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Bromine catalyzed conversion of *S-tert*-butyl groups into versatile and, for self-assembly processes accessible, acetyl-protected thiols†

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The facile and efficient conversion of a *tert*-butyl protecting group to an acetyl protecting group for thiols by catalytic amounts of bromine in acetyl chloride and the presence of acetic acid has been developed. The fairly mild reaction conditions are of particular interest for new protecting group strategies for sulfur functionalised target structures.

The fast growing area of nanotechnology demands reliable interfaces between fabricated nanostructures and the macroscopic world. In particular the integration of tailor-made molecular systems as functional units in nanoscale objects and on nanostructured surfaces is very promising. At present, the majority of interfaces between molecular systems and nanoscale- or even macroscopic structures is based on self-assembly of sulfur-terminated molecules on noble metals, e.g. gold.[1] The success of this linkage is based on its ambivalence, the covalent Au–S bond is stable enough at room temperature for subsequent processing of the samples but loose enough to allow dynamic processes like self-assembly on the surface.[2] In particular the fast growing field of molecular electronics benefits from the Au–S linkage to integrate molecular structures in electronic circuits for the investigation of their electronic transport properties. For example Au–S immobilised SAMs have been investigated in crossed-wire[3] or mercury drop junctions,[4] in small laterally limited assemblies of up to 1000 molecules in nanopores,[5] or even on a single molecule level, for instance in mechanically controlled break junctions.[6]

In spite of the rich established thiol chemistry, the introduction of the required thiol function into molecular structures of interest often remained challenging and troublesome. Unfortunately, free thiols tend to form disulfides in the presence of oxidation agents like traces of oxygen. A promising alternative to free thiols are acetyl protected ones, as they are air-stable and hydrolysable *in situ*.[7] However, *S*-acetyl derivatives do not tolerate harsh reaction conditions and consequently, synthetic strategies to exchange more stable protecting groups for the acetyl protecting group towards the end of a synthetic pathway are very promising. *S-tert*-butyl groups are stable to acidic and basic reaction conditions and hence an ideal precursor of an acetyl protected thiol. Furthermore, *tert*-butylsulfanyl groups can easily be introduced into target structures by nucleophilic substitution of *e.g.* halogenides with a *tert*-butyl thiolate anion as a strong nucleophile.‡ To the best of our knowledge, only two methods for the conversion *S-tert*-butyl to *S*-acetyl are reported, both being limited in application by the use of strong Lewis acids like $AlCl_3$[8] or BBr_3.[9]

Here we report a novel, simple and useful method for the conversion of *S-tert*-butyl groups into the versatile acetyl-protected thiols using fairly mild reaction conditions (Fig. 1).

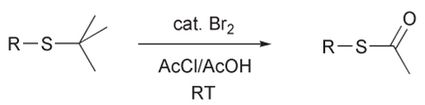

Fig. 1 Bromine catalyzed conversion of a *tert*-butyl thiol into an acetyl protected thiol.§

We demonstrate here, that various *S-tert*-butyl groups (Table 1) are smoothly converted into the corresponding *S*-acetyl-protected thiols in the presence of catalytic amounts of bromine in acetyl chloride–acetic acid at room temperature. The starting material was solved in acetyl chloride and the bromine was added slowly as diluted solution in acetyl chloride–acetic acid (1 : 1).§ It turned out to be important to keep the bromine concentration low, as larger bromine concentrations resulted in oxidative disulfide formation. The reaction has been found originally for aromatic *tert*-butyl thiophenylates. However, the reaction protocol seems to have much broader application potential, as the conversion of benzylic (d) and alkylic (e) *tert*-butyl protected thiols to acetyl protected thiols turned out to be similarly successful. To our surprise, the reaction is not even limited to thiols. The *tert*-butyl protected phenolic oxygen in (c) is converted to an acetyl protected phenol under the applied reaction conditions as well.[10] However, the reaction conditions seem to be selective for *tert*-butyl groups as, for example, the phenyl alkyl ether group (e) is not attacked. While excellent yields have been obtained in numerous cases (a–f) even for substrates comprising two *tert*-butyl protected groups (b–d,f), moderate (g–i) and poor (j) yields have been observed in other cases, probably due to competitive side reactions.

A proposed reaction mechanism is displayed in Scheme 1. Treatment of the *tert*-butyl protected thiol with bromine probably leads to the sulfenyl bromide intermediate **2** and hydrogen bromide, driven by the formation of isobutene, which is removed as volatile product. The formation of sulfenyl chloride by the reaction of Cl_2 and 1-*tert*-butoxy-4-*tert*-butylsulfanyl benzene has been reported in the literature.[11] Furthermore, sulfenyl halides and their reactions have already been described.[12–14] The proposed mechanism assumes an equilibrium between the sulfenyl halide **2** and hydrogen bromide on one side and the thiol **3** and bromine on the other side. While bromine is recovered for the next catalytic cycle, the thiol **3** is quenched by the excess of acetyl chloride forming the acetyl-protected thiol **4** and hydrogen chloride. The continuous consumption of bromine and thiol **3** out of the equilibrium, further induces their formation from sulfenyl halide **2** and hydrogen bromide to rebalance the equilibrium. The presence of acetic acid is crucial for the successful conversion, probably to stabilise one of the intermediates of the reaction mechanism.

The decreasing yields of isolated conversion products in the presence of electron rich multiple bonds (g–j), which are known to react with electrophilic sulfenyl cations,[13,14] further consolidate the proposed reaction mechanism with the intermediate species **2**. In particular the poor yield of 3% for the compound comprising a terminal acetylene (j) most likely

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data: experimental procedures for the synthesis of substrates and analytical data for the characterization of the substrates and products. See http://www.rsc.org/suppdata/ob/b4/b408677e/

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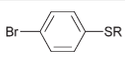
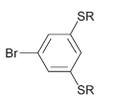
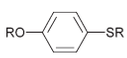
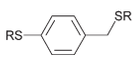
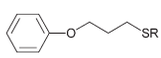
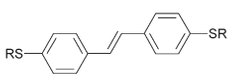
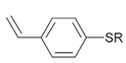
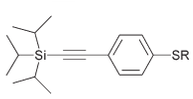
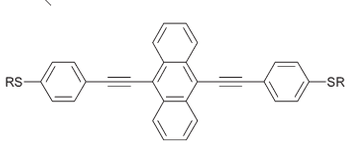
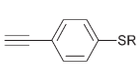
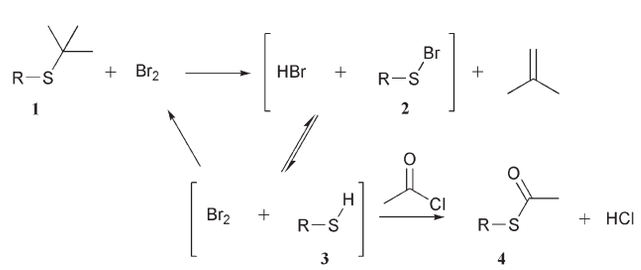
Table 1 The conversion of R = *tert*-butyl to R = acetyl in a variety of molecular structures using the new bromine catalysed reaction protocol

Entry	Structures[a]	Yield[b] [%]
a		94
b		95
c		89
d		97
e		86
f		96
g		33
h		29
i		42
j		3

[a]Starting materials and reaction products have been characterised by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry. [b]Isolated yields.



Scheme 1

points towards a faster addition reaction of the electrophilic sulfur species to the unprotected and electron rich triple bond.[13] Increased yields of conversion for substrates containing double bonds compared with triple bonds are expected, due to the less electron rich nature of the double bond. However, the excellent yield of 96% for the conversion of the stilbene species (f) in spite of the double bond was surprising and may be due to both, steric protection and electronic passivation of the double bond towards electrophilic attack in the conjugated aromatic stilbene structure.

Molecular rods designed to bridge the gap between metallic electrodes like (f) and (i) have been synthesised using the described protocol. The isolated yields turned out to be independent from the scale of the reaction. Furthermore, the rod (i) allows a comparison of the synthetic strategies: assembled from acetyl protected starting materials, only a yield of 5% has been isolated.[15] A similar coupling protocol using *tert*-butyl protected building blocks yielded over 70% for the coupling.[15] Subsequent transformation employing the described procedure afforded the acetyl protected compound in a yield of 42%, providing a yield of 30% over both steps.

In summary, we describe a new one-pot reaction protocol for the conversion of very robust *tert*-butyl protected thiol groups into more versatile and labile acetyl protected ones, which can be hydrolysed *in situ* to free thiols. The reaction is catalysed by traces of halogens and requires an acidic pH and acetyl chloride as solvent to quench the reactive intermediates. The described protocol is of particular interest as a fairly mild reaction condition that allows the exchange of the robust *tert*-butyl by the acetyl sulfur protecting group in a late stage of a synthetic strategy.

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Notes and references

‡ **Example for the introduction of *S*-*tert*-Bu by nucleophilic substitution: preparation of the starting material 1-*tert*-butyl-sulfanyl-4-*tert*-butylsulfanylmethyl benzene (d)**: To a solution of 4-bromobenzyl bromide (2.0921 g, 8.37 mmol) in dry DMF (20 ml), sodium-2-methyl-2-propanethiolate (2.8164 g, 25 mmol) was added portion wise. After heating to 135 °C for 16 hours, the reaction mixture was poured into NaCl saturated water and extracted with diethyl ether. After washing with water and drying over $MgSO_4$, column chromatography (silica gel, hexane–toluene 20 : 1) yielded 1-*tert*-butyl-sulfanyl-4-*tert*-butylsulfanylmethyl benzene (1.865 g, 83%) as white solid. Mp. 72.9–74.5 °C; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (9 H, s, CH_3), 1.35 (9 H, s, $ArSC(CH_3)_3$), 3.78 (2 H, s, CH_2), 7.31 (2 H, d, *J* 8.0, ArH), 7.45 (2 H, d, *J* 8.0, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 31.3 (CH_3), 33.5 (CH_2), 43.4 ($C(CH_3)_3$), 46.2 ($C(CH_3)_3$), 129.5, 131.3, 137.9, 139.8; *m*/*z* (EI) 268.0 [M^+, 61%], 212.0 [38, $M^+ - C_4H_8$], 156.0 [29, $M^+ - 2 \times C_4H_8$], 123.1 [100, $M^+ - C_4H_8 - C_4H_9S$]. Elemental analysis calcd (%) for $C_{15}H_{24}S_2$: C 67.10, H 9.01; found: C 67.46, H 8.75.

§ **General procedure for the conversion of R-*S*-*tert*-Bu into R-*S*-Ac**: To a well-stirred solution of starting compound (10^{-5} M) in acetyl chloride (10 ml), a solution of bromine (catalytic amount: *ca.* 5 mol%) in acetyl chloride–acetic acid (1 : 1) was added in 30 minutes at room temperature. The course of the reaction was monitored by thin layer chromatography. After completion of the reaction (1–30 minutes after the bromine addition), all solvents were removed by evaporation and the crude residues were purified by silica gel chromatography.

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10 It is noteworthy that in ref. 11 the same substrate 1-*tert*-butoxy-4-*tert*-butylsulfanyl benzene is treated with Cl_2 in CH_2Cl_2 and only the formation of sulfenyl chloride is reported, while the *tert*-butoxy group seems to resist the reaction conditions.

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