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LETTERS

A Novel Synthesis of Functional Dithioesters, Dithiocarbamates, Xanthates and Trithiocarbonates

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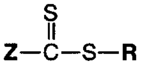
Abstract: A novel synthesis of functional dithioesters, dithiocarbamates, xanthates and trithiocarbonates is described. Heating a bis(thiocarbonyl) disulfide with an azo-compound results in the formation of (thiocarbonyl)sulfanyl derivatives in moderate to high yield. The process is proposed as the method of choice for preparing *tertiary* (thiocarbonyl)sulfanyl compounds and is compatible with a wide range of functionalities (*e.g.* carboxy, hydroxy and nitrile). © 1999 Elsevier Science Ltd. All rights reserved.

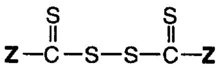
Recently, we reported a new living radical polymerization (the **RAFT** process[1,2]) that offers exceptional versatility and produces polymers of controlled molecular weight and narrow polydispersity (M_w/M_n usually < 1.2, sometimes < 1.1). This process is accomplished by performing a radical polymerization in the presence of a (thiocarbonyl)sulfanyl derivative Z-C(=S)-SR (**1**)[1-3] [or a bis(thiocarbonyl) disulfide (**2**)[4]] which acts as an efficient reversible addition-fragmentation chain transfer agent (a **RAFT** agent)[1-3,5] and confers living characteristics on the polymerization.

In the course of this ongoing investigation, we also developed a new strategy for combining condensation polymerization and the **RAFT** process to make narrow polydispersity AB and ABA block copolymers.[1,3,5] Examples of such block copolymers include polystyrene-*block*-poly(ethylene glycol), poly(benzyl methacrylate)-*block*-poly(ethylene glycol) and polystyrene-*block*-poly(ethylene glycol)-*block*-polystyrene. In order to put this strategy into practice, we required a **RAFT** agent[1-3,5] which incorporated functionality appropriate for coupling with an ω-hydroxy prepolymer (*e.g.* carboxy). The *tertiary* dithiobenzoate (**1a**) is one such compound.



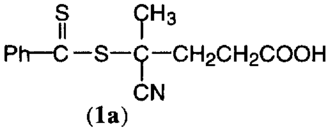
$$Z-\overset{\overset{S}{\|}}{C}-S-R$$

(1)



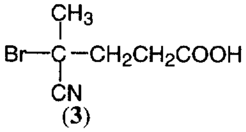
$$Z-\overset{\overset{S}{\|}}{C}-S-S-\overset{\overset{S}{\|}}{C}-Z$$

(2)



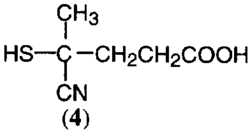
$$Ph-\overset{\overset{S}{\|}}{C}-S-\underset{CN}{\overset{CH_3}{C}}-CH_2CH_2COOH$$

(1a)



$$Br-\underset{CN}{\overset{CH_3}{C}}-CH_2CH_2COOH$$

(3)



$$HS-\underset{CN}{\overset{CH_3}{C}}-CH_2CH_2COOH$$

(4)

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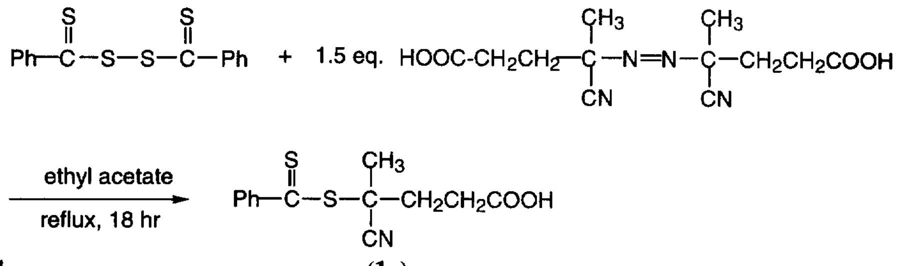
Literature methods available for the synthesis of dithioesters[6-12] [*e.g.*, (i) the alkylation of a $ZC(=S)S^-M^+$ (M=Na or K) or ZC(=S)SMgX with an appropriate alkyl halide,[6] (ii) the thiation of an *S*-substituted thioester using Lawesson's reagent[7] and (iii) trans-esterification of a dithioester with a thiol] suffer from a number of problems. These may include low yields or a slow rate of reaction when applied to the synthesis of tertiary esters, incompatibility with unprotected protic functionality, and the lack of suitable precursors [*ie.* the *tertiary* α-bromonitrile (**3**) or α-sulfanylnitrile (**4**) in the case of dithioester (**1a**)]. In this letter, we wish to report a simple synthetic route to the *tertiary* dithiobenzoate (**1a**) (shown in Scheme 1) and its extension to the synthesis of related compounds (**1b** - **1g**, see Table 1).



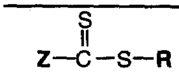
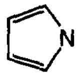
Scheme 1 (**1a**)

The process generally involves heating a solution of the appropriate bis(thiocarbonyl) disulfide[13-18] with 1.5 molar equivalents[19] of an azo compound (many are available commercially) in the absence of oxygen (this is readily achieved by either refluxing the solution or degassing by repeated freeze-evacuate-thaw cycles). A reaction time corresponding to 4-5 half-lives of the azo-compound was employed.

The scope of this simple reaction has been extended to the synthesis of other functional dithiobenzoates such as (**1b**) and (**1c**) from bis(thiobenzoyl) disulfide[13,14] with the corresponding azo-compound 4,4'-azobis(4-cyano-*n*-pentanol)[20] and 2,2'-azobis(isobutyronitrile) (AIBN) respectively. The generality of the reaction for the synthesis of other (thiocarbonyl)sulfanyl compounds was established by examining the reaction of AIBN with various bis(thiocarbonyl) disulfides, such as bis(pyrrole-*N*-thiocarbonyl) disulfide,[15] tetramethylthiuram disulfide,[16] *O*-ethyl xanthogen disulfide,[17] and bis(methylsulfanyl(thiocarbonyl)) disulfide,[18] to provide the corresponding 2-cyanoprop-2-yl dithiocarbamates (**1d**), (**1e**), xanthate (**1f**) and trithiocarbonate (**1g**) respectively. Results of all these experiments are shown in Table 1. It is noteworthy that the yield of compound (**1c**) obtained by the current process (69%) is significantly higher than that obtained by the alkylation of the (thiobenzoyl)sulfanyl magnesium bromide (prepared from phenyl magnesium bromide and CS_2 in THF) with α-bromoisobutyronitrile[21] (43% isolated yield).

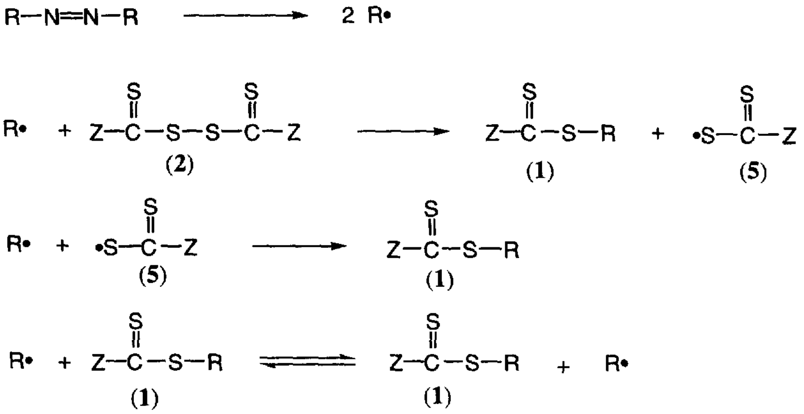
Representative Experiment: *Synthesis of 4-Cyano-4-((thiobenzoyl)sulfanyl)pentanoic Acid (1a)*
A solution of 4,4'-azobis(4-cyanopentanoic acid) (58.39g, 0.208 mol) and bis(thiobenzoyl) disulfide (42.5 g, 0.139 mol) in ethyl acetate (800 mL) was heated at reflux for 18 hours. After removal of the volatiles *in vacuo*, the crude product was subjected to column chromatography (Kieselgel-60, 70-230 mesh) with ethyl acetate : *n*-hexane 2:3 as eluent, to afford compound (**1a**) as a red oil (53.0 g, 68% yield). On keeping in a freezer at -20°C, the product turned into a red solid, m.p. 97-99 °C. ^{1}H-nmr ($CDCl_3$) δ (ppm) 1.95 (s, 3H, CH_3); 2.40-2.80 (m, 4H, CH_2CH_2); 7.42 (m, 2H, *m*-ArH); 7.60 (m, 1H, *p*-ArH) and 7.91 (m, 2H, *o*-ArH). ^{13}C-nmr ($CDCl_3$) δ (ppm) 24.2, 29.6, 33.1, 45.7, 118.6, 126.8, 128.7, 133.2, 144.6, 177.4 and 222.2. MS(CI): m/z 280 (M+1), 263, 169, 155, 142, 121, 99. IR (KBr disc): 3300-2500 (broad band, COO-H); 2232.5 (CN); 1708.4 (C=O); 1044.1 (C=S).

Table 1: Synthesis of compounds (**1a**)-(**1g**)[22]

 $Z-C(=S)-S-R$ (1)	Z	R	Condition	% yield[d]
1a	Ph	$C\ (CH_3)(CN)(CH_2CH_2COOH)$	a	68
1b	Ph	$C\ (CH_3)(CN)(CH_2CH_2CH_2OH)$	b	46
1c	Ph	$C\ (CH_3)_2(CN)$	a	69
1d		$C(CH_3)_2(CN)$	b	61
1e	$(CH_3)_2N$	$C(CH_3)_2(CN)$	c	93
1f	CH_3CH_2O	$C(CH_3)_2(CN)$	a	94
1g	CH_3S	$C(CH_3)_2(CN)$	c	47

a) reflux, EtOAc, 18hr; b) degas, EtOAc, 70°C, 24hr; c) reflux, benzene, 24hr; d) isolated yield.

A probable mechanism for the formation of compounds (**1**) is shown in Scheme 2. Radicals (**R•**) formed thermally from the azo-compound react with the disulfide (**2**) to form (thiocarbonyl)sulfanyl compound (**1**) and a (thiocarbonyl)sulfanyl radical (**5**). The radical (**5**) generated under the reaction conditions is most likely consumed by coupling with another free radical (**R•**) to form further compound (**1**) but may couple with another radical (**5**) to reform compound (**2**). Likely side reactions are the self reaction of species (**R•**) by combination or disproportionation and other reactions involving **R•**. Note that the reaction of **R•** with (**1**) is degenerate and does not lead to by-products.



Scheme 2: Suggested mechanism for the formation of compounds (**1**).

In conclusion, the work presented here provides a general method for the synthesis of functional dithioesters, dithiocarbamates, xanthates and trithiocarbonates which are otherwise difficult to obtain.

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