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The [1,2]-thio-Wittig rearrangement: evidence for a radical mechanism and its suppression

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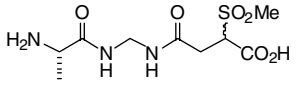
Abstract—The lithium enolate formed from methyl *S*-trityl mercaptoacetate can be C-alkylated in high yield at or below −40 °C, but at higher temperatures the [1,2]-thio-Wittig rearrangement of the enolate is the predominant process; ESR evidence indicates that this rearrangement occurs by a radical mechanism.

During a study of the synthesis of libraries based upon the structure of the antibiotic natural product pantocin B **1**,[1] we proposed to use a thio-ether link to anchor the library members to the solid phase synthesis resin, enabling us to investigate traceless cleavage by alkylation and/or oxidation.[2] The precedents using a thio-ether resin linkage suggested that a trityl resin would be the best choice,[3,4] so we sought to establish the chemistry in solution, using a trityl protecting group, before carrying out the solid phase synthesis. Thus we investigated the alkylation of methyl *S*-trityl mercaptoacetate (methyl *S*-trityl thioglycolate) **2**.



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Methyl *S*-trityl mercaptoacetate **2** was prepared in a 84% yield from trityl chloride and mercaptoacetic acid, following the procedure of Schill and co-workers.[5] Moreover, Schill and co-workers had sought to alkylate the lithium enolate of **2**, formed with LDA at 20 °C in THF; however, they did not obtain their desired alkylation product but rather a rearranged S-alkylated compound (analogous to **3**): they did not pursue this matter further, obtaining their target molecule by another route, and to the best of our knowledge, theirs is the only attempted alkylation of methyl *S*-trityl mercaptoacetate **2** described fully in the literature until this study.[6]

We anticipated that by appropriate choice of conditions we would be able to achieve C-alkylation of enolate **5** of methyl *S*-trityl mercaptoacetate **2**. Our initial studies used trimethylsilyl bromoacetate as the alkylating agent (in order to prepare **4a**, a precursor of the succinate fragment of pantocin B) under a variety of conditions, with LDA, LiHMDS, NaHDMS or KHMDS as base in THF and/or DMF or DMSO (−78 °C to rt). However, these reactions yielded only the desilylated, rearranged S-alkylated compound **3a** ($R = HO_2CCH_2$, ca. 60% yield after aqueous work-up),[7] corresponding to the result of Schill and co-workers,[5] or returned starting material **2** (40–95%) (Scheme 1).

In order to determine whether this rearrangement is a [1,2]-thio-Wittig rearrangement[8–10] of the enolate (**5**, see Scheme 2) and to identify conditions for C-alkylation, we conducted further experiments with simpler electrophiles/alkylating agents. We suspected that the return of starting material **2** in our attempted synthesis of **4a** was due to the initial silyl ketene acetal formation and subsequent hydrolysis; however, attempts to

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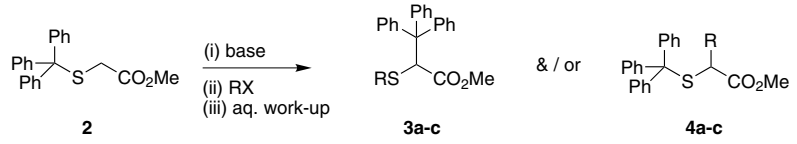
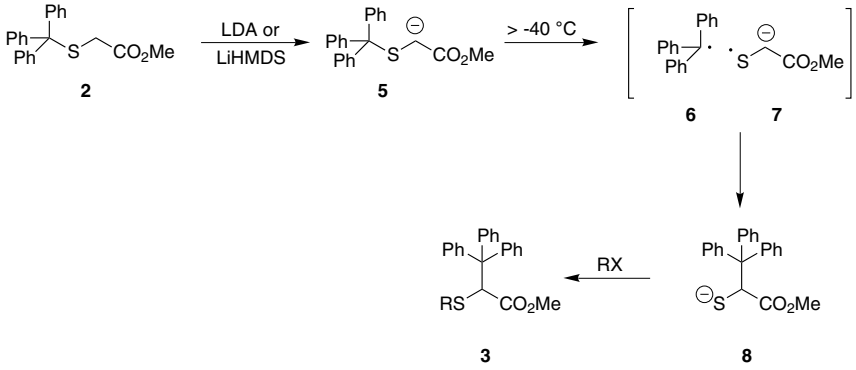


2 3a-c 4a-c

Scheme 1. RX = **a** TMS/HO_2CCH_2Br, **b** DOAc, **c** MeI, **d** BnBr, **e** MeO_2CCH_2Br.



2 5 6 7 3 8

Scheme 2.

prepare the silyl ketene acetal returned only starting material **2**. Further experiments therefore avoided the use of electrophiles/alkylating agents with the capacity for silyl transfer. Next, we investigated deuterium trapping of the enolate **5**, the best results being obtained by an inverse addition of the enolate solution to a solution of acetic acid-*d* (CH_3CO_2D) in THF. Thus, the formation of enolate **5** at rt with LDA (1 equiv) followed, after 15 min, by the inverse quench, resulted in an essentially complete rearrangement (i.e., formation of **3b**, R = H after an aqueous work-up,[11] accompanied by variable, small amounts of the corresponding disulfide). However, the formation of enolate **5** at −78 °C with LDA (1 equiv) followed, after 15 min, by the inverse quench also at −78 °C, resulted in enolate deuteration (i.e., formation of **4b**, R = D), with no rearranged product **3b** observed. The incorporation of deuterium (i.e., formation of **4b**, R = D) was confirmed by ^1H, ^2D and ^{13}C NMR spectroscopy but at a level of only ca. 30% (vs **2**, as determined by ^1H NMR spectroscopy); a maximum level of deuteration of ca. 50% was achieved by using excess LDA (2.5 equiv).[12] Thus we concluded from these experiments that we are observing an unusual [1,2]-thio-Wittig rearrangement of enolate **5**,[13] but that enolate **5** is stable at a low temperature, so C-alkylation should be possible.[14]

Therefore alkylation experiments were conducted, forming enolate **5** with LDA (1 equiv) at −78 °C for 5 min, followed by the addition of the alkylating agent (1 equiv) in THF, the reaction mixture then maintained at −78 °C and the progress of the reactions monitored by ^1H NMR spectroscopy of quenched aliquots.[15] With iodomethane, methylation at −78 °C was complete after 7 h and the final aliquot composition was C-methylated product **4c**,[16] 92%, and starting material **2**, 8%, no rearranged product **3c** was detected (no methine singlet at δ_H 4.73 ppm). Conversely, enolate **5** formation (LDA, 1 equiv, rt, 15 min) and methylation with iodomethane at rt gave the rearranged product **3c** only (in 75% yield). With benzyl bromide, benzylation of enolate **5** at −78 °C proceeded to only ca. 10% after 8 h. At −40 °C, however, no rearranged product **3** was observed (no methine singlet at δ_H ca. 4.7 ppm) and the product yields were 98% **4c** in 2 h with iodomethane, 86% **4d** in 8 h with benzyl bromide and 92% **4e** in 1 h with methyl bromoacetate, as determined by ^1H NMR spectroscopy. These results are summarised in Table 1. However, we have not achieved C-alkylation with trimethylsilyl bromoacetate under these conditions (Table 1, entries 7 and 8): we attribute this to silyl ketene acetal formation, as noted above, and ascribe our initial observations of the rearranged product **3a** to inadequate temperature control during those preliminary experiments.

As enolate **5** rearrangement was observed only above −40 °C, we had an opportunity to monitor the process by magnetic resonance spectroscopy. A mixture of methyl *S*-trityl mercaptoacetate **2** and LiHMDS[17] in THF_{d8} was prepared at −78 °C and ^1H NMR spectra recorded at regular temperature intervals as the mixture warmed up to rt in the NMR instrument. These spectra contained many broad signals and could not be assigned fully, but we concluded that at low temperature enolate **5** was present.[18] Rearrangement was observed (appearance and increase in the intensity of methine signal of **8** at ca. δ_H 5.3 ppm), was significant once the temperature increased above −40 °C, and was complete once rt was reached. A similar experiment was then undertaken with ESR monitoring. The solutions of LiHMDS and methyl *S*-trityl mercaptoacetate **2** in THF were frozen together in two layers in an ESR tube and warmed up in the instrument.[19] As the temperature increased, an ESR signal became discernible and a first spectrum was obtained at −53 °C. The radical concentration increased noticeably with temperature, giving more

Table 1. Summary of alkylation studies on lithium enolate **5**

Entry	Alkylating agent, RX	Temperature (°C)	Time (h)	Yield of **3**[a] (%)	Yield of **4**[a,b] (%)
1	MeI	−78	7	n.d.	92
2	MeI	−40	2	n.d.	98
3	MeI	rt	18	75	n.d.
4	BnBr	−78	8	n.d.	10
5	BnBr	−40	8	n.d.	86
6	MeO_2CCH_2Br	−40	1	n.d.	92
7	$TMSO_2CCH_2Br$	−78	10	n.d.	<5
8	$TMSO_2CCH_2Br$	−40	8	n.d.	<5

[a] n.d. = not detected.
[b] Determined by ^{1}H NMR spectroscopy, w.r.t. **2**.

intense, better resolved spectra. At −23 °C, the field modulation could be lowered to a minimum of 0.05 G, which still gave a strong enough signal at the highest possible resolution: the 196 line spectrum was centred at a *g*-factor of 2.00257 and corresponded with that of the trityl radical **6** by a comparison with the literature[20] and simulation (Fig. 1).[21] The intensity of the spectrum increased further as the temperature raised to −13 °C, indicating increased trityl radical **6** concentration. We interpret these observations as follows: we ascribe the detection of the relatively stable trityl radical **6** in this ESR experiment to its formation as an intermediate in the [1,2]-thio-Wittig rearrangement proceeding by a radical dissociation–recombination mechanism (Scheme 2). As the trityl radical **6** is a stable species it can escape from the solvent cage around the pair of radicals **6** and **7** and accumulate over time, as observed. Conversely, no escaped thio-radical anion **7** was detected, so it must be short-lived. Furthermore, we did not observe radicals **6** and **7** in their solvent cage due to their rapid recombination to form thiolate **8**.[22] The radical dissociation–recombination mechanism[23] is the widely accepted mechanism for the [1,2]-Wittig rearrangement,[9,24] but theoretical and experimental studies have shown that an anionic mechanism can operate in some circumstances.[25] These ESR spectroscopy results support the operation of the radical mechanism for the [1,2]-thio-Wittig rearrangement of enolate **5** (Scheme 2), but, due to the exclusivity of the ESR experiment, do not prove that this is the predominant mechanism.

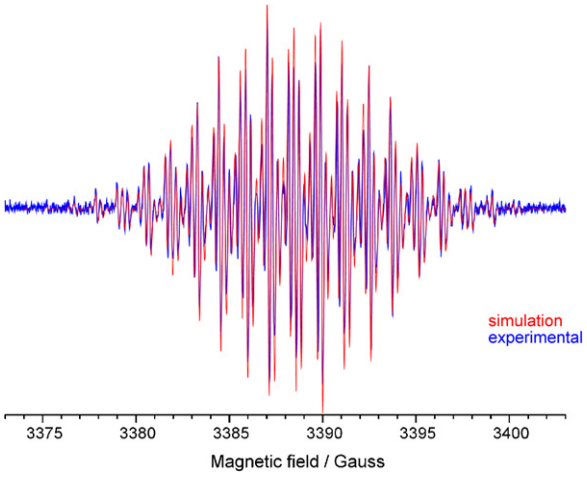


Figure 1. Experimental ESR spectrum at −23 °C and superimposed simulated trityl radical spectrum.

We have shown that enolate **5** formed from methyl *S*-trityl mercaptoacetate **2** can be C-alkylated in a high yield at or below −40 °C, but at higher temperatures the [1,2]-thio-Wittig rearrangement of enolate **5** is the predominant process; we have obtained ESR evidence that this rearrangement occurs by a radical mechanism: (Scheme 2).

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11. HSCHTrCO$_2$Me **3b**, white crystals mp 129 °C; ν_{max} ($CHCl_3$)/cm^{-1} 1957, 1734, 1595; δ_H (250 MHz; $CDCl_3$) 2.09 (1H, d, *J* 10.2 Hz, SH), 3.52 (3H, s, CH_3), 5.16 (1H, d, *J* 10.2 Hz, SCH), 7.20–7.43 (15H, m, Ph); δ_C (62.5 MHz; $CDCl_3$) 49.9 (CH), 52.3 (CH_3), 60.4 (C), 126.7 (CH), 127.6 (CH), 130.0 (CH), 144.8 (C), 172.3 (CO); *m*/*z* (CI) 366.1528 [$(M+NH_4)^+$. $C_{22}H_{24}NO_2S$ requires 366.1528], 334, 243 (Tr^+), 162. The structure confirmed by single crystal X-ray crystallography: crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 612593. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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