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Selective One-Pot Synthesis of Trithiocarbonates, Xanthates, and Dithiocarbamates for Use in RAFT/MADIX Living Radical Polymerizations

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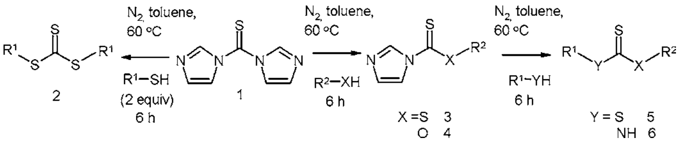
ABSTRACT

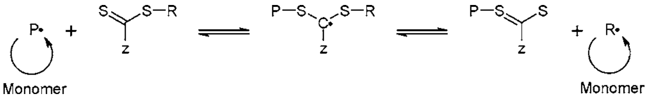


We report a facile route for the production of chain transfer agents for reversible addition fragmentation chain transfer (RAFT) and macromolecular design via the interchange of xanthates (MADIX) polymerizations, via a one-pot reaction. 1,1′-Thiocarbonyl diimidazole (TCDI) undergoes controlled monosubstitution when reacted with secondary thiols or alcohols. The intermediate *S*/*O*-esters of imidazole-*N*-thionocarboxylic acid react efficiently with a range of primary thiols, alcohols, and amines to form asymmetrical dithiocarbonates, trithiocarbonates, and dithiocarbamates, respectively. The synthesis provides a facile approach to the controlled radical polymerization of vinyl monomers through the reversible addition-fragmentation chain transfer (RAFT) mechanism.

Currently there is significant worldwide interest in the use of controlled radical polymerization techniques, with reversible addition fragmentation chain transfer (RAFT), and macromolecular design via the interchange of xanthates (MADIX) polymerizations being among the newest and fastest growing areas. The technique involves the reversible addition and fragmentation of a radical to a thiocarbonyl C═S bond. The most active compounds for this process are dithioesters, dithiocarbonates, dithiocarbamates, and trithiocarbonates and have the generic structures shown in Scheme 1, where R is a leaving/reinitiating group and Z is a group activating the C═S toward radical addition and stabilizing the intermediate radical formed.[1,2]

The chemistry employed to produce RAFT and MADIX chain transfer agents (CTAs) generally involves the use of CS_2[3] and therefore requires careful control of the hazards associated with volatile toxic liquids.[4] The most commonly employed routes to dithiocarbonates and trithiocarbonates also involve Grignard alkylation and nucleophilic addition, which pose significant challenges for large scale reactions.[3,5] These established methods have significant drawbacks for research laboratories that are unfamiliar with compounds with considerable safety concerns including high flammability, risks of explosion, nervous system toxicity, and water

Scheme 1. General Accepted Mechanism for RAFT/MADIX Polymerizations Mediated by a Thiocarbonyl-thio Chain Transfer Agent; P_n Describes a Polymeric Chain



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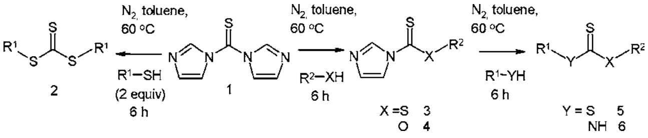
sensitivity. These handling and synthetic difficulties have contributed to the limited spread of RAFT and MADIX in academic and industrial laboratories worldwide. There have been very few reports on alternative syntheses of thiocarbonyl-thio compounds for RAFT polymerization, and all suffer from poor yields and the use of expensive reactants or are limited to dithiobenzoate synthesis.[3] Furthermore, there has recently been a surge of interest in the use of trithiocarbonates to mediate RAFT polymerization. Such chain transfer agents offer a better flexibility in terms of functionality, lead to faster polymerizations, eliminate the problem attached to retardation usually observed when increasing the ratio CTA/monomer in RAFT polymerization, and lead to polymers that are less colored than those formed from dithiobenzoates.[6]

1,1′-Carbonyl diimidazole (CDI) has proven to be a versatile reactant for the synthesis of carbonate and carbamate derivatives. During earlier work on the synthesis of polymers with controlled branching, some of us have formed dendrimers containing amides,[7] carbonates [8] and carbamate[7] groups using 1,1′-carbonyl diimidazole (CDI) as an easily handled alternative to phosgene gas.[9] The selectivity of the intermediate derivatives of CDI with alcohols and acids [7,8] has been of great importance and has allowed a high level of control that is not found when using phosgene or $SOCl_2$. The sulfur derivative of CDI, 1,1′-thiocarbonyl diimidazole (TCDI), has also been used in various areas of chemistry, such as in the synthesis of imidazolyl thiadiazoles and imidazolyl thiatriazoles by reaction with 1,3-dipolar reagents.[10] The reaction of TCDI with amines and thiols for the synthesis of dithiocarbamates[11] and thioureas [5] has been reported. The synthesis of dithiocarbonates from compounds similar to the intermediates (**3**) detailed in this paper has also been reported.[12] However, these routes do not involve the use of TCDI. To the best of our knowledge, the use of TCDI for the synthesis of trithiocarbonates and dithiocarbonates has not been reported. Katritzky et al. reported the use of a compound similar to TCDI, bis(benztriazolyl)methanethione, in the preparation of unsymmetrical di- and trisubstituted thioureas.[13] This work was recently extended to include routes to heteroaryl thioureas, thioamides, thionoesters, thiocarbamates, thiocarbonates, but more interestingly from a RAFT polymerization perspective, dithiocarbonates and dithiocarbamates.[14] It is noteworthy that the reported methodology is unsuitable for the synthesis of trithiocarbonates.

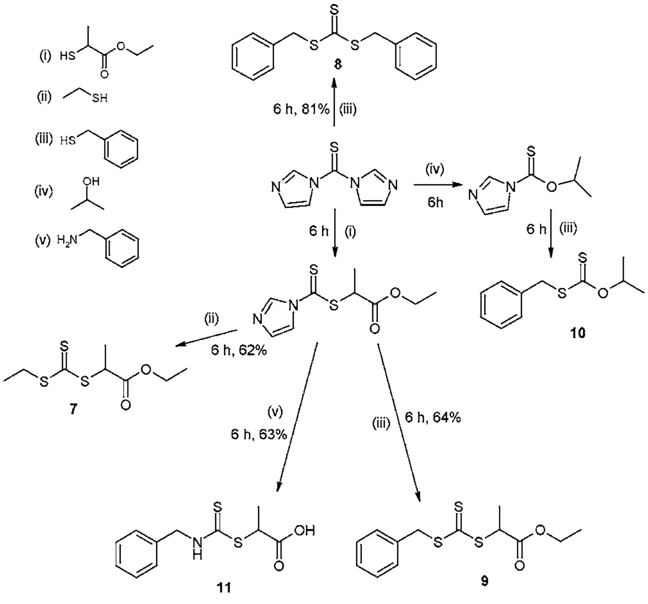
TCDI (**1**) can undergo substitution by primary or secondary thiols. Indeed, with 2 equiv of a primary thiol, the symmetrically disubstituted product (**2**) is readily obtained, Scheme 2. Furthermore, when TCDI is reacted with a secondary thiol or secondary alcohol, only the intermediate *S*/*O*-ester of imidazole-*N*-thionocarboxylic acid is produced (**3**, **4**), which may be further reacted with a primary thiol, to give a trithiocarbonate or a xanthate (**5**), or a primary amine, to give a dithiocarbamate (**6**). This one-pot reaction presents clear advantages in terms of yield, reaction time, and simplicity for the synthesis of chain transfer agents for RAFT or MADIX polymerization.

Scheme 2. Synthesis of Dithiocarbonates, Trithiocarbonates, and Dithiocarbamates from 1,1′-Thiocarbonyl Diimidazole



This strategy has been used to synthesize a range of symmetric and asymmetric candidate CTAs for use in RAFT and MADIX polymerizations, Scheme 3. Two primary thiols, a secondary thiol, a secondary alcohol, and a primary amine were chosen for evaluation, based on their ability, through the correct combinations, to either activate the C═S bond

Scheme 3. Various Thiocarbonyl-thio Compounds Reported in This Study Synthesized from 1,1′-Thiocarbonyl Diimidazole



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to radical attack, stabilize the radical formed, or provide an initiating/leaving group within the polymerization.

The arrangement of substituents around the thiocarbonylthio group makes 2-ethylsulfanylthiocarbonylsulfanyl-propionic acid ethyl ester, **7**, an excellent candidate CTA for controlled RAFT polymerization. The R group, originating from the ethyl 2-mercaptopropionate, is expected to perform well in the polymerization of methyl acrylate (MA), as the radical formed is structurally similar to the MA propagating radical.[15] The *S*-ethyl group, acting as the Z group, is expected to sufficiently activate the C═S group toward radical addition (relative to the corresponding *O*-ethyl or *N*-ethyl groups but will deactivate the C═S group with respect to alkyl or aryl groups) and stabilize the resultant intermediate radical. The successful synthesis of the trithiocarbonate **7** was confirmed by electrospray MS (m/z= 239.023, MH$^+$), ^{1}H NMR and ^{13}C NMR (δ = 221.9 ppm, C═S).

The formation of dibenzyl trithiocarbonate, **8**, was achieved in a one-pot synthesis, by reacting TCDI with 2 equiv of primary thiol. Compound **8** has been previously reported[16−20] using conventional CTA synthetic routes and acts as a disubstituted CTA, having two identical groups capable of leaving and reinitiating polymerization. Using conventional syntheses, reported yields of **8** vary considerably (40−95+%). The use of TCDI however gave **8** in a respectable purified yield (81%) using a one-pot facile reaction over 6 h. The success of the reaction was determined by ^{1}H NMR (δ = 4.6 ppm, 4H, Ar−CH$_2$; δ = 7.3 ppm, 10 H, Ar−H), ^{13}C NMR (δ = 222.8 ppm, C═S), and electrospray MS (m/z = 291.034, MH$^+$).

A novel CTA, substituted with two potential R groups, has also been synthesized using the TCDI approach. 2-Benzylsulfanylthiocarbonylsulfanyl-propionic acid ethyl ester, **9**, is an asymmetrical trithiocarbonate synthesized using the monosubstitution of TCDI with 1 equiv of secondary thiol followed by addition of one equivalent of a primary thiol (64% purified yield). Compound **9** was characterized using ^{1}H NMR (δ = 1.3 ppm, 3H, CH$_3$; δ = 1.6 ppm, 3H, CH$_3$; 4.6 ppm, 2H, Ar−CH$_2$; δ = 7.3 ppm, 5H, Ar−H), ^{13}C NMR (δ = 220.2 ppm, C═S) and electrospray MS (m/z = 269.067, (M$^+$ − S)H$^+$).[21]

Trithiocarbonates **7**−**9** are classified as RAFT CTAs whereas the MADIX process relies on the use of xanthates. The generic strategy using TCDI, outlined in Scheme 2, may be used to form xanthates through a similarly facile procedure, sharing all of the benefits of the laboratory scale syntheses of RAFT agents. Xanthates are of particular interest as they have been reported to successfully mediate the controlled polymerization of vinyl acetate (VAc).[22] Controlled radical polymerization of VAc is difficult to obtain because of the highly reactive nature of the monomer radical, which has a tendency to add to activated bonds such as C═S. The resultant radical is relatively stable and therefore unlikely to fragment in the required fashion. The Centre for Advanced Macromolecular Design (CAMD) group investigated the effect of different Z groups within the xanthate in order to avoid these complications and concluded that by incorporating an electron-withdrawing Z group, fragmentation could be promoted leading to enhanced control of the polymerization.[22] A Z group derived from 2-propanol, was shown to be particularly effective. The choice of R group is also crucial and groups derived from primary thiols have been successfully used. [22,23] To produce such a xanthate, monosubstitution of TCDI was achieved by reacting 1 equiv of 2-propanol with TCDI, followed by addition of benzyl mercaptan without purification of the intermediate. The resulting xanthate, **10**, was purified by flash chromatography (68% purified yield) and was characterized by ^{1}H NMR (δ = 1.4 ppm, 6H, CH3; δ = 4.3 ppm, 2H, Ar−CH$_2$; δ = 5.8 ppm, 1H, R$_2$CH; δ = 7.2 ppm, 5H, Ar−H), ^{13}C NMR (δ = 213.2 ppm, C═S) and electrospray MS (m/z = 227.056, MH$^+$).

The attempted synthesis of a xanthate by initial monosubstitution of TCDI with ethyl 2-mercaptopropionate, followed by addition of benzyl alcohol, led to the coupling of two benzyl alcohol residues via the thiocarbonyl group. This was confirmed by ^{1}H NMR and ^{13}C NMR. It is clear that the formation of the symmetric thiocarbonate was achieved through the displacement of the secondary thiol by the excess benzyl alcohol, possibly after initial xanthate formation. We have previously reported the displacement of tertiary alcohols from carbonates by neighboring hydroxyl groups to form cyclic carbonate structure,[8] but the displacement of secondary thiol groups by excess alcohol was not expected.

We report the use of TCDI in a one-pot controlled formation of an asymmetric dithiocarbamate through the coupling of benzylamine and ethyl 2-mercaptopropionate. Although this structure is not expected to function well as a RAFT/MADIX CTA, the formation of dithiocarbamates via the same strategy was designed to demonstrate the scope of the TCDI synthetic approach. Katritzky et al. have recently reported a similar approach for the synthesis of dithiocarbamates, via the reaction of thiols with thiocarbamoylbenzotriazoles (yields 60−99%).[14] To our surprise, the expected ethyl ester containing product was not formed, but the

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[21] As carbonyls and thiocarbonyls are particularly susceptible to fragmentation, the major peak in the MS analyses is assigned to the molecular ion, minus the carbonyl oxygen (sulfur). The nominal MS data show peaks with a lower intensity that do represent the expected molecular ion, but these peaks could not be analyzed with high-resolution MS because of too much interference from other fragments. The data are still correct and consistent with what could be expected from high-resolution MS.

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reaction conditions led to the cleavage of the ethyl ester and the formation of the acid functional dithiocarbamate **11** in 63% recovered yield. ^{1}H NMR analysis revealed the absence of the expected peaks at $\delta = 1.3$ and 4.2 ppm, corresponding to the ethoxy group. ^{13}C NMR analysis also showed the loss of a signal at $\delta = 171.1$ ppm corresponding to the ester carbonyl and a new signal at $\delta = 177.2$ ppm showing cleavage of the ester and formation of acid. The hydrolysis of the ethyl ester may be due to anchimeric assistance,[24] driven by the proximity of the nitrogen of the thiocarbamate.

To assess the synthesized CTAs, CTAs **7**−**9** were used to mediate the polymerization of methyl acrylate (MA), while CTA 10 was assessed in the polymerization of vinyl acetate (VAc). CTA **7** is an example of a traditional trithiocarbonate RAFT agent having a R group capable of reinitiating polymerization; **8** and **9** contain two potential R groups and examples of this type of CTA have been used previously to synthesize telechelic polymers.[16] The bulk polymerizations of methyl acrylate (MA) at 50 °C and Vac at 60°C were conducted using azobis(isobutyronitrile) (AIBN) as the radical initiator. Each polymerization contained 55 mmol of monomer, 0.55 mmol of CTA, and 0.11 mmol of AIBN, i.e., a ratio monomer:CTA:initiator of 100:1:0.2, respectively. The samples were degassed under nitrogen for 10 min each prior to polymerization. The characterization of polymers formed under these conditions are detailed in Table 1.

Table 1. Polymers Formed by RAFT/MADIX Polymerization Using CTAs Synthesized in This Study

CTA	monomer[a]	$M_{\mathrm{n\ theory}}$ g/mol	$M_{\mathrm{n\ GPC}}$[b] g/mol	PDI	conversion %
7	MA	5,200	4,700	1.07	60.9[c]
8	MA	4,000	3,900	1.20	46.8[c]
9	MA	4,600	3,900	1.20	53.7[c]
10	VAc	3,850	3,900	1.17	44.7[d]

[a] MA: methyl acrylate. VAc: vinyl acetate. [b] Referenced against polystyrene standards. [c] After 4 h of polymerization. [d] After 22 h of polymerization.

CTAs **7**−**9** controlled very well the RAFT polymerization of MA at 50°C, leading to polymers of predictable M_n and low polydispersity (PDI). Similarly, CTA **10** controlled the polymerization of VAc with great efficiency.

The synthesis of novel dithiocarbonates (xanthates), trithiocarbonates, and dithiocarbamates for use in controlled radical polymerization has been demonstrated using 1,1′-thiocarbonyl diimidazole (see typical experimental procedure).[25] This new approach avoids using toxic and hazardous materials in the search for new chain transfer agents for RAFT and MADIX polymerization (although it should be noted that exposure of TCDI to moisture can liberate toxic carbon oxysulfide) and, to the best of our knowledge, is the first demonstration of TCDI in the controlled, selective formation of dithiocarbonates and asymmetric and symmetric trithiocarbonates. However, the reported synthetic route requires anhydrous conditions. The products are easily purified via column chromatography and Kugelrohr distillation. Successful RAFT and MADIX polymerization of methyl acrylate, using compounds **7**−**9**, and vinyl acetate, using compound **10**, respectively, has also been demonstrated.

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Supporting Information Available: Analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[25] **Typical Experimental Procedures. Synthesis of 7.** Dry toluene (60 mL) was added to a stoppered three-necked flask. 1,1′-Thiocarbonyl diimidazole (TCDI) ((95%) 3.60 g, 19.2 mmol) and potassium hydroxide (0.05 g, 0.86 mmol) was added, in one portion, under nitrogen. To the solution was added ethyl 2-mercaptopropionate ((95%) 2.63 mL, 2.71 g, 19.2 mmol) dropwise. The reaction mixture was heated to 60 °C and refluxed for 6 h. After this time, the mixture was allowed to cool to room temperature and left to stand, under nitrogen, overnight. Ethanethiol ((99%) 1.34 mL, 1.49 g, 19.2 mmol) was added dropwise, under nitrogen, to the stirred solution. The reaction mixture was heated to 60 °C, refluxed for 6 h, and then left to cool to room-temperature overnight. The solution was filtered, concentrated under vacuum and subjected to flash chromatography (silica, 5% ethyl acetate in hexane as eluent). The desired fraction was concentrated under vacuum and subjected to Kugelrohr distillation, affording the product as a bright yellow oil (62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.30 (t, $J = 7.2$ Hz, 3H, SCH$_2$*CH*$_3$), 1.34−1.38 (t, $J = 4.2$ Hz, 3H, OCH$_2$*CH*$_3$), 1.57−1.61 (d, $J = 7.7$ Hz, 3H, SCH*CH*$_3$), 3.34−3.40 (q, $J = 6.5$ Hz, 2H, S*CH*$_2$CH$_3$), 4.17−4.23 (q, $J = 3.8$ Hz, 2H, O*CH*$_2$CH$_3$), 4.78−4.83 (q, $J = 7.4$ Hz, 1H, S*CH*CH$_3$); ^{13}C NMR (100 MHz) δ 221.9, 171.1, 61.9, 48.0, 31.5, 31.1, 17.0, 14.3; TOF-MS (ES$^+$) *m*/*z* = 239.023 (MH$^+$).