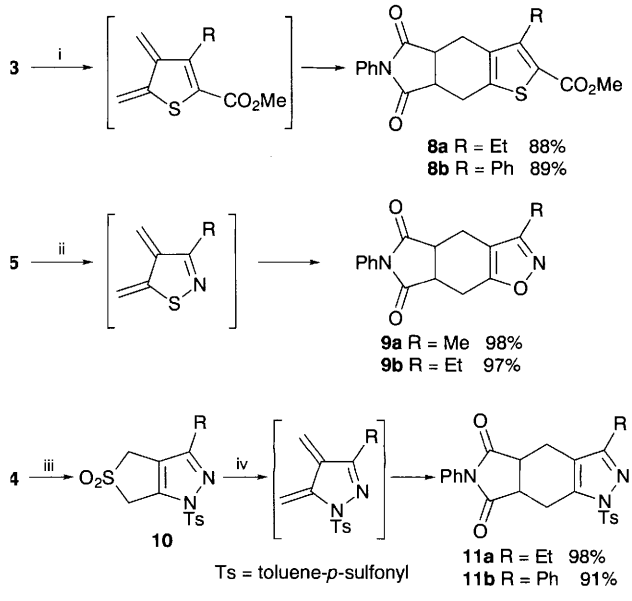
Table 1 Synthesis of 3-chloro-4-acyl-(**2**), thieno-(**3**), pyrazolo-(**4**), isoxazolo-3-sulfolenes (**5**) and 1-tosyl-4,6-dihydrothieno[3,4-*d*]pyrazole 5,5-dioxides (**10**)[a]

	Product, % Yield[b]				
	2	**3**	**4**	5	**10**
a (R = Me)	50	80	94	37	96
b (R = Et)	83	74	90	36	96
c (R = C_6H_{11})	88	62	85	11	95
d (R = Ph)	80	69	84	0	97

[a] All the products have been fully characterized by ^1H, ^{13}C NMR, IR, and mass spectroscopy. [b] Isolated yields by flash chromatography on silica gel.



Scheme 1 *Reagents and conditions*: i, PCC, molecular sieves 3 Å, CH_2Cl_2, room temperature; ii, $HSCH_2CO_2Me$, NaOMe, MeOH, reflux; iii, NH_2NH_2, EtOH, reflux; iv, $NH_2OH{\cdot}HCl$, NaOMe, MeOH, reflux.



Scheme 2 *Reagents and conditions*: i, *N*-phenylmaleimide **7**, toluene, sealed tube, 200 °C; ii, *N*-phenylmaleimide, toluene, sealed tube, 170 °C, iii, toluene-*p*-sulfonyl chloride, pyridine, CH_2Cl_2, room temp.; iv, *N*-phenylmaleimide, toluene, sealed tube, 180 °C.

The use of a dienophile to trap the *o*-dimethylene heterocyclic intermediate was performed by heating a toluene solution of the sulfones (0.03 mol dm^{-3}) and *N*-phenylmaleimide **7** (2 equiv.) in a sealed tube (Scheme 2). The [4 + 2] cycloadducts **8a** (R = Et) and **8b** (R = Ph), for example, were smoothly obtained in good yields when the thieno-3-sulfolene **3b** or **3d** were heated with **7** at 200 °C (Scheme 2). Likewise, heating **7** with isoxazole-fused sulfone **5a** or **5b** at 170 °C gave the corresponding cycloaddition products **9a** (R = Me) and **9b** (R = Et) in excellent yields. Thermolysis of **4** in the presence of **7** at 180 °C failed to give the Diels–Alder adduct.[5,7] However, using the *N*-tosyl pyrazole **10** (readily derived from **4**, Table 1) instead of **4** in the thermal reaction dramatically improved the result (Scheme 2). Treatment of the pyrazole **10b** or **10d** with **7** at 180 °C afforded the cycloadducts **11a** (R = Et) and **11b** (R = Ph) in 98 and 91% yields respectively. Compound **10b** begins to undergo extrusion of sulfur dioxide at 150 °C. Heating **10b** in solution below or above this temperature gave no trace of the isomer resulting from migration of the tosyl group. Since 2-tosyl-4,6-dihydrothieno[3,4-*d*]pyrazole 5,5-dioxide was reported to the stable at 230 °C,[12] therefore **10b**‡ was assigned as the 1-tosyl pyrazolo-3-sulfolene. The structure of **11a**‡ was determined on the basis of the ^1H NMR spectrum of which one methylene proton on C-8 (δ 4.05, dd, *J* = 17.1, 2.0 Hz) is deshielded by the proximate 1-tosyl group. The quantitative recovery of **11a** on heating it in a 1,2,4-trichlorobenzene solution at 190 °C for 1 h indicated that the isomerization of the tosyl group did not occur.

In summary, we have reported three new routes to the thieno-, pyrazolo- and isoxazolo-3-sulfolenes by use of 3-chloro-4-acyl-3-sulfolenes **2** as the common synthetic intermediates. Features of the described method include (*i*) the intermediates **2** are readily prepared; (*ii*) the reactions for the synthesis of heterocyclic fused sulfones are simple and (*iii*) the interception of the *o*-dimethylene heteroaromatics generated from those sulfones with dienophile **7** is efficient.

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Footnotes

† 3-Sulfolene = 2,5-dihydrothiophene 1,1-dioxide.

‡ NMR *spectral data* ($CDCl_3$), δ **10b**: ^1H, 1.19 (t, 3 H, *J* = 7.4 Hz), 2.45 (s, 3 H), 2.62 (q, 2 H, *J* = 7.4 Hz), 4.14 (s, 2 H), 4.52 (s, 2 H), 7.36 (d, 2 H, *J* = 8.3 Hz), 7.86 (d, 2 H, *J* = 8.3 Hz); ^{13}C, 12.1, 21.2, 21.7, 53.6, 54.9, 113.8, 128.1, 130.3, 133.6, 135.7, 146.4, 155.5. **11a**: ^1H 1.14 (t, 3 H, *J* = 7.5 Hz), 2.32 (s, 3 H), 2.58 (q, 2 H, *J* = 7.5 Hz), 2.71 (dd, 1 H, *J* = 15.6, 7.6 Hz), 3.07–3.17 (m, 2 H), 3.39–3.55 (m, 2 H), 4.05 (dd, 1 H, *J* = 17.1, 2.0 Hz), 6.82 (m, 2 H), 7.15 (d, 2 H, *J* = 8.0 Hz), 7.34 (m, 3 H), 7.80 (d, 2 H, *J* = 8.0 Hz); ^{13}C, 13.0, 20.2, 20.4, 21.6, 22.6, 39.2, 116.8, 126.1, 127.7, 128.5, 128.9, 129.8, 131.5, 134.5, 140.1, 145.1, 156.8, 177.5, 180.0.

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