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Tin-Free Generation of Alkyl Radicals from Alkyl 4-Pentynyl Sulfides via Homolytic Substitution at the Sulfur Atom[†]

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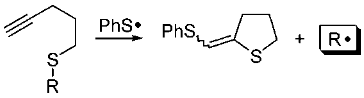
ABSTRACT



Homolytic substitution at the sulfur atom of β-(phenylsulfanyl)vinyl radicals, obtained by radical reaction of benzenethiol with easily accessible alkyl 4-pentynyl sulfides, is a mild, effective, tin-free route for the generation of all types of alkyl radicals. This protocol can be employed in reductive defunctionalizations as well as cyclizations onto both electron-rich and electron-poor C–C double bonds.

In recent papers[1a,b] we have shown that the radical reaction of benzenethiol with *S*-4-pentynylthiol esters provides a valuable method for the generation of acyl radicals, which arise from intramolecular homolytic substitution at the sulfur atom by initial β-sulfanylvinyl radicals. The protocol was employed both for the synthesis of cyclic compounds, by cyclization of suitable acyl radicals,[1a] and as a new synthetic method for the radical reduction of carboxylic acids to aromatic and aliphatic aldehydes under stannane/silane-free conditions.[1b] By adopting an analogous procedure, *N*-benzyl- and *N*-tosyl-substituted pentynyl carbamothioates were similarly found to release corresponding carbamoyl radicals in an efficient fashion.[2] *N*-Benzylcarbamoyl radicals gave pyrrolidinones/indolones through 5-*exo* cyclization onto internal alkenyl groups, whereas the *N*-tosylcarbamoyl counterparts displayed a peculiar tendency to yield isocyanates by β-elimination of tosyl radical. Recently, our method has been suitably adopted by Malacria to achieve a novel, effective generation of *P*-centered radicals from *S*-pentynyl thiophosphonates.[3]

Herein, we report that our original protocol can be interestingly extended even to the tin-free generation of unstabilized alkyl radicals via analogous homolytic substitution at the sulfur atom of alkyl 4-pentynyl sulfides. The intramolecular homolytic substitution of alkyl sulfides as a route to alkyl radicals is actually a long known process that has found considerable theoretical and synthetic attention. Recent studies have shown the precious utility of alkyl sulfides for generation of alkyl radicals, especially when other common radical precursors such as alkyl halides are inadequate. However, in the reported instances, not only were difficult to access alkyl haloaryl sulfides invariably employed, but additionally, those radical precursors were often undesirably reacted with toxic or rather expensive stannane/silane

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[†] This paper is dedicated to Prof. Luisa Benati on the occasion of her retirement.

(1) (a) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313. (b) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *Synlett* **2004**, 987. For a nice review on homolytic substitution at the sulfur atom as a tool for organic synthesis, see: (c) Crich, D. *Helv. Chim. Acta* **2006**, *89*, 2167. For comprehensive reviews on tin-free methodologies, see: (d) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (e) Studer, A.; Amrein, S. *Synthesis* **2002**, 835.

(2) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 3192.

(3) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A.-L.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2007**, *9*, 1061.

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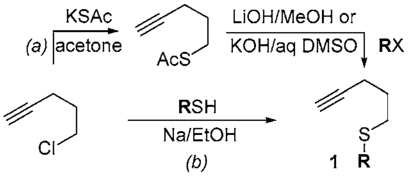
reagents.[1c,4] On the contrary, our procedure employs very easily accessible alkyl 4-pentynyl sulfides and thiophenol, which is rather inexpensive, definitely much less toxic than stannanes, and practically inert toward most functional groups.

The synthesis of the starting sulfides **1** can be smoothly accomplished in a very straightforward, convenient way by reacting either 5-chloro-1-pentyne with aliphatic thiols or 4-pentyne-1-thiol with alkyl chlorides, bromides, iodides, or tosylates (Scheme 1).[5]

Scheme 1 [a]



[a] X = Cl, Br, I, OTs.

5-Chloro-1-pentyne is a cheap, commercially available compound that is also a suitable starting material for the synthesis of 4-pentyne-1-thiol. This was indeed obtained in just two steps by reaction of 5-chloro-1-pentyne with potassium thiolacetate in acetone, followed by treatment with sodium methoxide in methanol.[6] However, there is no need to isolate the rather unstable thiol, since the desired alkyl sulfides can be directly obtained in good to excellent yields by treating *S*-(4-pentynyl) thiolacetate with either lithium hydroxide in methanol or potassium hydroxide in aqueous DMSO in the presence of the alkylating reagent.[7] The former conditions are appropriate only for primary alkyl groups, whereas the latter can be used for both primary and secondary alkyls (both stabilized and unstabilized). Tertiary alkyl sulfides can be readily obtained from the corresponding thiols and 5-chloro-1-pentyne. The prepared sulfides are reported in Table 1 together with their synthetic methods (see Scheme 1) and yields (yields for compounds **1e,g−i** are for the whole multistep syntheses; see Supporting Information).

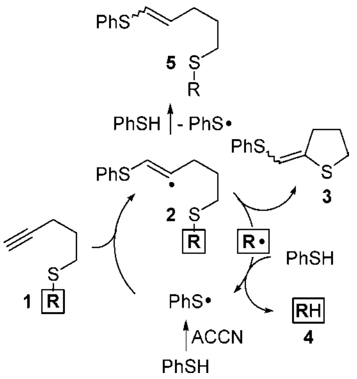
The optmized reaction conditions for generation of alkyl radicals from sulfides **1** entail syringe pump addition (2−4 h) of a degassed toluene (13 mL) solution of PhSH (1.1 equiv) and ACCN[8] (0.25 equiv) to a boiling toluene (13 mL) solution of **1** (1 mmol) kept under a nitrogen atmosphere, followed by additional 1 h of reflux.

The reaction mechanism involves addition of benzenesulfanyl radical to the triple bond of sulfide **1** to give vinyl radical **2**, which gives rise to homolytic substitution at the sulfur atom to afford the desired alkyl radical together with thiophene derivatives **3**[9] (Scheme 2). Hydrogen transfer from benzenethiol to the alkyl radical (or intermediates thereof, see below) yields alkane **4** and a new benzenesulfanyl radical that sustains the radical chain reaction. Under these optimized conditions byproducts such as diphenyl disulfide and, above all, vinyl sulfide **5**, arising from competing hydrogen transfer to vinyl radical **2**, were formed in trace amounts only.[10]

Table 1. Synthesis of Sulfides **1a−i**

entry	R	method	yield (%)
a	${}^{n}C_{12}H_{25}$	*a, b*	95, 98
b	$PhCH_2CH(Me)$	*a, b*	93, 98
c	1-adamantyl	*b*	95
d	4-MeO-C_6H_4-CH_2	*a, b*	95, 95
e	$Ph(CH_2)_3O(CO)CH_2$	*b*	78
f	$Ph(CH_2)_3$	*a*	96
g	$(allyl)_2N(CO)CH_2$	*a, b*	90, 85
h	$PhCH{=}CHCH_2O(CO)CH_2$	*b*	80
i	$Ph(CH_2)_3O(CO)CH{=}CH(CH_2)_4$	*a*	52

Scheme 2



Sulfides **1a−f**, when treated under the standard conditions described above and after column chromatography, afforded practically quantitative yields of the corresponding alkanes **4a−f** (Scheme 3). As one can see, the reaction outcome is

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[4] Ooi, T.; Furuya, M.; Sakai, D.; Maruoka, K. *Adv. Synth. Catal.* **2001**, *343*, 166.

[5] The whole synthetic array of possibilities was fully examined with sulfide **1f** (see Supporting Information).

[6] This is an improved procedure with respect to that previously reported (ref 1a), which started from 4-pentyn-1-ol. See also: Minozzi, M.; Nanni, D.; Spagnolo, P. 4-Pentyne-1-thiol. In *The Encyclopedia of Reagents for Organic Synthesis (eEROS)*; Wiley: Chichester, 2008; Build 13, in press.

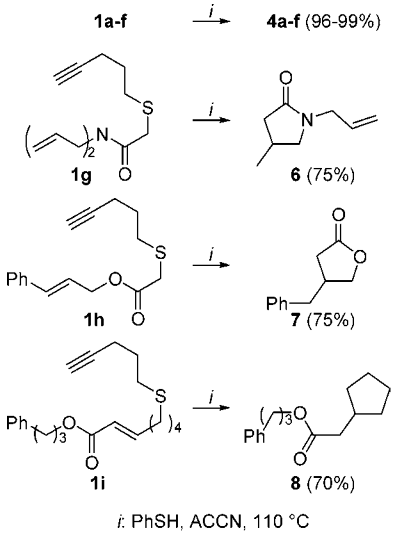
[7] For general methods for conversion of thiolesters into thiols, see: Zheng, T.-C.; Burkart, M.; Richardson, D. E. *Tetrahedron Lett.* **1999**, *40*, 603 and references therein.

[8] Azobis(cyclohexanecarbonitrile).

[9] Mixtures of *E*- and *Z*-isomers. Under certain conditions and with some substrates an isomeric form of **3** was also isolated; studies are underway to determine its structure.

[10] Very satisfactory results can be obtained also at 80 °C with AIBN as a radical initiator, but only with stabilized radicals (e.g. **1e**). With other unstabilized R groups significant amounts of vinyl sulfides **5** were always obtained. Other solvents such as alcohols, acetonitrile, THF, or fluorobenzene gave much poorer results. Unsatisfactory outcomes were also achieved with other thiols that, on a theoretical basis, would possess less powerful hydrogen-donor properties. Indeed, treatment of sulfide **1a** with *tert*-dodecanethiol and methyl thioglycolate ($HSCH_2COOMe$) yielded, respectively, only unreacted starting material and a mixture of starting material and vinyl sulfide **5a** (Ph = CH_2CO_2Me). The efficiency of the S_Hi mechanism at the sulfur atom is substantiated by the fact that unstabilized alkyl radicals can even be obtained by direct, one-pot treatment of the corresponding 4-pentynyl sulfides with benzenethiol, i.e., without syringe pump addition of the latter, although under these conditions significant amounts of vinyl sulfides **5** were also obtained.

Scheme 3



not influenced at all by the nature of the leaving R-group. Primary, unstabilized alkyl radicals (**1a,f**) are released with the same efficiency as more substituted or stabilized radicals (such as benzyl **1d**), which, on the other hand, are capable of abstracting hydrogen from the thiol at a sufficient rate as to maintain the chain reaction. Furthermore, both electrophilic (**1e**) and nucleophilic (**1a−d,f**)[11] radicals can be generated and reduced with comparable efficiencies.

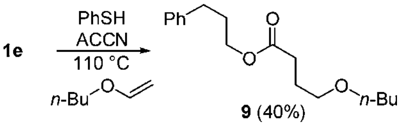
Since benzenethiol is totally inert to those functional groups that are potentially sensitive to the stannane/silane reagents commonly used in radical reactions and taking into account that sulfides **1** can be synthesized from both the corresponding halides (or tosylates) and thiols (see Scheme 1), this procedure can be regarded as a very mild, efficient defunctionalization method of halogen-, hydroxyl-, and thiol-containing molecules. Radical dehalogenations and deoxygenations (Barton−McCombie reaction) are common techniques in organic synthesis; this is however a realm still strongly dominated by tin reagents and mild, effective tin-free procedures to perform these transformations should always be welcome.[1d,e] Furthermore, to date only very few examples of radical desulfuration of thiols have been reported.[12]

Of course, one of the major breakthroughs of radical reactions in organic synthesis is the possibility to carry out C−C bond-forming processes by trapping alkyl radicals prior to hydrogen abstraction, for instance by cyclization or intermolecular addition to olefins. Therefore, we tested our methodology in 5-exo radical cyclizations and we were pleased to find that it works very well, both with electrophilic and nucleophilic radicals.[13] Indeed, the carbon radicals derived from sulfides **1g−h** gave smooth ring closure onto their electron-rich C−C double bonds to afford lactam **6** and lacton **7**, respectively, in good yields. Even more interestingly, the alkyl radical derived from **1i** gave rise to a very clean cyclization onto the electron-poor acrylate moiety to give cyclopentane **8** in 70% yield (Scheme 3).

The latter is a noteworthy result at least for two reasons. First, the alkyl radical arising from **1i** is nucleophilic in nature and should therefore be trapped very quickly by the thiol: however, under our conditions, this reaction is notably slower than cyclization and no traces of the product of premature reduction of the alkyl radical (**4i**) were observed. Second, this kind of alkyl radical is not accessible by desulfurization of the corresponding thiol, since the latter immediately cyclizes onto the C−C double bond upon every attempt of synthesis: this means that this kind of cyclization is not available by our previous tin-free procedure,[12] and the present methodology therefore represents a suitable complement of that.

Attempts of intermolecular addition of alkyl radicals to olefins were also carried out. Sulfide **1e** was indeed reacted with *n*-butyl vinyl ether (1−10 equiv) under the standard conditions. Although the resulting mixtures were always contaminated by some byproducts formed in variable amounts, the reaction proved again to be synthetically useful, since in the presence of 5 equiv of alkene it afforded the addition product **9** in 40% yield (Scheme 4).

Scheme 4



In conclusion, we have shown that homolytic substitution at the sulfur atom of vinyl radicals **2**, obtained by benzenesulfanyl radical addition to alkyl 4-pentynyl sulfides **1**, is a very effective tool for the generation of all types of alkyl radicals. Owing to the accessibility of the starting materials, the low cost and toxicity properties of benzenethiol, and its compatibility with most functional groups, this procedure can be an appealing substitute for many stannane/silane-mediated radical reactions and a valid complement to our previous tin-free methodology for generation of analogous radicals. Studies are underway to extend this procedure to other synthetically interesting targets.

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[11] Attempts were also made to generate α-oxy (ROCH$_2$-type) radicals (R = Ar, ^{n}C$_8$H$_{17}$). The corresponding pentynyl sulfides can be easily synthesised but cannot be purified, due to their instability under all types of workup. Some reactions carried out on the crude sulfides yielded the expected reduction products accompanied by unreacted starting material and other unidentified side products.

[12] (a) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3598. (b) Wan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9248, and references therein.

[13] Cyclizations were carried out by adding the toluene solution of benzenethiol and ACCN in 4 h instead of the 2 h required for defunctionalizations.

We also gratefully thank Prof. David Crich (Wayne State University, Detroit, MI) for helpful suggestions.

Supporting Information Available: Experimental procedures for the synthesis of alkyl 4-pentynyl sulfides **1a**−**i** and their radical reactions and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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