SYNTHESIS OF A 1,2-DITHIIN MEDIATED BY ELECTROPHILIC REAGENTS

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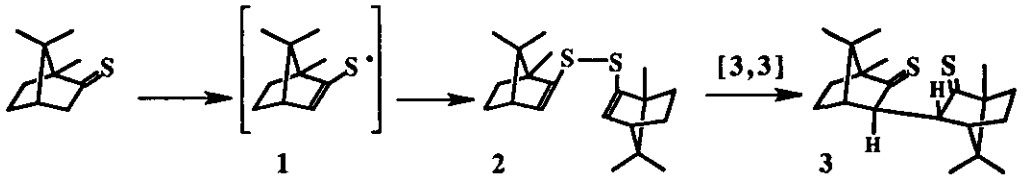
Abstract - The one step conversion of bis-thiocamphor into its corresponding 1,2-dithiin is achieved by using various electrophilic halides. The influences of solvent, temperature and acidity of the medium revealed that it is possible to selectively direct the reaction towards, either the 1,2-dithiin or a mixture of the thiophene/trithiepin homologues.

1,2-Dithiins constitute an interesting class of compounds, owing to their biological properties[1] and structural features.[1,2] Since the pioneer work of Schroth,[3] recent synthetic efforts based on bis-enethiols,[4] and on bis-thioenolates,[5] culminated in the first total synthesis of Thiarubrine B.[6] This prompted us to report the results of our own effort in this field.

Campbell *et al.*,[7] reporting the preparation of bis-thiocamphor (**3**), proposed a mechanism involving the intermolecular coupling of an *enethiyl radical* species (**1**) to form the disulfide (**2**) (Scheme 1).

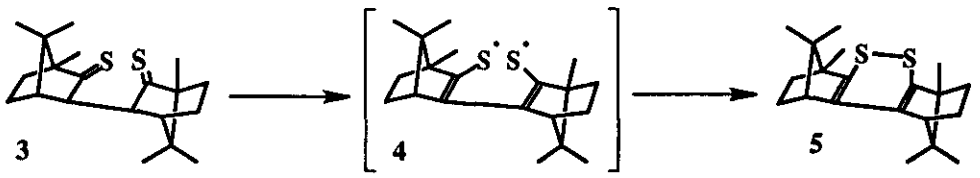


1 2 3

Scheme 1

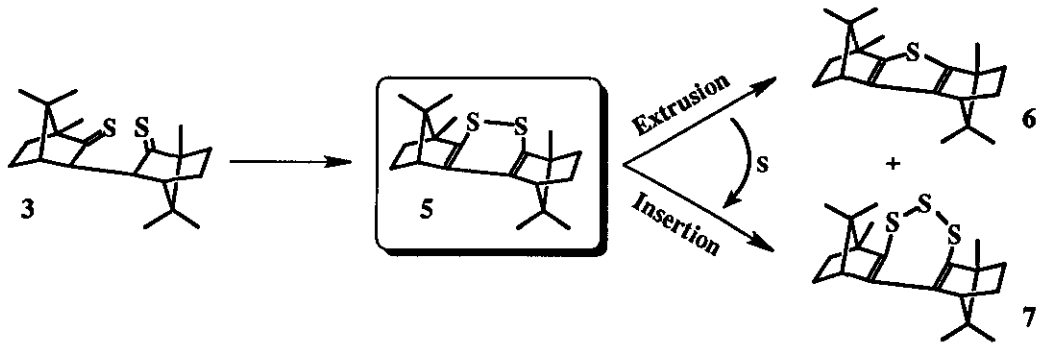
We envisioned to extrapolate this method, by applying its intramolecular version on the corresponding bis-enethiyl radical (**4**) of bis-thiocamphor (**3**), to reach the dithiin (**5**) (Scheme 2).

Thus, using chloramine T (whose coupling yield with thiocamphor reached 50% of the expected disulfide (**2**)),[7] we only got 46% (see Table 1, entry 2) of a mixture made of compounds (**6**) and (**7**).[8]



Scheme 2

In the same vein,[7] bis-thiocamphor was submitted to the action of NBS, only to afford a weak amount of the expected disulfide (5), while (6) and (7) were still largely predominant (entry 4). (Scheme 3)



Scheme 3

Hence, the need for more selective and efficient reagents led us to the use of thionyl and sulfuryl chlorides. Analysis of Table 1 indicates: a) the crucial influence of the reagent-solvent tandem; b) to a certain extent, the less pivotal incidence of the stoichiometry-temperature couple; and c) the negligible effect of the medium acidity (the presence of molecular sieve or a base did not significantly alter any results).

Interestingly, a 98% yield of mono- and trisulfide was obtained when thionyl chloride was used in dichloromethane (entry 5), though in acetonitrile and benzene (entries 6 and 7) the drastic drop of yield might suggest a polarity influence.

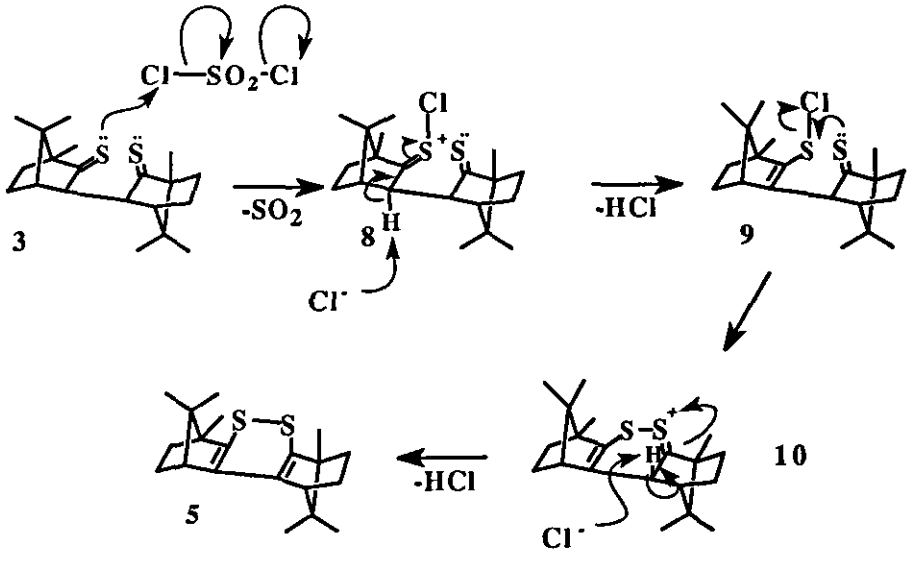
The use of one equivalent of sulfuryl chloride (entries 9 and 10) did not produce the expected yields because of the presence of a complex mixture of more polar products, along with (5), (6), and (7). These compounds are likely to be considered as side products obtained *via* the sulfenyl chlorides formed *in situ* by the action of sulfuryl chloride with (5). Thus, optimized conditions were observed when only half an equivalent of reagent was used (entry 12), avoiding the mixture of sulfides, and allowing the unconsumed starting material to be recycled. This 48% yield is then fully comparable with the 50% of acyclic disulfide (2) reported earlier, for the couple thiocamphor / chloramine T.[7]

Table 1. Influence of the Reaction Conditions on the Abundance of (5), (6) and (7).

	Reagents	Conditions	(5) % [a]	(6+7) % [a]	(6/7) [b]
1	Chloramine T	EtOH, 20°C, 24 h, 5 eq.	0	8	70/30
2		EtOH, Δ, 24 h, 5 eq.	0	46	70/30
3	NBS	CH_2Cl_2, 20°C, 15 min, 1 eq.	0	40	60/40
4		C_6H_6, 20°C, 30 min, 1 eq.	8	55	65/35
5		CH_2Cl_2, 0°C, 15 min, 1 eq.	0	98	75/25
6	$SOCl_2$	MeCN, 20°C, 10 min, 1 eq.	0	70	75/25
7		C_6H_6, 20°C, 30 min, 1 eq.	0	Traces	---
8		CH_2Cl_2, 20°C, 10 min, 1 eq.	Traces	65	75/25
9		C_6H_6, 20°C, 10 min, 1 eq.	47	14	40/60
10	SO_2Cl_2	C_6H_6, 5°C, 10 min, 1 eq.	55	10	45/55
11		C_6H_6, 20°C, 10 min, 0.5 eq.	40[c]	4	65/35
12		C_6H_6, 5°C, 10 min, 0.5 eq.	48[d]	Traces	---

a) *Isolated yields.* b) *Ratios determined by hplc.* c) 48% of recovered (**3**). d) 44% of recovered (**3**).

Nevertheless, and in sharp contrast with what has been observed in the case of thiocamphor,[7] bis-thiocamphor **does** react in the dark with halides. This would suggest that an ionic mechanism could be invoked, involving intermediate (**9**). (see Scheme 4) Furthermore, the fact that dithione (**3**) was inert to the action of AIBN would support indirectly such a pathway, and weaken our previous diradical hypothesis (outlined in Scheme 2).



Scheme 4

Consequently, starting with an enolizable 1,4-dithione, it was possible to prepare the corresponding 1,2-dithiin *via* a very simple and mild one step reaction.

EXPERIMENTAL SECTION

Preparation of 1,2-dithiin (5)[8]

To a solution of dithione (3) (100 mg, 0.3 mmol) in benzene (10 ml) at 5 °C was added a 1.24 M solution of sulfuryl chloride in benzene (0.120 ml, 0.15 mmol). After 10 min at this temperature, the resulting mixture was concentrated in vacuo. The residue was purified by filtration on a pad of silica gel (hexane) to give (5) as a dark red solid (48 mg, 48%); mp (uncorrected) 122-123°C, lit.,[5b] 123°C.

Preparation of the thiophene (6) and trithiepin (7) derivatives[8]

To a solution of dithione (3) (100 mg, 0.3 mmol) in dichloromethane (10 ml) at 0 °C was added a 1.37 M solution of thionyl chloride in dichloromethane (0.220 ml, 0.3 mmol). After 15 min at this temperature, the resulting solution was concentrated in vacuo. The residue was then filtered on a pad of silica gel (hexane) to give a mixture of (6) and (7) (93 mg, 98%), with a ratio of 75/25 as determined by hplc analysis (C_{18} reversed phase column, eluant: methanol/water - 95/5). The two products were separated by plate chromatography (silica gel G - hexane) in order to be caracterized. **Thiophene (6):** white solid, mp (uncorrected) 97-98°C (EtOH/H_2O), lit.,[5b] 98°C. **Trithiepin (7):** yellow solid, mp (uncorrected) 141-143°C (EtOH/H_2O), lit.,[5b] 143°C.

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8. During the course of this work, the preparation and caracterization of compounds (**5**), (**6**) and (**7**), involving basic deprotonation, was published; along with the disproportionation connecting them. (See ref. 5b)

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