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Generation and Intramolecular Reactivity of Acyl Radicals from Alkynylthiol Esters under Reducing Tin-Free Conditions

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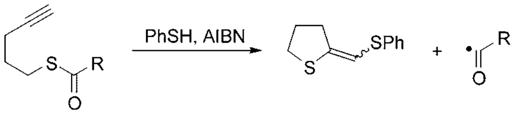
ABSTRACT



The radical chain reaction of benzenethiol with alkynylthiol esters provides a new, valuable protocol for the tin-free generation of acyl radicals that arise from intramolecular substitution at sulfur by the initial sulfanylvinyl radicals.

Radical reactions have become an important tool in synthetic organic chemistry.[1] In particular, inter- and intramolecular additions of nucleophilic acyl radicals to multiple (mainly carbon−carbon) bonds represent a useful method for the production of cyclic and acyclic ketones.[2]

Acyl aryl selenides are often the precursors of choice for acyl radicals due to their ability to participate smoothly in chain sequences with tri-*n*-butylstannane and tris(trimethylsilyl)silane.[2c,3,4] The replacement of acyl selenides by thiol esters would be attractive from a number of viewpoints, not least the enhanced stability and ease of preparation, but, unfortunately, thiol esters are normally very poor sources of acyl radicals, both photochemically and in conjuction with the standard stannanes and silanes.[2c,5] This lack of reactivity may be overcome, however, by the inclusion of an additional propagation step in which an aryl radical brings about an intramolecular homolytic substitution at sulfur.

In fact, Crich has recently devised a brilliant strategy using iodothiol ester precursors of type **2**, available by reacting the (iodophenyl)ethanethiol **1** with appropriate acyl chlorides. Compounds **2** smoothly release acyl radicals upon intramolecular attack at the sulfur by the aryl radicals that are initially formed by iodine atom abstraction by tributyltin or tris-

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[1] (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 4, pp 715−777, 779−831. (b) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (c) Renaud, P.; Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.

[2] For recent reviews on the chemistry of acyl radicals and their application in synthesis, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1051. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

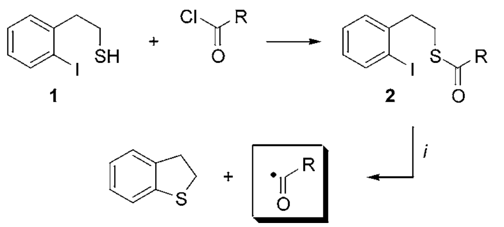
[3] For very recent examples of the use of selenoesters in acyl radical chemistry, see: (a) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697. (c) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268.

[4] For very recent productions of acyl radicals from acyl hydrazine precursors, see: (a) Braslau, R.; Anderson, M. O.; Rivera, F.; Jimenez, A.; Haddad, T.; Axon, J. R. *Tetrahedron* **2002**, *58*, 5513. (b) Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204.

[5] For a peculiar use of thiol esters in acyl radical chemistry, see: Ozaki, S.; Yoshinaga, H.; Matsui, E.; Adachi, M. *J. Org. Chem.* **2001**, *66*, 2503.

10.1021/ol034252r CCC: $25.00

Scheme 1 [a]



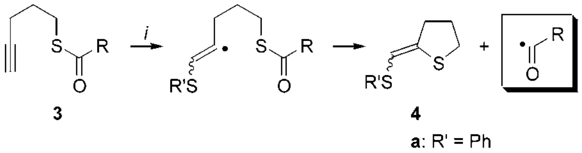
[a] Reagents: (i) Bu_3SnH/AIBN or $(TMS)_3SiH$/AIBN.

(trimethylsilyl)silyl radicals (Scheme 1).[6a] This strategy was subsequently extended to the use of arenediazonium salts as alternative precursors to aryl radicals with the principal goal of avoiding the attendant problems of the undesirable use of toxic and/or expensive organotin or organosilane reagents.[6b]

Very recently, our interest in the radical chemistry of azides prompted us to undertake a study of the intramolecular reactivity of acyl radicals toward the azido function. To this purpose, a number of aryl- and alkyl-derived azidoacyl radicals were generated from the iodothiol azidoesters by intramolecular homolytic substitution at sulfur, following the previous methodology reported by Crich. The derived acyl radicals were found to be interestingly capable of performing intramolecular five- and six-membered cyclizations onto the azido moiety, although to an extent dependent upon their structural features, to give eventually cylized lactams.[7]

In the course of this study, we became interested in a search for other thiol ester compounds that might similarly act as valuable precursors to acyl radicals under reductive conditions but avoid the need of stannanes or silanes. It thus occurred to us that, in principle, alkynylthiol esters of type **3** might represent attractive candidates in conjunction with standard thiols. Indeed, radical addition of a thiol to the terminal triple bond of **3** was expected to result in regioselective production of an intermediate sulfanylvinyl radical.[8] This intermediate, similar to the aryl congener of Crich, was considered to be presumably capable of performing intramolecular substitution at sulfur to yield thiophene **4** with concomitant release of an acyl radical (Scheme 2).

Scheme 2 [a]



[a] Reagents: (i) R′SH/AIBN.

In this paper, we report the preparation of the novel alkynylic thiol esters **5**−**10**, shown in Figure 1, as well as preliminary results of their radical reactions with benzenethiol. The choice of these substrates was essentially dictated by our additional interest in gaining suitable information about the intramolecular reactivity of the possible acyl radicals in the presence of the thiol H-donor rather than of tributylstannane[6a,7] or tris(trimethylsilyl)-silane.[6a,7]

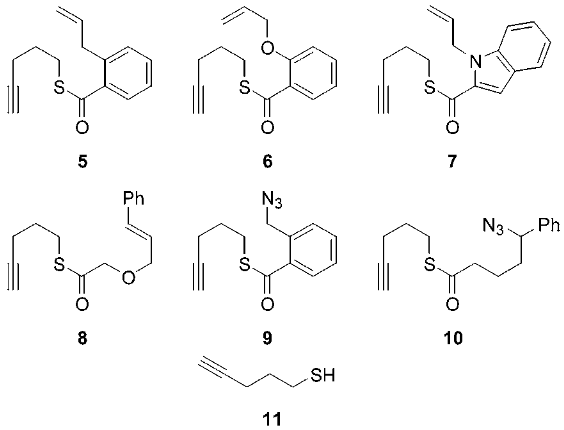


Figure 1.

Compounds **5**−**7**, **9**, and **10** were prepared by reacting the appropriate acid chlorides with the pentynethiol **11** in the presence of DMAP and compound **8** by direct coupling of **11** with the carboxylic acid in the presence of DCC and DMAP (Figure 1). Thiol esters **5**−**8** were obtained in good to fairly good yields, whereas those containing an azido function, i.e., **9** and **10**, for unclear reasons were achieved in rather modest yields. The requisite thiol **11** was in turn readily obtained from commercial 4-pentyn-1-ol through a three-step protocol involving conversion to mesylate and then to thiol acetate, followed by eventual treatment with methylthiolate.[9] It is worth noting that the present synthesis of **11** compares favorably with that devised by Crich for iodothiol **1**, which in fact required a rather tedious five-step procedure starting from much more expensive 2-(2-bromophenyl)ethanol.

Radical reactions of thiol esters **5**−**10** were normally performed by adding a benzene solution of PhSH (1.1 equiv) and AIBN (0.2 equiv) with a syringe pump over 3 h to a refluxing benzene solution of the appropriate substrate (2 mmol) under a nitrogen atmosphere. The resulting mixture was refluxed for an additional 2−3 h until virtual disappearance of the starting material and then separated by column chromatography.

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[6] (a) Crich, D.; Yao, Q. *J. Org. Chem*. **1996**, *61*, 3566. (b) Crich, D.; Hao, X. *J. Org. Chem*. **1997**, *62*, 5982.

[7] Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *Org. Lett.* **2002**, *4*, 3079.

[8] (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1305. (c) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1994**, *59*, 2818. (d) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 7941.

[9] Thiol **11** has recently been prepared from 4-pentyn-1-ol by means of a similar three-step procedure, but no experimental details have been furnished (see: Journet, M.; Rouillard, A.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **1997**, *62*, 8630); compound **11** has also been previously prepared from 1-chloro-4-pentyne through hydrolysis of the derived thiuronium salt (see: Dupuy, C.; Crozet, M. P.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1980**, Part 2, 353).

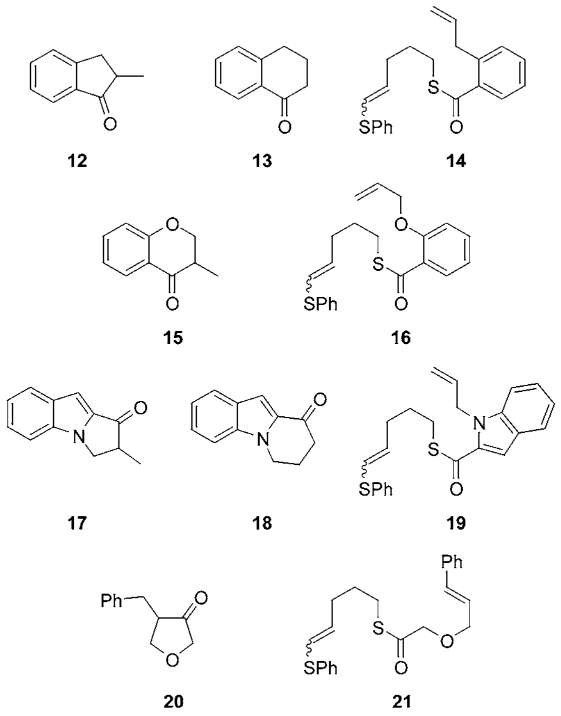


Figure 2.

Thiol ester **5** led to isolation of the cyclized indanone **12** and tetralone **13** in ca. 96:4 ratio and in 73% overall yield, along with comparable amounts of anticipated (*E*)- and (*Z*)-dihydrothiophene **4a**. Small amounts of the (*E*)- and (*Z*)-vinyl sulfide adduct **14** were additionally isolated (Figure 2 and Table 1, entry 1). In line with our prediction, the derived sulfanylvinyl radical proved to be fairly prone to perform intramolecular attack at sulfur to displace an allyl-substituted benzoyl radical. This intermediate in turn smoothly underwent 5-*exo* and 6-*endo* cyclization onto the adjacent double bond to furnish cyclized ketones **12** and **13**, respectively.[10] The transient sulfanylvinyl radical could also suffer competing reduction by benzenethiol yielding the adduct **14**, but fortunately to a very limited extent.

Table 1. Radical Reactions of Thiol Esters **5**−**10**

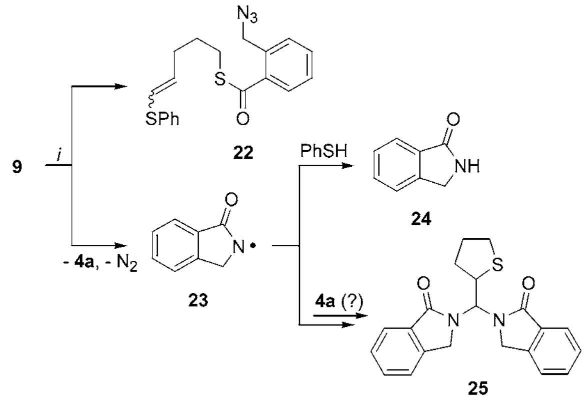
entry	substrate	products (%)[a]
1	**5**	**12** (70), **13** (3), **14** (5),[b] **4a** (86)[b]
2	**6**	**15** (78), **16** (5),[b] **4a** (75)[b]
3	**7**	**17** (80), **18** (4), **19** (6),[b] **4a** (80)[b]
4	**8**	**20** (54), **21** (15),[b] **4a** (59)[b]
5	**9**	**22** (18),[b] **24** (31), **25** (30), **4a** (42)[b]
6	**10**	**26** (71), **27** (17),[b] **4a** (70)[b]

[a] Yields isolated by column chromatography. [b] Mixture of (*E*)- and (*Z*)-isomer.

Strictly comparable results were provided by thiol esters **6** and **7**. Both compounds similarly furnished, besides thiophene **4a**, good yields of cyclized products, i.e., chromanone **15**[11] and indolones **17** and **18**, respectively,[12] while yielding only small amounts of their vinyl sulfide adducts **16** and **19** (Figure 2 and Table 1, entries 2 and 3). In the case of thiol ester **8**, the yield of the ensuing furanone **20**, as well as that of the accompanying thiophene **4a**, was, however, found to be significantly depressed in favor of the corresponding adduct **21** (Figure 2 and Table 1, entry 4).[13] The above findings thus revealed that the chain reaction of benzenethiol with our alkynylthiol esters could actually provide a novel entry to acyl radicals and their use in intramolecular cyclizations onto carbon−carbon double bonds.

Our subsequent study of the radical reactions of the azidothiol esters **9** and **10** led us to discover that under these circumstances, the possible acyl radical cyclization onto the azido group might result in a curious outcome or even be prevented. The azidoaroyl radical derived from **9** furnished only a modest yield of the expected isoindolinone **24**,[7] due to comparable occurrence of the bis-isoindolinone **25** (Scheme 3 and Table 1, entry 5).

Scheme 3 [a]



[a] Reagents: (i) PhSH/AIBN.

Compound **25**, whose structure was fully established by X-ray crystallographic analysis,[14] possibly arose from trapping of the cyclized amidyl radical **23** by the alkene moiety of thiophene **4a** rather than by benzenethiol. In fact, the electrophilic nature of radical **23**, while discouraging H-abstraction from the thiol, would encourage addition to the activated alkene moiety of the thiophene **4a**. Moreover, the

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[10] Cyclized ketones **12** and **13** were obtained by Crich in strictly comparable yields when the same aroyl radical was generated from the iodothiol ester precursor (see ref 4a).

[11] Chromanone **15** was obtained by Crich in a similar yield when the same aroyl radical was generated from the iodothiol ester precursor (see ref 4a).

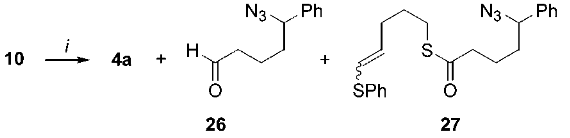
[12] 2-Indolylacyl radicals have very recently been generated from selenoesters, aldehydes, and α-keto acids and used in intermolecular additions to alkenes (see ref 3b).

[13] Amount of the resulting vinyl sulfide adduct was not diminished when an alkanethiol such as 1-butanethiol or methyl thioglycolate was used instead of benzenethiol.

[14] Data of the X-ray crystallographic analysis of compound **25** are included in Supporting Information.

azidoalkanoyl radical derived from **10** provided no evidence at all for any lactam or decarbonylated product[7] and instead yielded the reduced azidoaldehyde **26** in fairly good yield (Scheme 4 and Table 1, entry 6). In this case, the alkanoyl radical, being more nucleophilic than the aroyl congener[2c] and additionally possessing a greater degree of conformational and configurational freedom, preferred to undergo only intermolecular trapping by the thiol H-donor.[15]

Scheme 4 [a]



[a] Reagents: (i) PhSH/AIBN.

It is worth noting that in the case of substrates **8** and **10**, the outcoming yields of the corresponding vinyl sulfide adducts **21** and **27** (15 and 17%, respectively) were strictly comparable and, additionally, significantly higher than those observed for substrates **5**−**7** (ca. 5−6%), in which cases displacement of an aroyl radical can evidently occur. In our opinion, such evidence, in addition to that previously encountered by Crich in his related work,[6a] suggest that displacement of an alkanoyl radical from a thiol ester is somewhat less feasible than that of an aroyl congener.

In conclusion, in this work we have devised a valuable protocol for the generation of acyl radicals using accessible alkynylthiol ester precursors and avoiding the employment of undesirable organotin or organosilane reagents. The present protocol can be usefully employed to achieve acyl radical cyclizations onto carbon−carbon double bonds, but it seems of scarce utility for those onto azides. Studies are in progress aiming at extending its synthetic application to other intra- and intermolecular acyl radical reactions.

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Supporting Information Available: Experimental procedures for the preparation of pentynethiol **11**, thiol esters **5**−**10**, and radical reactions of **5**−**10** with PhSH; spectral data for new compounds (*E*)-**4a**, (*Z*)-**4a**, **5**−**10**, **14**, **16**, **17**, **19**, **20**−**22**, and **25**−**27**; and the X-ray molecular structure, crystal data, and structure refinement, as well as a CIF file, for compound **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] It is known that alkanethiols and especially arenethiols are excellent H-atom donors towards nucleophilic carbon radicals; indeed, thiols are normally better H-donors than Bu_3SnH or $(TMS)_3SiH$ even though sulfur−hydrogen bonds in the alkanethiols are relatively strong (see: Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem*. **1989**, *54*, 4603. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188).