

The Reaction of Thiols with Electron-deficient Thioaldehydes. A New Synthesis of Unsymmetrical Disulfides

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Thiols react with thioaldehydes bearing an α -electron-withdrawing substituent in a thiophilic manner to give unsymmetrical disulfides in medium to good yields.

The recent discovery of convenient methods for the *in situ* generation of thioaldehydes¹ has allowed their potential in synthesis to be explored.² However, until now only a few reactions of these very reactive molecules, such as the Diels–Alder³ and the ene reactions,⁴ have been extensively studied. We have decided to enlarge the possible uses of thioaldehydes, and have studied their reaction with thiols.

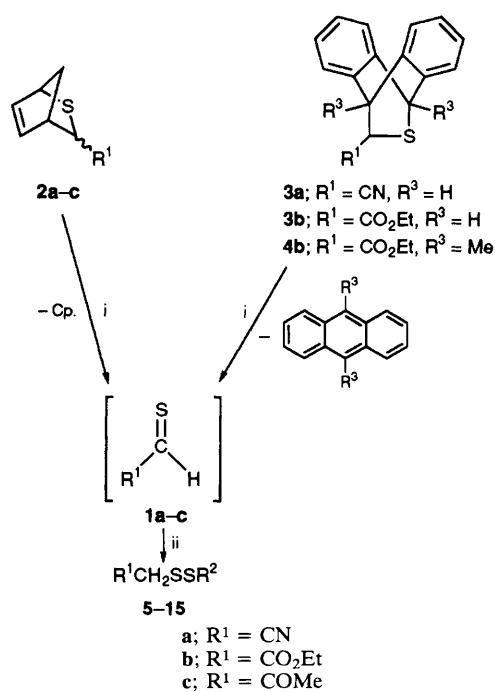
Bulpin and Masson⁵ have recently reported that phosphonodithioformates react with thiols in the presence of triethylamine in a thiophilic manner. Similar reactions⁶ were observed for other thiocarbonyl compounds bearing electron-withdrawing substituents. Thus, it could be expected that electron-poor thioaldehydes should give unsymmetrical disulfides in reactions with thiols in basic solution.

We first studied the reaction between thioformyl cyanide **1a**⁷ and 2-methylpropane-2-thiol (Scheme 1). When the thioaldehyde precursor **2a**⁸ (0.5 mmol) was heated in refluxing toluene (5 ml) for 3 days in the presence of 2 equiv. of the thiol and 2 equiv. of triethylamine, the disulfide **6** was isolated in 90% yield after work-up and purification by preparative TLC on silica gel. The use of only 1 equiv. of thiol and amine decreased the yield to 55% owing to the competitive oligomerization of the thioaldehyde.

Other examples (Table 1)[†] show that the yields are lower with non-tertiary thiols. The major by-product was then the symmetrical disulfide R^2SSR^2 , resulting from the attack of the excess of thiol on the unsymmetrical disulfide formed. Such a reaction is of course not unexpected when a disulfide is heated in the presence of a thiolate for a relatively long time.⁹ As this long time was required to complete the cycloreversion of the thianorbornenes **2a–c**, we decided to try the 11-thiaethanoanthracene precursors **3a,b** and **4b** which are known to give

good yields of the corresponding thioaldehydes in a few hours at 110 °C.^{3c}

In fact, reasonable yields were then obtained for secondary (compare the two syntheses of disulfide **7**) and primary thiols (**13–15**). The 9,10-dimethylantracene adduct **4b**^{3c} was found to be particularly convenient for the trapping of ethyl thioacetate **1b** with thiols. Comparison of the three syntheses of the disulfide **9** clearly demonstrates that adduct



[†] The unsymmetrical disulfides **5–15** gave ¹H NMR, ¹³C NMR, IR and mass spectra (including HRMS) in agreement with their proposed structures. Selected diagnostic NMR data (CDCl₃): **5**, ¹H, δ 3.41 (s, CH₂); ¹³C, δ 116.2 (CN); **8**, ¹H, δ 2.91 (t, CH₂) and 3.46 (s, CH₂); ¹³C, δ 116.8 (CN); **9**, ¹H, δ 3.49 (s, CH₂); ¹³C, δ 169.3 (CO); **10**, ¹H, δ 2.30 (s, CH₃) and 3.49 (s, CH₂); ¹³C, δ 203.1 (CO).

Scheme 1 Reagents and conditions: i, toluene, reflux; ii, R²SH, Et₃N (2 equiv. of each)

Table 1 Preparation of the disulfides 5–15

Precursor	R ²	Reaction time	Product	Yield (%) ^a
2a	Bu ^t	3 days	5	90
2a	EtCMe ₂	3 days	6	82
2a	Pr ⁱ	3 days	7	54
2a	Pr ⁿ	3 days	8	60
2b	Bu ^t	3 days	9	20
2c	Bu ^t	3 days	10	55
2c	EtCMe ₂	3 days	11	64
2c	Pr ⁿ	3 days	12	35
3a	Pr ⁱ	120 min	7	75
3b	Bu ^t	120 min	9	55
4b	Bu ^t	90 min	9	90
4b	Pr ⁿ	90 min	13	52
4b	Me[CH ₂] ₅	90 min	14	78
4b	Me[CH ₂] ₇	90 min	15	77

^a Yield of purified product based on the thioaldehyde precursor.

4b is the best retro-Diels–Alder precursor for the thioaldehyde **1b**, at least for this reaction.

We have also attempted the reaction of thiobenzaldehyde, generated from its anthracene adduct,^{3a} with 2-methylpropane-2-thiol. However, in this case, no disulfide could be isolated (nor could products resulting from the alternative carbophilic attack).¹⁰ This clearly points to the fact that a strong electron-withdrawing substituent, creating a partial positive charge on the sulfur atom, is necessary to observe the nucleophilic addition of the thiolate. In the same way, no reaction was observed between *tert*-butyl methyl thioketone and benzyl thiol.

In conclusion, the reaction of electron-deficient thioaldehydes with thiols complements the previously known routes to unsymmetrical disulfides¹¹ and once again shows the usefulness of these reactive thiocarbonyl compounds.

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