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Feature article

Thiol-yne 'click'/coupling chemistry and recent applications in polymer and materials synthesis and modification

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ABSTRACT

This review highlights recent applications of the thiol-yne reaction in polymer synthesis and modification and also gives some representative examples of its application in small molecule (bio)organic chemistry. A brief introduction to the history of the thiol-yne reaction is given followed by a description of the mechanism for the common radical-mediated manifestation of the reaction. This is followed by a review of its use in network/gel syntheses and modification, as a tool for polymer synthesis and copolymer modification; its applicability in the preparation of dendrimers and hyperbranched polymers and finally how it has been employed as a tool for surface modification and functionalisation. This review is not intended to be exhaustive but rather to serve as an overview of research areas within which this important reaction is currently attracting interest.

1. Introduction

Within the last several years several thiol-based reactions [1–4] have attracted significant attention in the polymer/materials science communities including the various manifestations of the thiol-ene reaction [5–9], thiol-isocyanate coupling [10], thiol-halo reactions [11–13] as well as examples of thiol–thiol coupling reactions [1]. Amongst these, the radical mediated addition of thiols to alkynes, the thiol-yne reaction, has emerged as a useful tool for both polymer/network synthesis as well as an efficient coupling chemistry in post-polymerization modification and several highlights/perspectives and mini-reviews have already appeared on the topic [14–17]. The reaction should be considered a sister reaction to the better known radical-mediated thiol-ene reaction and as a complimentary process to the Cu(I) catalysed alkyne-azide (CuAAC) cycloaddition reaction. Herein we will review some general background literature related to the thiol-yne reaction followed by some fundamentals related specifically to the radical-mediated thiol-yne process, and finally highlight applications in polymer and materials synthesis and modification that have emerged within the last few years.

2. Background and practical considerations

As noted, the thiol-yne reaction should be considered a sister reaction to the better-known thiol-ene process and very much as a complimentary reaction to the Cu-mediated alkyne/azide 'click' reaction. In the context of this review, it is perhaps prudent to make several comments regarding the much more thoroughly studied radical thiol-ene reaction prior to highlighting the thiol-yne process. The thiol-ene reaction, known since the turn of the twentieth century [18], is extremely well-documented having been studied extensively over the decades [6]. The reaction has experienced somewhat of a renaissance in recent years due, in part, to the recognition of its 'click' characteristics, and several excellent reviews have appeared detailing its features and applications [5–8,19]. Readers are directed to these for a more in-depth description of the thiol-ene reaction. Broadly, when considering the addition of a thiol to a C=C bond several things need to be considered in terms of general efficiency: 1) the reactivity of alkenes under radical-mediated conditions varies dramatically depending on the electronic nature of the C=C bond with electron rich (e.g. vinylethers) or highly strained substrates (e.g. norbornenes) exhibiting very high reactivity. However, virtually any C=C bond is susceptible to hydrothiolation; 2) side reactions, and specifically competing polymerization under radical-mediated conditions, are possible with electron-deficient C=C bonds such as acrylates or, indeed, any alkene susceptible to radical chain-growth polymerization; 3) terminal C=C bonds exhibit

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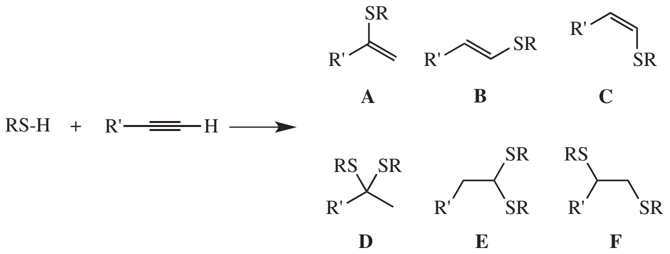


Scheme 1. Possible addition products for the mono- and bis-hydrothiolation of a terminal alkyne bond.

significantly higher reactivity than internal C=C bonds with anti-Markovnikov addition being the predominant stereochemical pathway while the hydrothiolation of internal alkenes can be 'complicated' by a competing thiyl radical-mediated *cis-trans* isomerization process that can significantly impact reaction kinetics; 4) the hydrothiolation of electron-deficient C=C bonds is, arguably, best performed under Michael-addition conditions employing certain phosphines or amines as ***nucleophilic*** initiators/catalysts since it negates potential undesirable polymerization [20,21]. However, it is reiterated that these points are general and researchers are directed to the source literature for system-specific details that can vary dramatically. We will note, however, that while the thiol-ene reaction (both radical and ionic variants) are widely regarded as efficient 'click' processes there are certain circumstances under which it fails to meet the common criteria to be classified as such. Specifically, the use of radical thiol-ene chemistry for the conjugation of a polymer with a terminal thiol group with a macromolecular end functional alkene can be inefficient and low yielding [22].

2.1. Early literature examples of the thiol-yne reaction

While much less exploited, the earliest literature reports describing the hydrothiolation of an alkyne bond can also be traced to the beginning of the twentieth century [23,24]. We note, that when considering the addition of a thiol to a terminal ***alkene*** there are two possible products – the Markovnikov and anti-Markovnikov species, with the latter being the common, essentially exclusive product in most instances, at least under radical-mediated conditions. In contrast, for the addition of a thiol(s) to a terminal C≡C bond there are ***six*** possible products, Scheme 1, each of which can be obtained essentially quantitatively under specific experimental conditions.

The formation of the monoaddition products **A**–**C** and the bis addition species **D** and **E**, Scheme 1, are governed largely by the nature of the reaction conditions employed to effect hydrothiolation. Each of the monoaddition products **A**–**C** and the double addition dithioacetal derivatives, **D** and **E**, can be obtained employing appropriate catalysts [25].

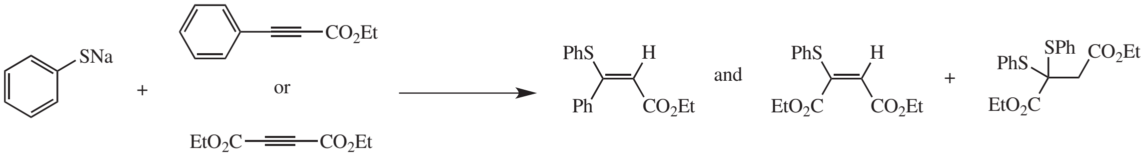
Some of the earliest literature reports concerning small molecule thiol-yne hydrothiolation reactions actually involve substrates with electron-deficient C≡C bonds and date to the beginning of the twentieth century [23,24]. In 1900 Rhuemann and coworkers described reactions between sodium thiophenolate and ethyl phenylpropiolate or ethyl acetylenedicarboxylate – both examples of internal alkyne substrates, Scheme 2.

For ethyl phenylpropiolate, the authors noted the formation of the single addition product with C–S bond formation occurring at the more electrophilic C atom as expected in a Michael-type conjugate addition reaction. In contrast, in the case of ethyl acetylenedicarboxylate both the mono- and bis-addition products were reported. For the double addition adduct the authors noted addition occurring at the *same* carbon atom giving a dithioacetal derivative.

In 1935, Kholer and Potter [26] reported the synthesis of *cis* and *trans* benzal methyltolyl sulfide in the reaction of phenylacetylene with thiocreosol as part of their studies involving α,β-unsaturated sulfones. Owen and Sultanbawa [27] subsequently examined the addition of toluene-ω-thiol to propiolic acid and reported the formation of β-mono vinylthioether adducts. In the same paper the authors noted that the addition of thiolacetic acid to propiolic acid yielded only the *cis* and *trans* β-(acetylthiol)acrylic acids whereas with methylpropiolate the *cis* and *trans* isomers were formed along with the double addition product α,β-bisacetylthiopropionate. The reaction of 2 equivalents of thiolacetic acid with acetylene dicarboxylic acid (or the bis methyl ester) yielded in both instances the α,α′-double addition products (**D**-like species). All of these later Michael-type addition reactions were performed in the absence of any added catalyst.

Later, in 1949, Bader and co-workers [28] detailed the reaction between thiolacetic acid and a variety of alkynes including 1-hexyne, phenylacetylene, 1,7-octadiyne and methyl propargyl ether in the presence of peroxides and or UV irradiation. As a representative example, for 1-hexyne both the mono (2-substituted) and di (1,2-substituted) adducts could be obtained in good yield. Additionally, the authors noted that the mono substituted adduct could be readily converted to the 1,2-disubstituted species simply by further heating in the presence of additional thiolacetic acid. Hydrothiolations conducted in the presence of peroxides or under irradiation were found to give increased yields of thioether adducts. The effect of peroxide catalysis was most pronounced in the reactions with phenylacetylene and *p*-methoxyphenylacetylene where significant improvements in the yield were observed, however in both instances only 2-substituted mono adducts were obtained.

Sauer [29] detailed the radical-mediated reaction of acetylene with 1-butanethiol, benzyl mercaptan and thiophenol and reported the formation of the 1,2-double addition products. It was also shown that when the acetylene–thiol reaction was performed in the presence of CO that it was possible to form thiopropenals although the preferred reaction product was the bis-thioether. Blomquist and Wolinsky described a study on the addition of ethyl mercaptan to a range of acetylenic species including propargyl alcohol, propargyl acetate, 2-butyn-1,4-diol, 1-hexyne, 2-methyl-3-butyn-2-ol, propiolic acid, dimethyl acetylenedicarboxylate and phenylacetylene. All reactions were performed under UV



Scheme 2. Reaction of sodium thiophenolate with ethyl phenylpropiolate or ethyl acetylenedicarboxylate and identified products.