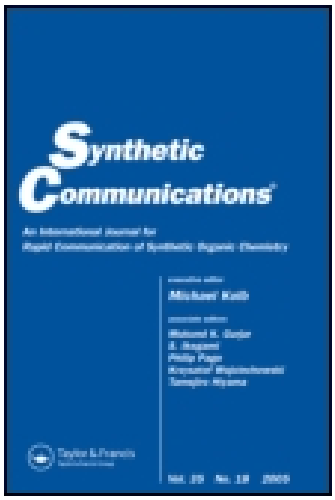

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The tert-Butyl Moiety—A Base Resistent Thiol Protecting Group Smoothly Replaced by the Labile Acetyl Moiety

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The *tert*-Butyl Moiety—A Base Resistent Thiol Protecting Group Smoothly Replaced by the Labile Acetyl Moiety

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ABSTRACT

Aryl *t*-butyl sulfides underwent quantitative *tert*-butyl/acetyl exchange reactions affording thioacetic acid *S*-aryl esters when treated with acetyl chloride and boron tribromide.

The *t*-butyl group is widely used as a thiol protective group[1] in organic synthesis since it is stable towards bases. In contrast to the *n*-alkyl and isopropyl groups it can be cleaved off with Lewis acids under relatively mild conditions. Reported reagents for the cleavage of

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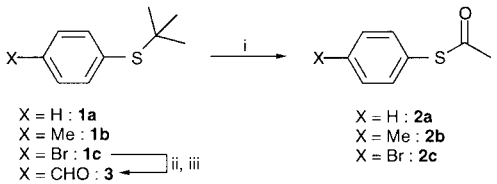
the *t*-butyl/S bond include mercury(II) acetate in TFA/anisole followed by treatment with hydrogen sulfide,[2] hydrogen fluoride in anisole,[3] and 2-nitrobenzenesulfenyl chloride followed by reduction of the unsymmetrical disulfide with sodium borohydride.[4] It has been reported that thioacetic acid *S*-aryl esters form upon treatment of aryl *t*-butyl sulfides with acetyl chloride/aluminum chloride,[5] whereas the thiols form in absence of acetyl chloride by toluene scavenge.[6] We have studied the clean reaction between aryl *t*-butyl sulfides and acetyl chloride/boron tribromide and found a high-yielding alternative to the $AcCl/AlCl_3$ couple.

The reaction between *t*-butyl aryl sulfides and boron tribromide in dichloromethane/toluene gave thiols after quenching in water. Irreversible scavenging of the *t*-butyl group by means of toluene pulled the reaction in direction of thiol resulting in quantitative GC-MS yields of thiols and *t*-butyltoluene after two days reaction at room temperature.

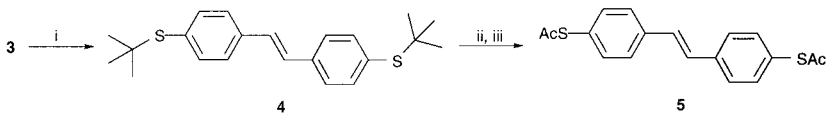
For synthetic applications thiols needed to be trapped effectively in order to speed up the deprotection of the thiol moiety. Acetyl chloride and boron tribromide in dichloromethane/toluene quantitatively converted the aryl *t*-butyl sulfides **1a–c** into thioacetic acid *S*-aryl esters **2a–c**. Thioesters may easily be further hydrolyzed into thiols[7] under mild acidic or mild basic conditions.

Extreme base stability of *t*-butylthio structural unit was shown by a new facile synthesis of 4-(*t*-butylthio)benzaldehyde **(3)** via 4-(*t*-butylthio)-lithiobenzene in search for building blocks for preparation of stilbenes carrying mercapto termini (Sch. 1).

Aryl *t*-butyl sulfides, in contrast to thioesters, were found tolerable towards McMurry conditions. **3** was smoothly coupled with low valent titanium in THF forming solely *trans*-4,4′-*bis*(*t*-butylthio)stilbene **(4)**. Upon treatment of with boron tribromide and acetyl chloride under standard conditions the new protected stilbenedithiol formed as an



Scheme 1. *Reagents and conditions*: (i) Boron tribromide (1.0 M in dichloromethane, 1.1 equiv.)/acetyl chloride/toluene, r.t., 2 h, **2a**: 96%, **2b**: 93%, **2c**: 89%; (ii) Butyllithium (2.5 M solution in hexanes)/THF, −78°C, 15 min; (iii) DMF, r.t., 15 min, **3**: 83%.



Scheme 2. *Reagents and conditions*: (i) Zn (2.4 equiv.)/$TiCl_4$ (1.2 equiv.)/THF, reflux, 2 h, **4**: 67%; (ii) Boron tribromide (1.0 M in dichloromethane, 1.1 equiv.)/acetyl chloride/toluene, r.t., 2 h; (iii) I_2 (cat.) in toluene, **5**: 89%.

isomerized *cis*/*trans* mixture. Upon treatment with iodine in boiling toluene pure *trans*-4,4′-*bis*(*S*-acetyl)stilbenedithiol **(5)** was isolated in high yield (Sch. 2).

The presented method for deprotection and reprotection of a thiol group by converting the base stable *t*-butyl sulfide into the base labile and readily cleavable acetyl sulfide may be of broad scope. The technique can be incorporated in synthetic sequences as an excellent alternative to trityl protection.

EXPERIMENTAL

***t*-Butyl phenyl sulfide[8] (1a) and *t*-butyl 4-tolyl sulfide[9] (1b)** were prepared according to literature.

4-Bromophenyl *t*-butyl sulfide[10] (1c): To a slurry of 4-bromothiophenol (100 g, 0.53 mol) in *t*-butylchloride (400 mL) was added aluminum chloride (3.5 g, 0.03 mol) in small portions. The reaction became vigorously foaming and evolved HCl was lead through solid sodium hydroxide. Stirring at room temperature was maintained at room for 30 min and the orange reaction mixture was poured into water (700 mL) and extracted with pentane (3×150 mL). The pooled extracts were washed with water (40 mL), then dried with magnesium sulfate and filtered. After evaporation the residual oil was purified by distillation affording the *t*-butyl sulfide **1c** (113.2 g, 87%) as a colorless liquid; b.p. 93–95°C/12 Pa. Purity >98% (GC-MS). MS: EI (*m*/*z*, relative intensity): 246 (M^+, 10), 190 (100), 108 (45). ^{1}H NMR (400 MHz, $CHCl_3$-*d*): $\delta = 1.27$ (s, 9H), 7.38 (d, 2H, $J = 8.6$), 7.45 (d, 2H, $J = 8.6$).

4-(*t*-Butylthio)benzaldehyde[11] (3): 1c (12.26 g, 50 mmol) was added dropwise under a nitrogen atmosphere to a mixture of butyllithium (2.5 M in hexanes, 20 mL, 50 mmol) and THF (50 mL) cooled in a dry ice/acetone bath. The reaction mixture was stirred at −78°C for 15 min, then DMF (10 mL) was added in one portion and stirring was maintained

at room temperature for 30 min. The clear reaction mixture was poured into water (200 mL) and extracted with heptane (3 × 50 mL). The pooled extracts were washed with water (40 mL), then dried with magnesium sulfate, and concentrated. The residual oil was purified by kugelrohr distillation (air-bath 130°C, 100 Pa) affording the protected 4-mercaptobenzaldehyde **3** (8.11 g, 83%) as a colorless liquid. Purity >98% (GC-MS). MS: EI (*m*/*z*, relative intensity): 194 (M^+, 13), 179 (3), 138 (100), 109 (29). ^{1}H NMR (250 MHz, $CHCl_3$-*d*): $\delta = 1.31$ (s, 9H), 7.65 (d, 2H, $J = 6.4$), 7.80 (d, 2H, $J = 6.4$), 10.00 (s, 1H).

***trans*-4,4′-*bis*(*t*-Butylthio)stilbene (4):** Titanium(IV) chloride (2.6 mL, 24 mmol) was added dropwise to a slurry of zinc dust (3.14 g, 48 mmol) in THF (100 mL). **3** (3.89 g, 20 mmol) was added. The reaction mixture was refluxed for 2 h, poured into water (200 mL) and extracted with dichloromethane–heptane (1:2, 3 × 50 mL). The pooled extracts were washed with water (40 mL), then dried with magnesium sulfate, and concentrated to give a crystalline residue. Recrystallization from heptane gave the stilbene **4** (2.38 g, 67%) as white plates; m.p. 159–160°C. ^{1}H NMR (250 MHz, $CHCl_3$-*d*): $\delta = 1.31$ (s, 18H), 7.13 (s, 2H), 7.46 (d, 4H, $J = 8.5$), 7.53 (d, 4H, $J = 8.5$). ^{13}C NMR (250 MHz, $CHCl_3$-*d*): $\delta = 30.9$, 46.1, 126.4, 128.7, 132.2, 137.4, 137.6. MS: EI (*m*/*z*, relative intensity): 356 (M^+, 17), 300 (4), 244 (100), 210 (9). Anal. calcd. for $C_{22}H_{28}S_2$: C 74.10, H 7.91, S 17.98; Found: C 73.77, H 7.96, S 17.90.

Thioacetic Acid *S*-Aryl Esters 2 and 5; General Procedure

To a mixture of *t*-butylthiobenzenes (**1**, 10 mmol; or **4**, 5 mmol), acetyl chloride (5 mL), and toluene (20 mL) was added boron tribromide (1.0 M solution in dichloromethane, 11 mL, 11 mmol). Stirring for 2 h at room temperature. The dark reaction mixture was poured into ice (100 g), then the phases were separated and the water phase was further extracted with ether:heptane (1:2, 2 × 20 mL). The pooled extracts were washed with water (40 mL), then dried with magnesium sulfate, and concentrated. The residual materials were (except from **5**) purified by kugelrohr distillation (air-bath 160°C, 100 Pa).

Thioacetic acid *S*-phenyl ester[12] (2a): Colorless liquid; 1.46 g (96%). MS: EI (*m*/*z*, relative intensity): 152 (M^+, 13), 110 (100), 84 (7), 65 (19).

Thioacetic acid *S*-4-tolyl ester[13] (2b): Colorless liquid; 1.54 g (93%). MS: EI (*m*/*z*, relative intensity): 166 (M^+, 10), 124 (100), 108 (5), 91 (64).

Thioacetic acid *S*-4-bromophenyl ester[14] (2c): Colorless liquid; 2.05 g (89%); crystallizes into white crystals at room temperature; m.p. 51–52°C

(lit.[15] m.p. 51.5–52°C). MS: EI (*m*/*z*, relative intensity): 232 (M^+, 4), 188 (36), 143 (2), 109 (27), 82 (7), 69 (12), 43 (100).

***trans*-4,4′-*bis*(*S*-Acetyl)stilbenedithiol (5):** The white crystalline material was boiled in toluene (30 mL containing 0.01 M iodine) for 12 h. After evaporation of toluene in vacuo recrystallization from heptane gave the protected stilbenedithiol **5** (1.46 g, 89%) as white needles; m.p. 165–166°C. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.43$ (s, 6H), 7.14 (s, 2H), 7.41 (d, 4H, $J = 8.4$ Hz), 7.55 (d, 4H, $J = 8.4$ Hz). MS: EI (*m*/*z*, relative intensity): 328 (M^+, 66), 286 (33), 244 (100), 210 (8). Anal. calcd. for $C_{18}H_{16}O_2S_2$: C 65.83, H 4.91, S 19.52; Found: C 65.53, H 4.83, S 19.51.

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