

» Desire pulls  
stronger than  
experience  
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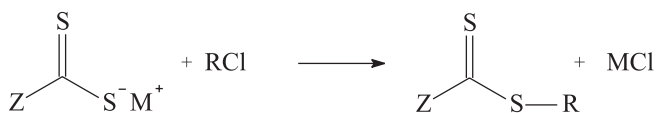
## 3. Experimental Procedures

### Synthetic pathways *en route* towards desirable transfer agents

*Synopsis: This chapter presents an overview of various possible routes that yield dithioesters, structures suitable as transfer agents for reversible addition–fragmentation reactions. Though not all of these routes were actively explored, they do provide a guideline for future syntheses, indicating specific advantages and drawbacks of the various approaches. Furthermore, the experimental part of this chapter details the synthesis of all transfer agents used in this thesis, thereby providing examples of several of the aforementioned synthetic pathways.*

#### 3.1. Introduction

In chapter 2 the general structure of the RAFT agents applied in this study was introduced along with several specific examples. Although numerous different structures may permit reversible addition–fragmentation chain transfer reactions, it was already pointed out that several classes of sulfur containing species are especially designed to be applied as such. Dithioesters are unsurpassed in activity by xanthates, trithiocarbonates and thiocarbamates which can be used as well. The work in this thesis makes use exclusively of aromatic dithioesters that contain a dithiobenzoate moiety. An overview will be presented to the reader detailing the most common known synthetic pathways to such dithioesters. Furthermore, the experimental details on the synthesis of several dithiobenzoate esters are provided. For clarity and consistency, general reaction schemes will make use of **Z** and **R** to



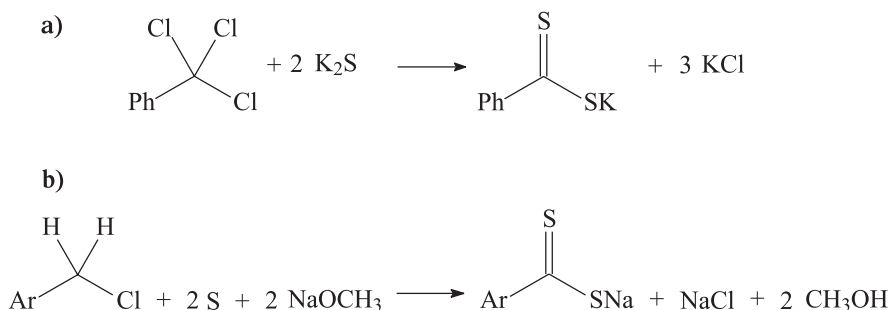
**Scheme 3.1.** Nucleophilic substitution of an alkyl halide by a dithiocarboxylate salt forming a dithioester. The dithiocarboxylate can be an alkali(-earth) or ammonium salt.

indicate the activating group and the leaving group of the RAFT agent in the same way as in chapter 2 (see Scheme 2.8 on page 27). By doing so, one can quickly identify the starting materials needed to prepare a specific RAFT agent via the various pathways outlined in this chapter.

## 3.2. Synthetic Approaches to Dithioesters

### 3.2.1. Substitution Reactions with Dithiocarboxylate Salts.

The approach first requires the formation of a dithiocarboxylic acid salt which can be prepared in a number of different ways, which are outlined below. The dithiocarboxylate takes the role as nucleophile in substitution reactions with *e.g.* alkyl halides that are added directly to the reaction mixture or to the salts after isolation (Scheme 3.1). Most dithiocarbonate salts (alkali and alkali-earth) have a limited stability and should be used directly after preparation without isolation or extensive purification.<sup>2,3</sup> For conservation purposes, the conversion to an ammonium salt (in particular the piperidinium salt) appears to be the only acceptable option. These crystalline salts have been reported to be fairly stable. They allow facile generation of the free acid or can be used directly in substitution reactions.<sup>4,5,6</sup> Stable lead and zinc salts have been prepared as well for identification processes but these lack synthetic utility.<sup>7,8,9</sup> Both the ammonium and the alkali(-earth) salts can serve as nucleophiles in substitution reactions of alkyl halides, alkyl sulfates or alkyl sulfonates to produce the desired dithioesters.<sup>6,10,11,12</sup> When the substitution reaction is omitted, the dithioacid can be obtained by protonation of the salt with a strong acid. The dithioacid in turn can be converted to a dithioester by several other routes discussed in the sections 3.2.2, 3.2.3 and 3.2.7.



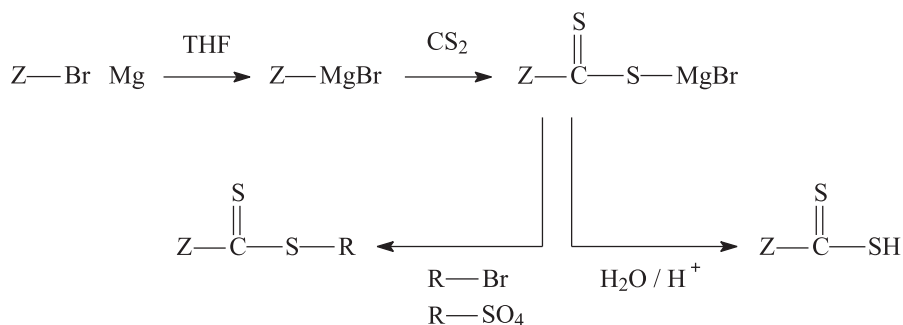
**Scheme 3.2.** a) Conversion of benzotrichloride to potassium dithiobenzoate. b) Conversion of aromatic monohalidemethylates to dithio carboxylates by the reaction with elemental sulfur and alkali alkoxylates. Both reactions take place in an alcoholic medium.

### from Aromatic Mono-, Di- and Trihalidemethylates

The first synthesis of a dithiocarboxylate was reported by Fleischer<sup>13</sup> who prepared dithiobenzoic acid from benzalchloride ( $\text{C}_6\text{H}_5\text{CHCl}_2$ ) and potassium sulfhydrate in ethanol and water, which yielded traces of the acid as a red oil upon the addition of hydrochloric acid. Wood *et al.*<sup>14</sup> later showed that the success of this synthesis was most likely due to impurities in the potassium sulfhydrate, most notably potassium sulfide. The latter reacts with benzal chloride to form thiobenzaldehyde as an unstable intermediate which, depending on the reaction conditions, can undergo the Cannizzaro reaction to yield potassium dithiobenzoate amongst other products.

Benzotrichloride can be converted to potassium dithiobenzoate by slow addition to a suspension of potassium sulfide in boiling methanol (Scheme 3.2, a).<sup>15</sup> The reaction is exothermic and needs to be cooled once it has started.

Another method to come to aromatic dithiocarboxylates is documented by Becke and Hagen.<sup>16</sup> Here, aromatic monohalidemethylates are treated with elemental sulfur and (earth) alkali alkoxides (Scheme 3.2, b). The synthesis is compatible with a variety of substituents on the aromatic ring. Alkyl, alkoxy and halogen groups remain untouched while additional methylhalide groups will lead to multiple dithiocarboxylates moieties. This approach is taken in the synthesis of 2-phenylprop-2-yl dithiobenzoate (section 3.4.3, page 79). The methods outlined in Scheme 3.2 typically produce a variety of side products and salts and some degree of purification will be required before substitution reactions are performed.



**Scheme 3.3.** The Grignard synthesis. The reaction between a Grignard reagent and carbon disulfide yields a reactive dithiocarboxylic acid salt which may be quenched and acidified to access the protonated acid or alternatively, an alkyl halide may be added to participate in a nucleophilic substitution.

### from Grignard Reactions

Houben<sup>7</sup> was the first to report the use of Grignard salts in the synthesis of dithioacids. Arylmagnesiumhalides were allowed to react with carbon disulfide in dry ether, producing the magnesiumhalide salt of the corresponding dithioacid. These reactive species can be transformed directly into a dithioester by addition of a suitable alkyl halide or alkyl sulfate<sup>17,7</sup> to the reaction mixture. The literature reports reasonable yields for the coupling of especially aromatic but also of aliphatic intermediates with alkyl iodides and bromides.<sup>12</sup> RAFT agents, applicable to a wide range of monomers, generally require a tertiary halide (*e.g.* *tert*-butyl bromide) to be coupled to the active intermediate. The alkyl halide will form the **R**-group and needs to possess a good homolytic leaving-group character. Unsurprisingly, such groups are the most difficult to attach to the dithio carbonate moiety in the first place. This route was followed for the synthesis of 2-(ethoxycarbonyl)prop-2-yl dithiobenzoate which is detailed in section 3.4.2. According to Meijer *et al.*<sup>18</sup> the procedure can be optimized in several ways. First, the yield improved considerably when tetrahydrofuran was used as the reaction medium instead of ether. Second, the reaction rate of alkyl magnesium chlorides was found to be higher than that of the corresponding bromides in both the formation of the dithiocarbonate intermediate and that of the final ester, which could prove useful for the preparation of dithioesters with more sterically hindered **R**-groups. Third, it was found that reactions could be conducted at much lower temperatures when 10–20% hexamethylphosphoramide (HMPA, [(CH<sub>3</sub>)<sub>2</sub>N]<sub>3</sub>PO) was added to the reaction. The alkylation of *e.g.* C<sub>2</sub>H<sub>5</sub>C(S)SMgBr with CH<sub>3</sub>I could be conducted at –35°C whereas the same reaction without HMPA requires 30 to 40°C to proceed at an acceptable rate. Although they only showed the temperature effect for relatively

easy-coupling alkyl halides, the results could imply that also the yields for tertiary halides would benefit from the addition of HMPA. Westmijze *et al.*<sup>19</sup> found that the addition of catalytic amounts of copper(I)bromide to Grignard reaction significantly increased the yield of several dithioesters derived from rather unreactive starting materials. The more reactive organocopper intermediates allowed the preparation of dithioesters with sterically hindered and unsaturated *Z*-groups.

Beside the direct esterification of the dithiocarbonate magnesiumhalide, the Grignard may also be quenched at this point with water and a strong acid, to gain access to dithiocarboxylic acid. These acids are generally very unstable and should not be isolated as such.<sup>12,15,20</sup> They are readily oxidized by oxygen to bis(thioalkyl)disulfides and should be used directly in further reactions or be converted to more stable ammonium salts. The formation of the acid is performed in the synthesis of 2-cyanoprop-2-yl dithiobenzoate (section 3.4.4, page 80).

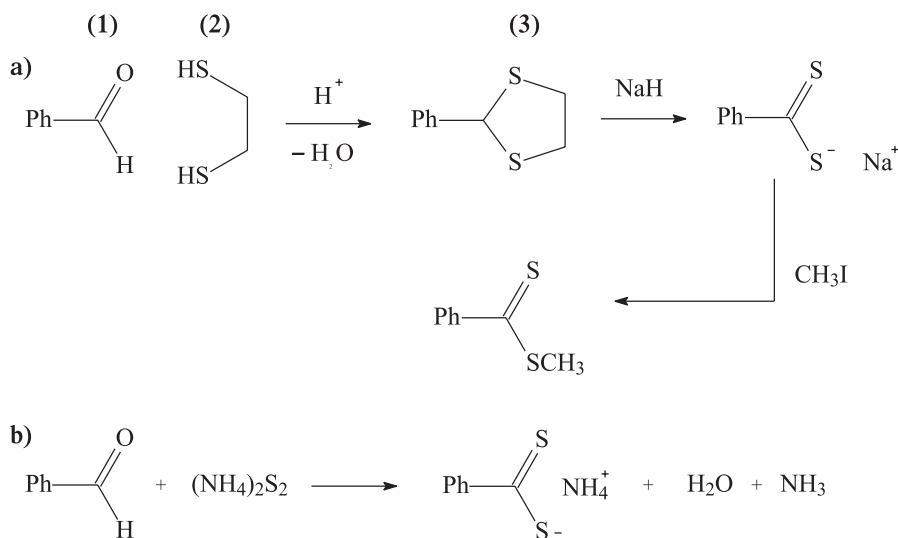
### from Aromatic Aldehydes

Gonella *et al.*<sup>21</sup> reported a convenient route to come to aromatic dithioesters using benzaldehyde (1) as the starting material (Scheme 3.4). Reacting this compound with ethanedithiol (2) in the presence of a catalytic amount of *p*-toluenesulfonic acid affords a thioketal (3). When a solution of the thioketal in dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) is treated with sodium hydride and an alkyl halide a dithioester is formed in varying yields (40–90%). The addition of the alkyl halide may also be omitted to gain access to the sodium salt of the aromatic dithioacid. The method has the advantage that it is tolerant to various functional groups on the aromatic ring.

Aromatic aldehydes can also serve as the starting material for the reaction with ammonium polysulfides. This approach was pioneered by Bost and Shealy<sup>22</sup> and later followed by Jensen and Pedersen.<sup>23</sup> The method is tolerant to various functional groups but gives only low to moderate yields (20–40%).

### 3.2.2. Addition of Dithio Acids to Olefins

The dithioacid in its protonated form can add to olefins to yield various dithioesters.<sup>24</sup> The ambivalent character of the dithioacid functionality allows addition to proceed by either a nucleophilic or electrophilic mechanism, depending on the nature of the olefin. Electrophilic olefins like acrylonitrile and vinylpyridine force the dithioacid to act as nucleophile. The reactions with (meth)acrylonitrile



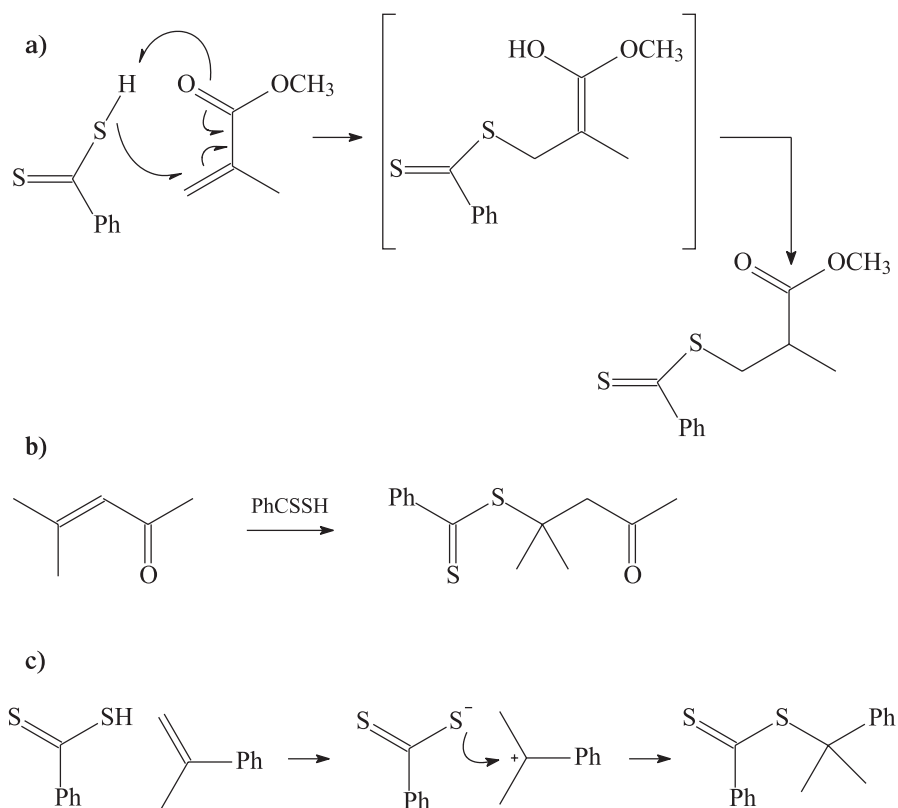
**Scheme 3.4.** a) The conversion of benzaldehyde to the sodium dithiobenzoate via a thioketal and subsequent esterification. b) Reaction between benzaldehyde and ammonium polysulfide of average composition  $(\text{NH}_4)_2\text{S}_2$ .<sup>22</sup>

and (meth)acrylic acid and their esters give dithioesters where the sulfur-containing group becomes attached to the least substituted side of the carbon-carbon double bond, making it inefficient raft agents (Scheme 3.5, a). Few electrophilic olefins exist that would result in good RAFT agents of which the addition to mesityl oxide (4-methyl-3-penten-2-one) is an example. This would give a dithioester possessing a good homolytic leaving group (Scheme 3.5, b).

The reaction with nucleophilic olefins obeys Markovnikov's rule. The olefin is protonated and the resulting carbocation combines with the negatively charged dithiocarboxylate group. The reaction with  $\alpha$ -methylstyrene yields 2-phenylprop-2-yl dithiobenzoate (Scheme 3.5, c). Experimental details of this synthesis are found in section 3.4.3.

### 3.2.3. Thioalkylation of Thiols and Thiolates.

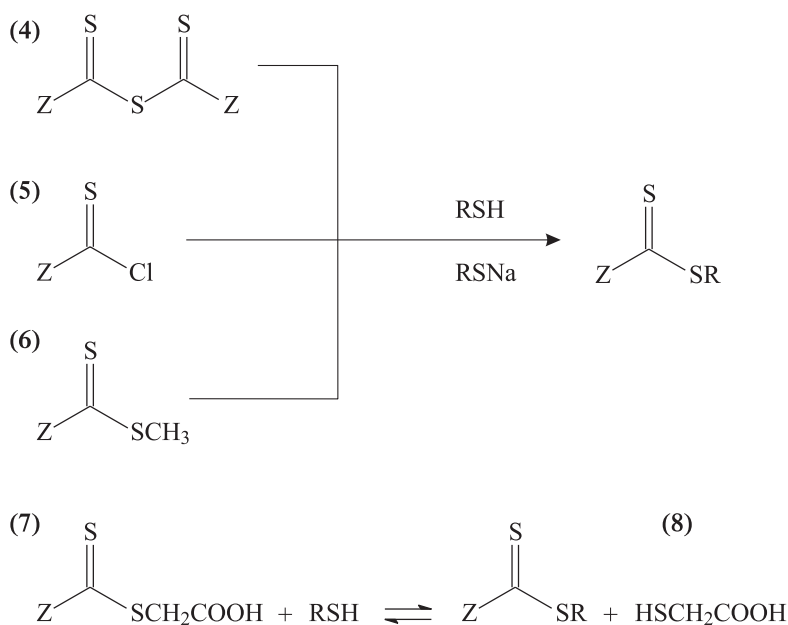
Thiols and alkali thiolates can be converted into dithioesters by thioacylation with *e.g.* bis(thioacyl) sulfides (4), thioacyl halides (5) and dithioesters (6, 7, Scheme 3.6). These reactions typically proceed in good to excellent yields (70–95%) and the main advantage over the use of dithio acid salts lies in the increased reactivity of the thioacylating species. The reaction can be considered as a nucleophilic displacement at the thiocarbonyl carbon by a sulfur nucleophile.



**Scheme 3.5.** a) Nucleophilic addition of dithiobenzoic acid to the carbon–carbon double bond of methyl methacrylate. The concerted mechanism of the addition is speculative.<sup>24</sup> The result is a RAFT agent with a poor homolytic leaving group. b) Nucleophilic addition of dithiobenzoic acid to mesityl oxide. The result is a RAFT agent with a good homolytic leaving group. c) Electrophilic addition of dithiobenzoic acid to  $\alpha$ -methylstyrene. The nucleophilic olefin is protonated, followed by the electrophilic attack of the sulfur.

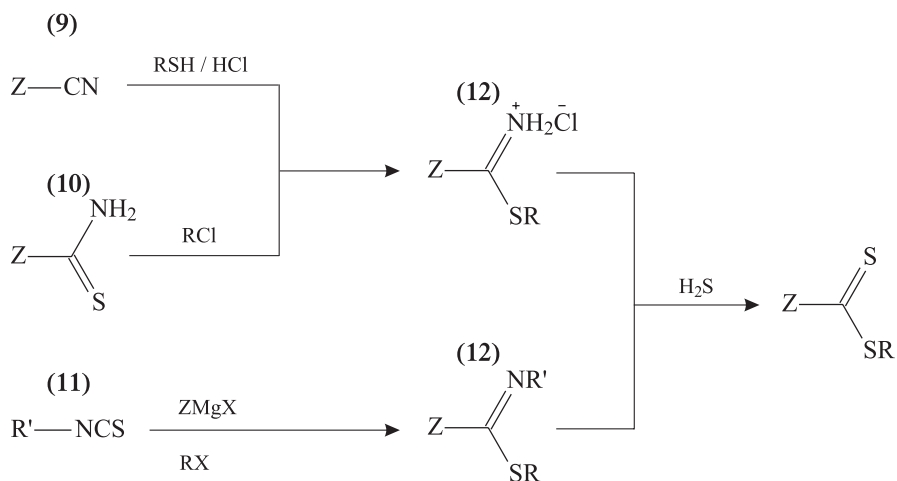
Bis(thioacyl) sulfides (**4**) are prepared by the reaction between dithio acids and 1,3-dicyclohexylcarbodiimide (DCC). The reaction between 4-methyl dithiobenzoic acid and half an equivalent of DCC in hexane at 0 °C gave bis(4-methylthiobenzoyl) sulfide in 80% yield.<sup>25</sup> Thioacyl halides (**5**) are prepared from dithioacids and thionyl chloride. In the case of dithiobenzoic acid, the reaction completes with 50 to 61% yield.<sup>26,27</sup>

Methyl dithiobenzoate (**6**) has been prepared in 50–90% yield by various methods outlined in section 3.2.1.<sup>18,21</sup> The transesterification of **6** and **7** can be considered as a special case of thioacylation of mercaptanes. The thioacylating agent is in this case a dithioester itself. The process can be used to convert dithioesters that are easily prepared (*e.g.* methyl dithiobenzoate, **6**) or commercially available (*e.g.*



**Scheme 3.6.** Thioalkylation of thiolates. Thiols and alkali thiolates can be converted into dithioesters by thioacylation with bis(thioacyl) sulfides (4), thioacyl halides (5) and dithioesters (6, 7).

*S*-(thiobenzoyl)thioglycolic acid, 7, Scheme 3.6) to more suitable RAFT agents.<sup>28</sup> These reactions take place selectively in the presence of other functional groups like hydroxides.<sup>29</sup> An equilibrium is established but this can be shifted entirely to the product side by removal of the volatile methanethiol (b.p. 6°C) in the case of 6. The reaction of 7 can be conducted in aqueous solution from which the hydrophobic dithioester separates. If the mercaptane is insoluble in water, a suitable organic medium will have to be found and the equilibrium can be shifted to the product side by washing the organic phase with an alkaline solution to preferentially remove thioglycolic acid (8). The main disadvantage lies in the fact that besides a suitable thioacylating agent, the desired R group (Scheme 3.6) should be available in the form of a mercaptane. The supply of tertiary mercaptanes is limited to *e.g.* *tert*-butyl mercaptane and *tert*-dodecyl mercaptane, but nonetheless, for these compounds, the routes presented in this section may be favoured to the substitution reactions of section 3.2.1, due to the higher yields.



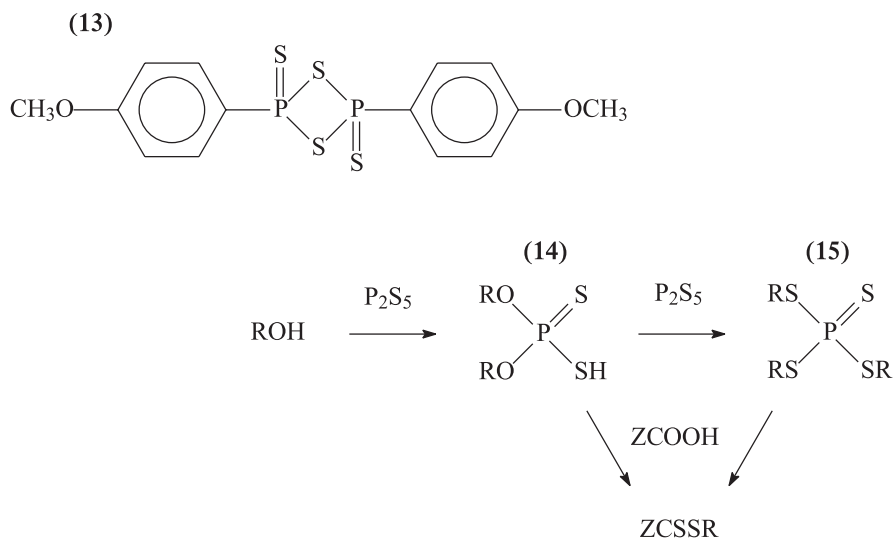
**Scheme 3.7.** Preparation of imidothioate esters and subsequent conversion to dithioesters with hydrogen sulfide.

### 3.2.4. via Imidothioate Intermediates

Treatment of imidothioates (**12**, Scheme 3.7) with hydrogen sulfide under acidic conditions is a widely used method to prepare dithioesters because of the broad range of available precursors. The imidothioate ester can be derived from a number of starting materials, *viz.* nitriles<sup>30</sup> (**9**), thioamides<sup>31</sup> (**10**) and isothiocyanates<sup>32</sup> (**11**). The yields of the process range from moderate to good (50–90%), but like in the majority of other routes, the **R** group should be available in the form of a halide or a mercaptane.

### 3.2.5. with Sulfur Organo-Phosphorus Reagents

Thiolesters (ZCOSR) are converted to dithioesters by the action of various sulfur organo-phosphorus reagents. When exposed to 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, **13**, Scheme 3.8) dithioesters are obtained in high yields ( $\geq 90\%$ ).<sup>33,34</sup> The thiolesters themselves are obtained from the esterification reaction of thiols and carboxylic acids.<sup>35,36,37</sup> Unlike the esterification of carboxylic acids and alcohols, this reaction is not successfully catalyzed by protons alone, but requires an activator like 1,3-dicyclohexylcarbodiimide to shift the equilibrium to a more favorable position.<sup>38</sup> Alternatively, thiols



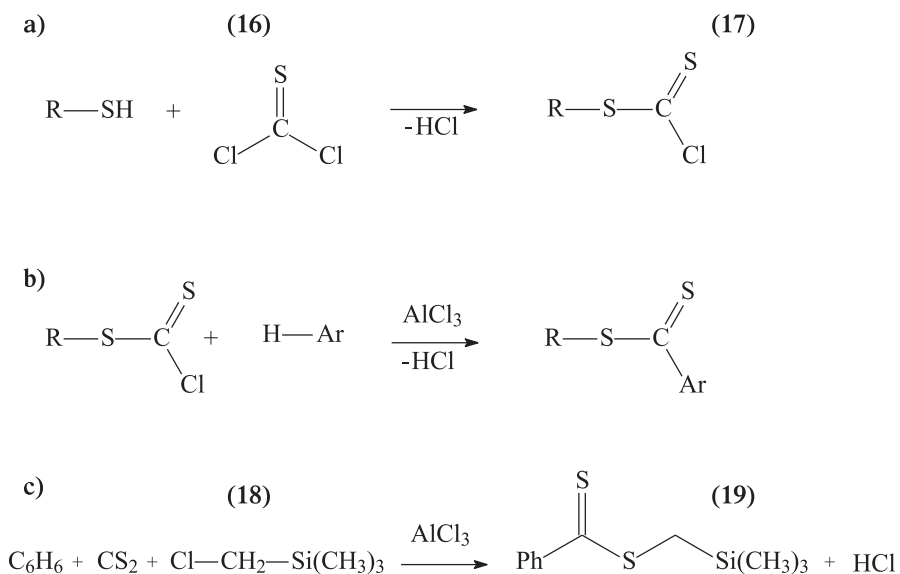
**Scheme 3.8.** Structure of Lawesson's reagent (13) and various intermediates (14, 15) that are formed in the reaction between alcohols, diphosphorus pentasulfide and carboxylic acids.

can be reacted with acyl halides (ZCOCl) under mild conditions, catalyzed by tertiary amines,<sup>39</sup> or the thioesters can be obtained from the reaction between carbonyl sulfide and Grignard salts.<sup>40</sup>

*O,O*-dialkyl dithiophosphoric acids (14, Scheme 3.8) can be used to convert carboxylic acids directly to dithioesters in moderate yields.<sup>41</sup> The *O,O*-dialkyl dithiophosphoric acids are prepared from alcohols and diphosphorus pentasulfide. If an excess of the latter is applied, the reaction proceeds to ultimately form trialkyl tetra-thiophosphates (15),<sup>42</sup> which react with carboxylic acids in higher yields. Davy and Metzner<sup>43</sup> showed that the procedure can be simplified to a one pot synthesis, directly converting carboxylic acids and alcohols into dithioesters with diphosphorus pentasulfide in moderate to good yields (40–90%) for methyl and ethyl esters. Although the method uses convenient starting materials and allows for upscaling, the applicability to secondary and tertiary alcohols remains unexplored.

### 3.2.6. Friedel-Crafts Chemistry

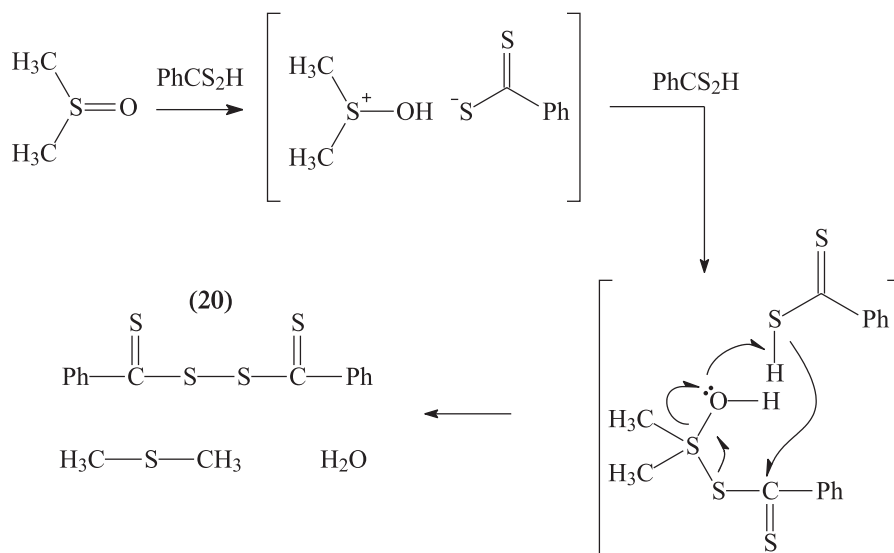
An alternative route to (substituted) dithiobenzoate esters is reported by Viola *et al.*<sup>44</sup> In their approach, the dithiocarbonate group is first attached to the **R**-group to form a reactive chlorodithioformic acid ester (17), which, under Friedel-Crafts conditions, adds to activated arenes in high yields (Scheme 3.9, b). The chlo-



**Scheme 3.9.** Synthesis of dithioesters by Friedel-Crafts reactions. a) Preparation of chlorodithioformic acid ester. b) Coupling between the chlorodithioformic acid ester and a benzene ring. c) Participation of carbon disulfide in selective Friedel-Crafts reactions.

rodithioformic acid esters themselves are prepared from the reaction between thiophosgene (16) and mercaptanes<sup>45</sup> or from dithio acids and thionyl chloride.<sup>46</sup> The first process takes place with 80–90% yield in the case of methyl mercaptane.<sup>45</sup> For RAFT synthesis a tertiary mercaptane would be desired which is commercially available in *e.g.* *tert*-dodecylmercaptane. The branched alkyl would make a good leaving group and has the additional advantage that the behavior of the radical has been thoroughly investigated in both homogeneous and heterogeneous polymerization systems, as it is used as a chain transfer agent itself.<sup>47</sup> The coupling of the chlorodithioformic acid ester to an aromatic ring is unlikely to be influenced strongly by the R-group but largely depends on the substituents on the benzene ring. With methyl, methoxy, hydroxyl or halogen substituents, the dithioesters were obtained in 60–95% yield. The hydroxyl substituted aromatic ring is inaccessible by the Grignard method, besides, differently substituted benzenes are more easily available than their brominated analogues that are required in the Grignard synthesis.

Another report on the formation of dithioesters using Friedel-Crafts chemistry comes from George,<sup>48</sup> who described a one pot synthesis of trimethylsilylmethyl dithiobenzoate (19) from a mixture of benzene, carbon disulfide and (chloromethyl)methyldichlorosilane (18). The success of this method strongly depends on the

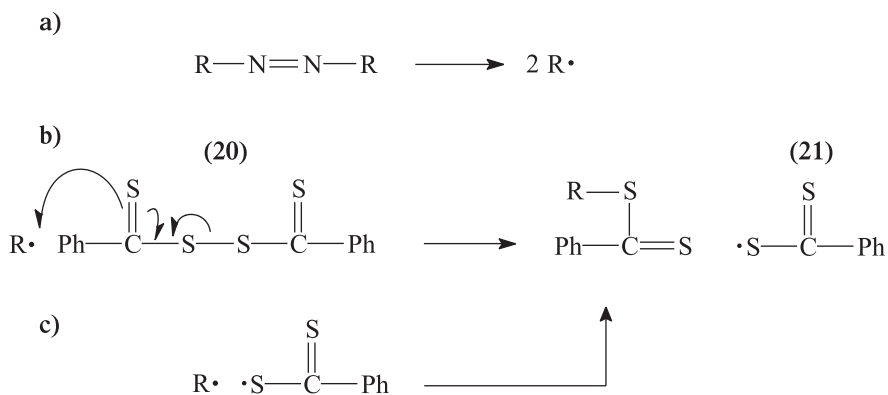


**Scheme 3.10.** Formation of bis(thiobenzoyl)disulfide (**20**) via the oxidative coupling of dithiobenzoic acid by dimethyl sulfoxide.

structure of the alkyl halogenide as in numerous other accounts, carbon disulfide is used as an inert solvent for the coupling between the alkyl halogenide and the aromatic ring. The details of the mechanism remain unclear, however, as the aluminium chloride appears to be a reactant rather than a catalyst.

### 3.2.7. via Bis(thioacyl)disulfides

A novel addition to the field of synthetic routes is that of the reaction between carbon-centered radicals and bis(thioacyl)disulfides.<sup>49,50,51</sup> The bis(thioacyl)disulfides (**20**) are prepared by oxidative coupling of dithioacids or their salts. Most dithioacids are oxidized by oxygen from the air, or in a more rapid and controlled manner by other mild oxidizing agents like iodine or hydrogen peroxide. Stronger oxidizers like potassium permanganate typically destroy the dithiocarbonate moiety. The coupling of dithiocarboxylates with iodine is an established process.<sup>7,10</sup> In the case of dithiobenzoate salts, the reaction is typically conducted in an aqueous medium from which the product precipitates. This procedure has been attempted initially in the synthesis of 2-cyanoprop-2-yl dithiobenzoate, which is described in section 3.4.4 on page 80. A very large amount of potassium iodide was needed to solubilize the required iodine in the water phase and the large reaction volume complicated upscaling. Besides, the product did not precipitate in crystals but separated out in the form of a sticky oil-like layer which was difficult to purify. The reaction



**Scheme 3.11.** Preparation of dithioesters by radical reactions. **a)** Radicals are generated by the dissociation of an initiator. **b)** Reaction between a radical and the bis(thioacyl)disulfide generates a dithioester molecule and a relatively stable dithiobenzoate radical (21). **c)** The dithiobenzoate radical (21) recombines with a initiator derived radical R, forming another instance of the dithioester.

can be conducted under more convenient conditions when dimethyl sulfoxide is used for the oxidation (Scheme 3.10).<sup>24</sup> The reaction could be performed in an open vessel at ambient conditions in bulk or in solution and produced bis(thiobenzoyl)disulfide in excellent yield (>90%, based on crude dithiobenzoic acid).

Carbon-centered radicals react with bis(thioacyl)disulfides (20) by the mechanism postulated in Scheme 3.11.<sup>50</sup> The radicals are generated by a conventional azo initiator (Scheme 3.11, a) in the first step and these react with a bis(thioacyl)disulfides, forming a dithioester together with a sulfur centered radical (21). This radical in turn can recombine with a carbon-centered radical to form the same dithioester species (Scheme 3.11, c). The advantage of this process is that functional and sterically hindered R groups can be introduced with great ease and without the formation of many side products. The only significant contamination is the product of the reaction between two carbon-centered radicals. The reaction between two sulfur-centered radicals regenerates the starting material (20), while the reaction between a carbon-centered radical and the dithioester is degenerate, *i.e.* the products are identical to the reactants. This route is followed in the synthesis of 2-cyanoprop-2-yl dithiobenzoate (section 3.4.4)

### 3.3. Conclusion

It is hard to recommend any of the aforementioned syntheses as *ideal* or *the best*. In terms of overall yield, values given in the literature for the various routes can hardly be compared because of the large discrepancies between primary, secondary and tertiary **R** groups. Within a certain route, the structure of the **R** group seems to be the ‘yield-determining’ factor. This is especially true for the most frequently applied substitution reactions discussed in section 3.2.1. The other chemistries intuitively do not seem to be affected so strongly by the structural details of the **R** group, but this hypothesis lacks experimental confirmation. If this indeed proves to be the case, then tertiary thiols – commercially available in the form of *tert*-butyl mercaptane or *tert*-dodecyl mercaptane – will form interesting compounds for thioacylation (section 3.2.3) or a useful ingredient for the procedures outlined in the sections 3.2.4, 3.2.5 and 3.2.6. When it comes to functionalized **R** groups, the reaction of bis(thioacyl)disulfides with radicals derived from azo initiators remains the author’s top-notch pick, because of the large variety of initiators available on the market nowadays. For a further overview of all the dithioesters that have been prepared by the various routes up to 1988 reference 52 can be consulted, while a larger overview of the synthetic pathways can be found in reference 53 as well.

### 3.4. Experimental Section

#### 3.4.1. Synthesis of Benzyl Dithiobenzoate<sup>54</sup>

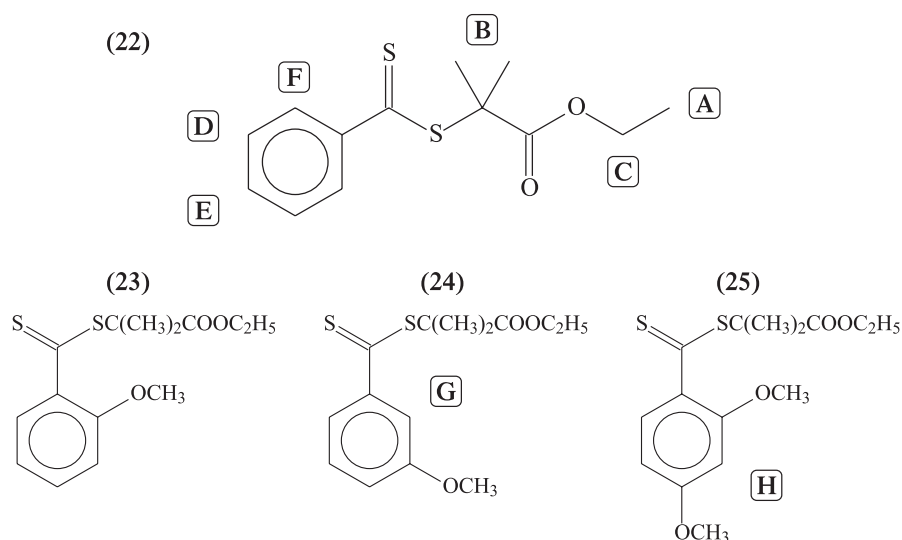
Phenylmagnesium bromide was prepared from bromobenzene and magnesium turnings. A three-necked 2L round bottom flask was fitted with two 500ml dropping funnels. All glassware was dried before use at 130°C overnight. Tetrahydrofuran (THF, Biosolve, PA [109-99-9]) was freshly distilled from lithium aluminium hydride (Aldrich, 95% [16853-85-3]). 100ml THF was put in the round bottom flask while 500ml was put in one of the dropping funnels. A few iodine crystals (Aldrich, 99+ % [7553-56-2]) and 20 g (0.82 mol) of magnesium turnings (Aldrich, 98% [7439-95-4]) were added to the flask and the other dropping funnel was filled with 125.6g (0.80 mol) bromobenzene (Aldrich, 99% [108-86-1]). Approximately 10% of the bromobenzene was allowed to flow into the magnesium/THF mixture, which was then carefully warmed with a powerful heat gun (Bosch PHG 630-2 LCE, 2000 W) until the reaction started. This is indicated

by the sudden disappearance of the brownish iodine color. Both bromobenzene and THF were then added dropwise at such rates that the reaction kept on going and that the temperature remained between 30 and 35 °C. An ice bath was used to remove the heat of reaction. Upon completion of the addition, the mixture was left to stir until no energy was produced anymore. The mixture possessed the dark greenish translucent shade of black, typical for such Grignard compounds. The empty dropping funnels were recharged with 61 g (0.80 mol) of anhydrous carbon disulfide (Aldrich, 99+ % [75-15-0]) and 154 g (0.90 mol) benzyl bromide (Aldrich, 98 % [100-39-0]). The ice bath was reapplied to keep the temperature below 35 °C while carbon disulfide was added. Upon formation of the dithiobenzoate salt, the reaction mixture turned to a dark opaque brown. The reaction was allowed to reach completion and then the benzyl bromide was poured in. An oil bath was used to heat the mixture to 55 °C for two hours. Some water (approx. 20ml) was added to neutralize remaining reactive Grignard compounds and part of the THF was removed under reduced pressure. The concentrated solution was taken up in 1 L water and extracted with three portions (250ml each) of diethyl ether (Lamers-Pleu, [60-29-7]). The combined organic phase was washed with water and dried over anhydrous magnesium sulfate (Aldrich, 97+ % [7487-88-9]). The solution was then filtered and the ether removed under reduced pressure. Vacuum distillation yielded 130 g benzyl dithiobenzoate (67%) as a red oil. The product was identified by <sup>1</sup>H NMR;  $\delta$ (ppm): 4.57 (s, CH<sub>2</sub>), 7.20–7.60 (m, 8H) and 7.95 (m, 2H ortho to the CS<sub>2</sub> group)

### 3.4.2. Synthesis of 2-(ethoxycarbonyl)prop-2-yl Dithiobenzoate<sup>54</sup>

EMA-RAFT will be used as a trivial name for 2-(ethoxycarbonyl)prop-2-yl dithiobenzoate (**22**) throughout this thesis, as the **R**-group is identical to the ethyl methacrylate monomeric radical (Scheme 3.12).

The procedure that is followed is identical to the synthesis of benzyl dithiobenzoate. Instead of benzyl bromide however, 140 g ethyl 2-bromoisobutyrate (Aldrich, 98 % [600-00-0]) was added. When the addition was complete, the mixture was kept at 75 °C for two days. The reaction was then allowed to come to room temperature. A small amount of water was added and the mixture was concentrated under reduced pressure. The residue was taken up in water and extracted three times with diethyl ether. The combined organic phases were washed with water and dried over anhydrous magnesium sulfate. After removal of the ether under reduced pressure, the viscous red oil that resulted was subjected to column chromatography



**Scheme 3.12.** 2-(ethoxycarbonyl)prop-2-yl dithiobenzoate (22) and three substituted derivatives.

on silica gel (Merck, 60 Å, 230–400 mesh [112926-00-8]) using pentane:heptane:diethyl ether (9:9:2) as the eluent. Starting from the same quantities as in the synthesis of benzyl dithiobenzoate, the yield was 69.6 g (32.5%) of a red oily substance which was stored at  $-20^{\circ}\text{C}$ . At this temperature, the substance remained liquid. The product was identified by  $^1\text{H}$  NMR;  $\delta$  (ppm): 1.25 (t, 3H, **A**); 1.80 (s, 6H, **B**); 4.15 (q, 2H, **C**); 7.37 (t, 2H, **D**); 7.52 (t, 1H, **E**); 7.95 (d, 2H, **F**), see Scheme 3.12 for proton assignments.

Substituted derivatives of 2-(ethoxycarbonyl)prop-2-yl dithiobenzoate (**23**, **24**, **25**; Scheme 3.12) were prepared through the replacement of bromobenzene by 2-bromoanisole (Aldrich, 97% [578-57-4]), 3-bromoanisole (Aldrich, 98+% [2398-37-0]) and 1-bromo-2,4-dimethoxybenzene (Aldrich, 97% [17715-69-4]) respectively. These syntheses typically produced a lot of (unidentified) side products, sometimes requiring multiple passes through a column, using the same conditions as for their unsubstituted counterparts. Yields ranged from 10 to 25% and the products were identified by  $^1\text{H}$  NMR. There was no significant change in the spectrum for the proton groups **A**, **B** and **C**. The methoxy protons on the aromatic ring gave a singlet signal at a chemical shift of 3.8 ppm corresponding to 3 protons for **23** and **24**, and to 6 protons for **25**. The four remaining protons in **23** produced multiplet signals centered around 6.9 and 7.4 ppm. In **24**, **G** gave a singlet at 7.5 ppm while the remaining 3 protons produced a multiplet ranging from 7.0 to 7.6 ppm. The aromatic protons in **25** produced signals at 6.4 and 7.6 ppm (**H**).

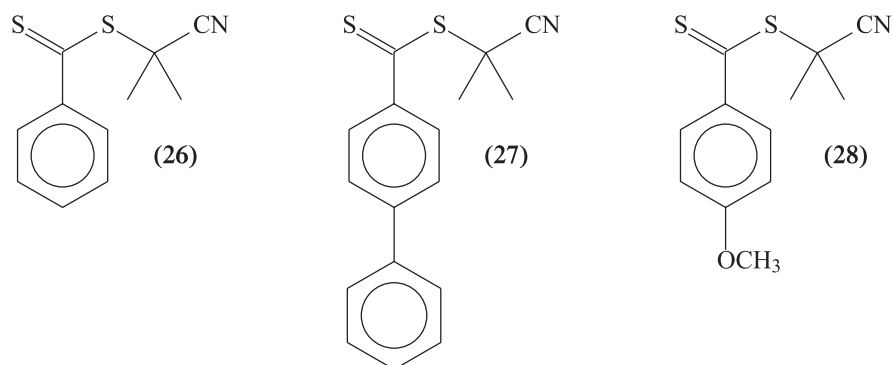
### 3.4.3. Synthesis of 2-phenylprop-2-yl Dithiobenzoate<sup>54</sup>

Cumyl-RAFT will be used as a trivial name for 2-phenylprop-2-yl dithiobenzoate throughout this thesis due to the cumyl radical that is expelled upon fragmentation.

**sodium dithiobenzoate:** 256 g of benzyl chloride (2.0 mol) was added dropwise to a stirred suspension of elemental sulfur (128 g, 4.0 mol, Merck, [7704-34-9]) and sodium methoxide (720 g of 30% solution, 4.0 mol, Merck [124-41-4]) in dry methanol ( $\approx$ 500 ml) at 70 °C. The methanol (Biosolve, abs. PA [67-56-1]) was dried over anhydrous molecular sieves (Merck, 4 Å) before use. Upon addition of the benzylchloride, a dark brown color appeared. The mixture was then stirred overnight. After cooling, the suspension was decanted and filtered over a Büchner funnel to remove the cooking salt (whitish yellow shade). Methanol was largely removed under reduced pressure and the oily brownish residue was taken up in water. The dispersion was refiltered over a glass filter, removing a second batch of the unidentified cooking salt after which a solution of sodium dithiobenzoate in water remained.

**dithiobenzoic acid:** Concentrated hydrochloric acid (Aldrich, 37 w% [7647-01-0]) was added until the brown color of the solution had disappeared completely and the dithiobenzoic acid had formed a separate layer below the waterphase. The organic layer was isolated and the waterphase was extracted twice with dichloromethane (Biosolve, PA [75-09-2]). The combined organic fractions were washed with a small portion of water, after which the dichloromethane was removed under reduced pressure ( $T < 40$  °C) to yield dithiobenzoic acid (208 g, 1.4 mol) as an intensely colored purple oil. Combined yield (steps a & b) is 68%.

**2-phenylprop-2-yl dithiobenzoate:** A mixture of dithiobenzoic acid (53 g, 0.35 mol),  $\alpha$ -methylstyrene (50 g; 0.42 mol, Aldrich, 99% [98-83-9]) and carbon tetrachloride (40 ml, Aldrich, 99.9% [56-23-5]) was heated at 70 °C for 4 hours. The resulting mixture was reduced to a crude oil which was purified by column chromatography over aluminum oxide (Merck, standardized, Brockmann activity II–III, 60–200 mesh, 90 Å [1344-28-1]) using pentane:heptane (1:1, both Biosolve, PA [109-66-0] and [142-82-2]) as eluent to give 2-phenylprop-2-yl dithiobenzoate (27 g, 28% yield) as a dark purple oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ (ppm): 2.03 (s, 6H); 7.20–7.60 (m, 8H) and 7.86 (m, 2H). Note that the use of activity I aluminium oxide resulted in impractically low  $R_f$  values. In repetitive experiments, attempts to



**Scheme 3.13.** 2-cyanoprop-2-yl dithiobenzoate (26) and two substituted derivatives that were synthesized.

increase the yield of the reaction with Brønsted and Lewis acid catalysis, an inert atmosphere and even more delicate handling of the intermediate dithioacid (low T) did not result in any significant improvement of the yield.

#### 3.4.4. Synthesis of 2-cyanoprop-2-yl Dithiobenzoate<sup>50</sup>

Cyano-RAFT will be used as a trivial name for 2-cyanoprop-2-yl dithiobenzoate, derived from the cyano functional **R** group.

**dithiobenzoic acid:** This compound was prepared in section 3.4.3, but an alternative route to this species is by the use of the Grignard reaction described in section 3.4.1. Once the reaction of phenyl magnesium bromide and carbon disulfide had completed, water ( $\approx 50$ ml) was added slowly and carefully to the cooled reaction mixture with the aim of neutralizing the Grignard compound. The mixture was then concentrated on a rotary evaporator and the resulting solution was diluted with water. The mixture was filtered to remove insoluble magnesium salts and subsequently treated with concentrated hydrochloric acid until the brown color had disappeared completely and pure dithiobenzoic acid separated from the resulting pink opaque liquid in the form of a purple oil. The pink liquid is extracted twice with dichloromethane and this organic phase was combined with the purple oil. Removal of the dichloromethane under reduced pressure yielded dithiobenzoic acid. This method was found to yield a considerably cleaner product than the dithiobenzoic acid obtained by the method described in section 3.4.3, which became obvious in the next step.

**bis(thiobenzoyl) disulfide (20):** 208 g of dithiobenzoic acid (1.36 mol) was mixed with 200 ml of ethyl acetate (Biosolve [141-78-6]). A few crystals of iodine (Aldrich, 99+% [7553-56-2]) were added to the solution and dimethylsulfoxide (53 g, 0.68 mol, Acros, [67-68-5]) was added dropwise. The mixture was kept in the dark overnight, though it was expected that the reaction had reached completion within an hour. Ethyl acetate was then removed under reduced pressure to yield the desired product in 90% yield (186 g, 0.61 mol). When the reaction was performed in a concentrated ethanol solution, the product crystallized upon formation in shiny red flakes. A second, considerably smaller batch was obtained by cooling the ethanol solution to  $-20^{\circ}\text{C}$ . The same procedure was also followed with a batch of dithiobenzoic acid generated by the reaction described in section 3.4.3. In this case the product failed to crystallize most likely due to large amounts of contaminants. Bis(thiobenzoyl) disulfide is characterized by the following signals in the  $^1\text{H}$  NMR spectrum,  $\delta(\text{ppm})$ : 7.45 (dd, 4H, meta position), 7.61 (m, 2H, para position), 8.09 (d, 4H, ortho position).

**2-cyanoprop-2-yl dithiobenzoate (26):** Bis(thiobenzoyl) disulfide (180 g, 0.59 mol) and 2,2'-azobis(isobutyronitril) (135 g, 0.83 mol, Wako Chemicals) are dissolved in ethyl acetate. The mixture is brought to reflux under an argon atmosphere for 30 minutes. Then the solution is then stirred overnight at  $65^{\circ}\text{C}$ . Ethyl acetate is removed under reduced pressure to give a red oil which was subjected to flash chromatography using pentane:heptane:diethyl ether as eluent (9:9:2). The red product which was obtained in 59% yield (154 g, 0.69 mol), crystallized when stored at  $-20^{\circ}\text{C}$  and is a red oil at ambient temperature. The  $^1\text{H}$  NMR spectrum showed the following peaks,  $\delta(\text{ppm})$ : 1.93 (s, 6H,  $\text{CH}_3$ ), 7.40 (m, 2H, meta), 7.55 (m, 1H, para), 7.90 (d, 2H, ortho). The major byproduct of this synthesis is the combination product of two AIBN derived radicals (2,3-dicyano-2,3-dimethyl-butane), which gives a singlet at 1.55 ppm.

Substituted derivatives of 2-cyanoprop-2-yl dithiobenzoate (**27**, **28**) were synthesized by a completely analogous procedure, replacing the bromobenzene that is applied in the Grignard reaction by 4-bromobiphenyl (Aldrich, 98% [92-66-0]) and 4-bromoanisole (Aldrich, 99% [104-92-7]) respectively. Biphenyl derivative **27** is characterized by the following peaks in the  $^1\text{H}$  NMR spectrum;  $\delta(\text{ppm})$ : 1.95 (s, 6H), 7.4 (m, 6H), 7.6 (d, 1H), 8.0 (d, 2H) and methoxy derivative **28** gave 1.91 (s, 6H), 3.9 (s, 3H), 6.9 (d, 2H), 8.0 (d, 2H).

Ortho substituted derivatives similar to the ones discussed in 3.4.2 could not be prepared via this route. Starting from 2-bromoanisole (Aldrich, 97% [578-57-4]), 1-bromo-2,4-dimethoxybenzene (Aldrich, 97% [17715-69-4]) and 2-bromobiphenyl (Aldrich, 96% [2052-07-5]) the Grignard reaction proceeded smoothly, but the coupling of the protonated acid with dimethyl sulfoxide failed. Several alternative methods were attempted. The traditional approach applies a solution of iodine in water (with potassium iodine), to an aqueous solution of the potassium or sodium salt of the dithio acid.<sup>7</sup> Coupling of the magnesiumbromide salts of these ortho-substituted dithiobenzoic acids with iodine proved ineffective. Also the oxidation with benzenesulfonyl chloride (Aldrich, 99% [98-09-9]) did not result in the desired bis(thioacyl) disulfides. Benzenesulfonyl chloride was reported to efficiently oxidize both the protonated form of dithioacids, as well as the magnesiumbromide derivative formed by a Grignard reaction.<sup>8</sup> Both variations on the process failed for ortho-substituted dithiobenzoic acids.

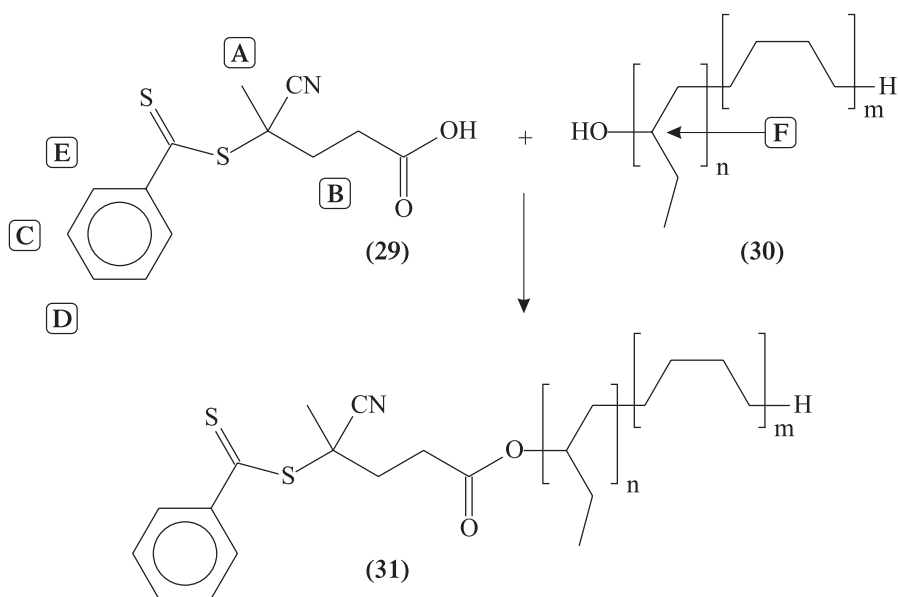
#### 3.4.5. Synthesis of 4-cyano-4-((thiobenzoyl)sulfanyl)pentanoic Acid<sup>50</sup>

The preparation of 4-cyano-4-((thiobenzoyl)sulfanyl)pentanoic acid (**29**) closely follows the route to 2-cyanoprop-2-yl dithiobenzoate (section 3.4.4), except for the last step in which 4,4'-azobis(4-cyanopentanoic acid) substitutes 2,2'-azobis(isobutyronitril).

Bis(thiobenzoyl)disulfide (103 g, 0.34 mol) and 4,4'-azobis(4-cyanopentanoic acid) (132 g, \* 0.47 mol, Aldrich, 75+ % [2638-94-0]) are dissolved in ethyl acetate (Biosolve, [141-78-6]). The mixture is brought to reflux under an argon atmosphere for 30 minutes. The solution is then stirred overnight at 70 °C. Ethyl acetate was removed under reduced pressure. The resulting product was dissolved in a small amount of dichloromethane and subjected to column chromatography on silica gel, using pentane:heptane:ethyl acetate (1:1:2) as eluent. Removal of the eluent from the product yielded a red solid (123 g, 0.44 mol, 65 % yield), m.p. 94 °C (lit.<sup>50</sup> 97–99 °C). <sup>1</sup>H NMR analysis revealed the following peaks (see Scheme 3.14 for assignments), δ(ppm): 1.93 (s, 3H, **A**), 2.4–2.8 (m, 4H, **B**), 7.42 (m, 2H, **C**), 7.58 (m, 1H, **D**), 7.93 (d, 2H, **E**).

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\* weighed quantities are 33% higher to correct for the low purity of the product (75%).

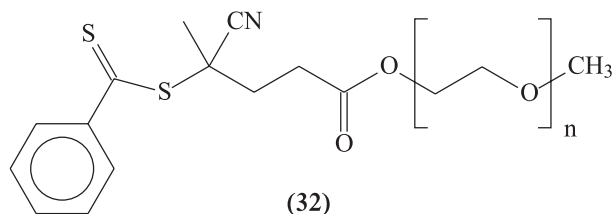


**Scheme 3.14.** Synthetic pathway to the Kraton-based macromolecular RAFT agent. The reaction proceeds in excellent yields and under mild conditions when 1,3-dicyclohexylcarbodiimide is used to activate the carboxylic acid group in **29**. Note that the representation of the polyolefin structure is simplified. Kraton is a more or less statistical sequence of ethylene and butylene units.

### 3.4.6. Synthesis of a Polyolefin Macromolecular Transfer Agent<sup>55</sup>

Kraton L-1203 (**30**) was obtained from Shell Chemicals ( $\bar{M}_n \approx 3800 \text{ g}\cdot\text{mol}^{-1}$ ;  $\bar{M}_w/\bar{M}_n \approx 1.04$ ) and dried under reduced pressure for several days before use. Anhydrous dichloromethane was prepared by distillation from lithium aluminum hydride, and stored over molecular sieves.

Kraton L-1203 (29.5 g, 8 mmol), *p*-toluenesulfonic acid (0.30 g, 1.6 mmol, Aldrich, 98.5% [6192-52-5]), 4-(dimethylamino)pyridine (0.29 g, 2.4 mmol, Aldrich, 99+% [1122-58-3]) and 1,3-dicyclohexylcarbodiimide (3.9 g, 19 mmol Aldrich, 99% [538-75-0]) were dissolved in anhydrous dichloromethane in a 1 L three necked round bottom flask equipped with a magnetic stirrer. 4-cyano-4-((thiobenzoyl)sulfanyl)pentanoic acid (2.5 g, 9 mmol) was dissolved in anhydrous dichloromethane and added dropwise to the reaction mixture at room temperature. Upon completion, the reaction mixture was heated to 30°C and allowed to stir for 48 hours. A few milliliters of water was added to convert remaining 1,3-dicyclohexylcarbodiimide into the insoluble dicyclohexylurea. The mixture was then filtered and washed with water. The solution was dried with anhydrous magnesium sulfate,



**Scheme 3.15.** A watersoluble macromolecular RAFT agent prepared from 4-cyano-4-((thiobenzoyl)sulfanyl)pentanoic acid and poly(ethylene glycol) methyl ether.

filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica with heptane:ethyl acetate (9:1) as eluent. Removal of the solvent under high vacuum gave a purplish red viscous liquid (29.4g, 92% yield, based on Kraton). The  $^1\text{H}$  NMR spectrum indicated a quantitative yield based on the number of hydroxyl groups. The chemical shift of the set of protons in the Kraton situated next to the hydroxyl (**F**, Scheme 3.14) group changed from 3.6 to 4.2ppm upon esterification.

### 3.4.7. Synthesis of a Poly(ethylene oxide)-based RAFT Agent

The synthesis of a water soluble poly(ethylene oxide)-based RAFT agent follows the same procedures as that of the polyolefin based RAFT agent discussed in section 3.4.6, but with the hydroxyl terminated poly(ethylene-*co*-butylene) replaced by a poly(ethylene glycol) methyl ether which is dried under vacuum before use for several days. A typical recipe consisted of *p*-toluenesulfonic acid (0.30g; 1.6mmol), 4-(dimethylamino)pyridine (0.18g; 1.5mmol) and 1,3-dicyclohexylcarbodiimide (5.0g; 25mmol) dissolved in anhydrous dichloromethane together with 9mmol of the poly(ethylene glycol) methyl ether (Aldrich [9004-74-4]). The synthesis was conducted with material of different chain lengths, requiring 18g of material with a molar mass of approx.  $2000\text{g}\cdot\text{mol}^{-1}$  or 6.75g with  $\bar{M}_n \approx 750\text{g}\cdot\text{mol}^{-1}$ . The reaction proceeds completely analogous to the synthesis in section 3.4.6. The product was not purified, but used as obtained after removal of the dichloromethane.

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