Radical Reactions

A Novel Tin-Free Procedure for Alkyl Radical Reactions**

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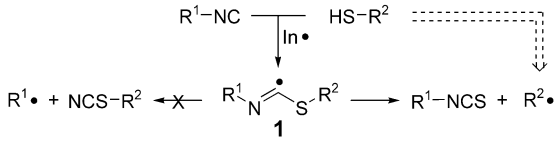
Radical reactions have definitely become a very powerful tool for synthetic organic chemists. Very useful defunctionalizations, formation of C–C (or even C–heteroatom) bonds, and an assortment of intra- or intermolecular cascade processes can be conducted, also with high stereoselectivity, under extremely mild conditions, and many sensitive functional groups are tolerated without any tedious protecting/deprotecting procedures.[1] This success owes much to tin reagents, and over the last four decades radical chemistry in synthesis has been literally monopolized by chain methods based on a variety of organotin derivatives. So pervasive is the presence of tin reagents in efficient radical syntheses that this dominance has been referred to as the "tyranny of tin".[2] Unfortunately, tin-based chemistry is associated with two critical drawbacks, that is, the toxicity of organotin compounds and the problems very often encountered in product purification. The quantitative removal of organotin residues from the reaction products is usually a difficult task, and this disadvantage, along with the high toxicity of those residues, can severely limit the application of tin reagents, for example for the synthesis of pharmaceuticals. It is therefore no surprise that alternative ways of carrying out radical reactions are under intensive investigation, in a search for both efficient purification protocols (special workup procedures, modified and polymer-bound tin reagents, etc.) and, above all, tin substitutes.[2,3]

The great upsurge of alternative processes to tin-based methodologies that has marked the last decade prompted us to verify whether isocyanide-based radical chemistry, which we have been studying for several years, could be also useful for performing free-radical chain reactions under reductive tin-free conditions.[4] Indeed, isocyanides are very efficient radical traps and, by addition of sulfanyl radicals, they are a valuable source of α-thioimidoyl radicals **1** (Scheme 1).[5]



Scheme 1. Fragmentation paths of thioimidoyl radicals. In• = initiator.

Although *N,S*-dialkyl-substituted thioimidoyl radicals can in principle fragment by β-scission of either the C–N or the C–S bond, giving thiocyanates and isothiocyanates, respectively, we have demonstrated that usually only fragmentation of the latter occurs.[6] This behavior is substantially independent of the relative stability of the released radicals and even primary, nonstabilized alkyl radicals can be smoothly generated at relatively low temperatures from various N-substituted thioimidoyls (Scheme 1).

As far as the precursors of thioimidoyl radicals are concerned, isocyanides are easily accessible, stable derivatives,[7] and some of them are also commercially available, for example, *tert*-butyl isocyanide. Thiols as well are very handy compounds that can be readily synthesized from haloalkanes, alcohols, or their derivatives in manifold ways.[8] Recently, treatment of halides, epoxides, or alcohols with polymer-supported hydrosulfide under very mild conditions gave the products in high yields and excellent chemoselectivity after a very easy workup.[9] This novel methodology seems to have made thiols much more easily accessible than ever.

In light of both the fast C–S β-scission of thioimidoyl radicals and the ready access to their precursors, we reasoned that thioimidoyl fragmentations could provide a clean, convenient entry to alkyl radicals from thiols. In this paper we show that this procedure can be an efficient substitute for other radical methods, mainly in defunctionalization reactions and intermolecular addition to olefins.

Trial experiments were initially performed with alkanethiols and various isocyanides to test the efficiency of the simple desulfuration reaction. The tests were carried out by adding a 0.1M solution of the thiol in benzene (10 mL) over one hour to a solution of isocyanide (1.1 equiv) in benzene (10 mL) heated at reflux and with azobisisobutyronitrile (AIBN, 0.1 equiv) as an initiator. Under these conditions the alkyl radical generated by fragmentation of the intermediate thioimidoyl radical is smoothly reduced by the starting thiol

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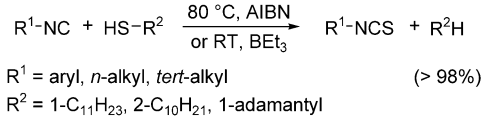
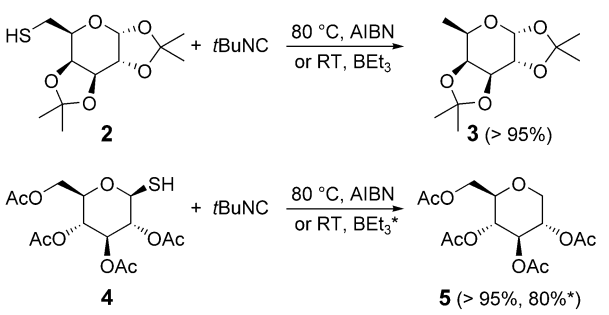
giving the corresponding alkane in nearly quantitative yield (Scheme 2). The reactions can be also conducted in toluene solution at 80 °C and even at room temperature, when AIBN is replaced with triethylborane.[10] The reaction outcome was



Scheme 2. Defunctionalization of thiols with isocyanides.



Scheme 3. Defunctionalization of thiol-sugars (Barton–McCombie-type reaction).

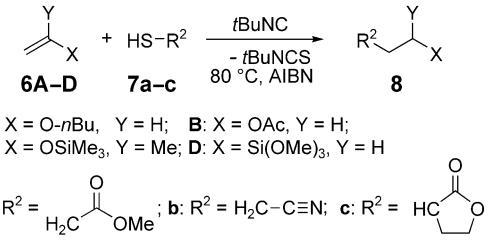
influenced neither by the thiol alkyl chain—tertiary, secondary, and even nonstabilized primary thiols were all desulfurated quantitatively—nor by the nature of the isocyanide—both aromatic and aliphatic isocyanides were used without any lowering of the reaction efficiency.

The latter point has two important consequences as far as accessibility of starting materials and workup are concerned. First, the experiments can be carried out with commercially available *tert*-butyl isocyanide without any need to synthesize suitable congeners. Second, the low boiling points of both the starting isocyanide and its by-product *tert*-butyl isothiocyanate (91 °C and 140 °C at 760 torr, respectively) allow for an extremely straightforward workup procedure: concentration of the final reaction mixture under reduced pressure results in concomitant elimination of solvent, by-product, and excess starting isocyanide, and the final desulfurated product can be recovered quantitatively in very high purity simply after rotary evaporation.[11] In light of all of these features, we think that this method can therefore be regarded as a very mild, efficient defunctionalization of thiols and, consequently, their precursors, that is, halides and alcohols.

The subsequent, logical step was to extend this procedure to Barton–McCombie-type reactions. Deoxygenation reactions are of huge importance in organic synthesis, and the Barton–McCombie reaction developed in the 1970s is a major milestone in the application of radical reactions in synthesis.[12] Although a few catalytic or tin-free deoxygenations have already been reported,[13] the Barton–McCombie realm is still strongly dominated by tin reagents. Taking into account that thiols, like xanthates, thiocarbonyl imidazolides, and dithiocarbonates, can be synthesized directly from alcohols,[9c,d,14,15] we reasoned that our isocyanide-mediated radical desulfuration of thiols could be a valid alternative to traditional Barton–McCombie procedures.

The reaction was examined on thiol-sugars **2** and **4** (Scheme 3). Under the usual conditions, at 80 °C, both compounds gave nearly quantitative yields of the corresponding desulfurated sugars **3** and **5**.[16] At room temperature, the reactions required longer times and greater amounts of initiator (BEt_3, 5 equiv) to reach completion—probably due to the presence of the oxygen atoms on the substrates—but afforded again very good yields of **3** and **5**. The result with substrate **2** is particularly noteworthy, since Barton–McCombie reactions are known to proceed quite ineffectively when primary radicals are involved.[12c,17] Our reaction proceeds instead very smoothly and without any significant side product even at room temperature. The ease of workup (see above) allows for isolation of the final sugar in very high purity without any other purification procedure (for proof of the purity of the crude product, see the ^{1}H NMR spectrum of **3** in the Supporting Information). It is worth noting that, in the case of **4**, the corresponding anomeric radical is easily produced and reduced without the 1,2-shift of the acetoxy group that is usually observed in tin-based defunctionalization procedures.[18]

In tin-based radical chemistry, the defunctionalization reactions are very often combined with intra- or intermolecular C–C bond-forming processes, in which the initial alkyl radical is trapped, for instance, by an alkene prior to hydrogen abstraction: this is undoubtedly one of the major breakthroughs of radical reactions in organic synthesis. Our isocyanide-based method does not seem suitable for Giese-type reductive additions of nucleophilic alkyl radicals to activated olefins. Indeed, hydrogen transfer from the thiol to the alkyl radical is much faster than its addition to the olefin, and the yields of adduct products are always very low, even in the presence of a large excess of alkene and very low concentrations of thiol. On the contrary, due to polar effects in the hydrogen-abstraction reaction,[19] electrophilic alkyl radicals are not easily trapped by the thiol, and they can be smoothly generated in the presence of nucleophilic olefins to give the corresponding adducts in good to almost quantitative yields. Scheme 4 and Table 1 show the results obtained at 80 °C with our standard method with four alkenes (**6A–D**, 10 equiv) and three different thiols (**7a–c**, 1 equiv). Evaporation of the final reaction mixtures removes simultaneously solvent, excess isocyanide, by-product isothiocyanate, and excess olefin giving the pure adducts **8**. Chromatography is sometimes needed to further purify compounds **8** and remove trace amounts of side products.[20]



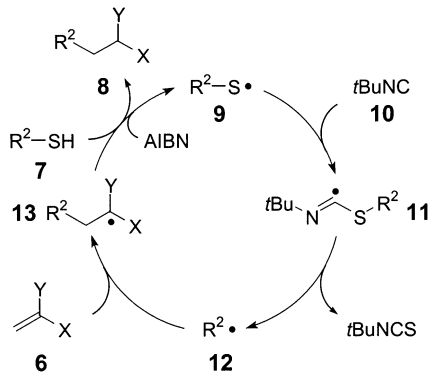
Scheme 4. Intermolecular addition of electrophilic alkyl radicals to olefins.

Table 1: Yields of the adducts **8** obtained by the reaction of alkenes **6A–D** with thiols **7a–c** and *tert*-butyl isocyanide in benzene or toluene at 80 °C.

Entry	Alkene	Thiol	Adduct	Yield [%][a]
1	**6A**	**7a**	**8Aa**	66 (75)
2	**6A**	**7b**	**8Ab**	82 (91)
3	**6A**	**7c**	**8Ac**	75 (85)
4	**6B**	**7a**	**8Ba**	67 (74)
5	**6B**	**7b**	**8Bb**	75 (81)
6	**6B**	**7c**	**8Bc**[b]	79 (85)
7	**6C**	**7a**	**8Ca**	– (95)[c]
8	**6C**	**7b**	**8Cb**	– (83)[c]
9	**6C**	**7c**	**8Cc**	– (92)[c]
10	**6D**	**7a**	**8Da**	55 (64)
11	**6D**	**7b**	**8Db**	81 (92)
12	**6D**	**7c**	**8Dc**	– (70)[c]

[a] Yields are for pure products isolated by column chromatography; yields in parentheses were determined by ^{1}H NMR analysis of the crude mixtures. [b] This compound is an important intermediate for the synthesis of crop protection agents; see Supporting Information, ref. [20]. [c] Partial or total decomposition of product was observed by column chromatography.

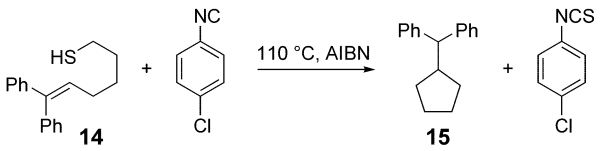
The mechanism of the efficient radical chain reaction involved in this transformation is presented in Scheme 5. Sulfanyl radical **9**, smoothly generated from thiol **7** by AIBN initiation, adds to isocyanide **10** to give the alkyl radical **12** by fast β-fragmentation of the thioimidoyl radical **11**. The



Scheme 5. Radical chain reaction of alkenes **6**, thiols **7**, and *tert*-butyl isocyanide.

electrophilic radical **12** adds to alkene **6** to generate the nucleophilic radical adduct **13**, which is eventually trapped by the starting thiol **7** to yield the final product **8** together with a new chain-propagating species **9**.

A preliminary experiment also showed that even intramolecular C–C bond formation can occur, although under slightly different conditions. Treatment of thiol **14** with 4-chlorophenyl isocyanide at 110 °C in toluene afforded the cyclization product **15** in 80 % yield after column chromatography (Scheme 6). In this case, fast 5-exo ring closure prevented premature trapping of the nucleophilic alkyl radical by the thiol and no reduction product was observed; no compounds ascribable to 6-exo cyclization of the sulfanyl radical were isolated either.



Scheme 6. Radical cyclization of thiol **14** with 4-chlorophenyl isocyanide at 110 °C.

In summary, we have shown that C–S β-scission of thioimidoyl radicals is a very effective route for the generation of alkyl radicals that can be employed in reductive defunctionalizations and intermolecular additions to electron-rich olefins. Owing to the accessibility of the starting materials, the efficient production of any kind of alkyl radical even at relatively low temperatures, and extreme ease of workup and product purification, this procedure can be an appealing substitute for many stannane/silane-mediated radical reactions. Studies are underway to find alternative ways of generation of thioimidoyl radicals not involving the thiol/isocyanide pair, with the aim of extending the method to other reactions that could suffer from the presence of a too efficient hydrogen-transfer reagent.

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Keywords: fragmentations · isocyanides · radical reactions · synthetic methods · thiols

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