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Iodine mediated deprotection of *N*-tertbutanesulfinyl amines: a functional group compatible method[†]

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In the presence of iodine, a functional group compatible method for the deprotection of *tert*-butanesulfinyl and *p*-toluenesulfinyl units was developed.

Since the introduction of enantiomerically pure tert-butanesulfinamide in asymmetric organic synthesis by Ellman in 1997,¹ this synthetic reagent has gained ever increasing popularity in chemical society.² The chiral tert-butanesulfinamide has been widely used in the synthesis of agrochemicals, pharmaceuticals and natural products as a reliable and versatile reagent for the introduction of amine units.^{2e} As indicated in Scheme 1, the procedure is common for the synthesis of amines from chiral tert-butanesulfinamide. The first step is the condensation of 1 with ketones or aldehydes to yield imines. The second step is the addition of nucleophiles towards the sulfinyl imines to give N-tert-butanesulfinyl amines. The final step in the preparation of amines is the deprotection of the tertbutanesulfinyl group under acidic conditions.^{1,2b} We recently started a research program towards the synthesis of amines bearing acid sensitive functional groups; a method for the deprotection of the tertbutanesulfinyl group under neutral or basic reaction conditions was needed. Although the syntheses of amines based upon tertbutanesulfinamide prevail in the literature, we noticed that few nonacidic conditions have been reported for deprotection of N-tertbutanesulfinyl amines.³ Herein, we report a highly functional group compatible method for the deprotection of tert-butanesulfinyl groups and some mechanism insights into this iodine mediated process.

Recently, we conducted a deprotection of substrate **1a** in order to get amine **2a** bearing two acid sensitive ketal groups (Scheme 2). The initial experiment was conducted using 2N HCl in dioxane and methanol. This reaction unfortunately provided



Scheme 1 Synthesis of amines based on tert-butanesulfinamide.



Scheme 2 Deprotection of the *tert*-butanesulfinyl group under acidic conditions.

a complex mixture, with a small amount of compound **3a** (1%) being isolated.

Although thiophenolysis based methods for the deprotection of *tert*-butanesulfinyl^{3a} or *p*-toluenesulfinyl⁴ units have been reported in the literature, unfortunately we failed to get the desired amine (2a) under the conditions of thiophenolysis. The Dess-Martin periodinane oxidation⁵ also failed to give the desired product, with sulfinyl amine **3a** being obtained in 47% yield. These results prompted us to seek alternative ways for the deprotection of the *tert*-butanesulfinyl unit in the presence of an acid sensitive group. We began our research with screening of reaction conditions by treatment of sulfinyl amine **1a** with additives in the presence of bases. Some of the reaction conditions are listed in Table **1**. To our delight, addition of iodine finally led to the desired amine (**2a**) in 71% isolated yield (entry 12).

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Table 1 Studies on the deprotection of tert-butanesulfinyl amine 1a^a

| Entry | Additives | Bases, solvents | Yields |
|-------|-------------------------------|--|----------------------------|
| 1 | KI, CuSO ₄ | K_2CO_3 , EtOH-H ₂ O (1:1) | $0\%^b$ |
| 2 | IBD, $CuSO_4$ | DMAP (0.2 eq.), EtOH | 0% ^c |
| 3 | <i>n</i> -Bu ₄ NBr | K_2CO_3 , PhMe-H ₂ O (2:1) | $0\%^d$ |
| 4 | I_2 (0.5 eq.) | K_2CO_3 , DMAP, THF-H ₂ O | 2: trace e,j |
| 5 | I_2 (2.5 eq.) | K_2CO_3 (3.0 eq.), THF-H ₂ O | 2: 14% ^f |
| 6 | I_2 (2.5 eq.) | DMAP (3.0 eq.), THF $-H_2O$ | 2: 10% ^f |
| 7 | I_2 (2.5 eq.) | Na_2CO_3 (3.0 eq.), THF-H ₂ O | 2: 27% ^f |
| 8 | I_2 (2.5 eq.) | K_2CO_3 (3.0 eq.), THF-H ₂ O | 2: 44% ^g |
| 9 | I_2 (2.5 eq.) | Na_2CO_3 (3.0 eq.), acetone-H ₂ O | 2: 21% ^g |
| 10 | I_2 (2.5 eq.) | Na_2CO_3 (3.0 eq.), MeCN-H ₂ O | 2: 51% ^g |
| 11 | I_2 (2.5 eq.) | $KHCO_3$ (6.0 eq.), THF-H ₂ O | 2: 53% ^g |
| 12 | I_2 (2.5 eq.) | Na_2CO_3 (3.0 eq.), THF-H ₂ O | 2: 71% ^g |
| | | | |

^{*a*} Yields represent isolated yields. Reactions were conducted at 0.25 mmol scale in designated solvents (5 mL) at 20 °C for 14 hours. ^{*b*} K₂CO₃ (2.0 eq.), KI (2.0 eq.) and CuSO₄ (0.2 eq.). ^{*c*} IBD (2.0 eq.), CuSO₄ (0.2 eq.). ^{*d*} *n*-Bu₄NBr (0.2 eq.), K₂CO₃ (2.0 eq.). ^{*e*} K₂CO₃ (0.5 eq.), DMAP (0.5 eq.). ^{*f*} THF: H₂O = 1:1. ^{*g*} DMAP (0.2 eq.) was added, organic solvents: H₂O = 1:1.

In order to develop a general iodine mediated method for the deprotection of both *tert*-butanesulfinyl and *p*-toluenesulfinyl units, *tert*-butanesulfinyl amine **1b** was then prepared and used as a typical substrate for screening other possible reaction conditions. It was found that bases such as sodium carbonate or DMAP were not necessary for deprotection of compound **1b** bearing a moiety less labile to acid hydrolysis. The reaction occurred efficiently in the absence of bases and required only catalytic amounts of iodine (entry 5, 0.2 eq.). Although the reaction could be conducted at room temperature (entry 5), elevating the reaction temperature (50 °C oil bath, entry 9) could significantly shorten the reaction times. To the best of our knowledge, this is the first example of iodine catalyzed deprotection of a *tert*-butanesulfinyl amine, a complementary process to the acid hydrolysis.

With the optimal reaction conditions (Table 1, entry 12 for acid sensitive substrates; Table 2, entry 9 for regular substrates) in hand, we next conducted a number of deprotections, the results are summarized in Table 3. The new deprotection procedures afforded the amines in good to excellent isolated yields, and a number of functional groups were well tolerated. Delightfully, this method could also be used for the deprotections of *p*-toluenesulfinyl units (Table 3, substrates **1u** and **1v**).

In order to get some insights into this iodine catalyzed process, a number of experiments with tert-butanesulfinyl amine 1b were carried out. We firstly elaborated the amine salts (Scheme 3, also see ESI⁺) obtained in the aqueous phase. Based on HRMS analysis (ESI-MS), the salt was identified as compound 3b, a sulfate of amine 2b. It was deduced that the sulfate ion might come from the oxidation of the sulfinyl unit by iodine. Next, we carried out the reaction in deuterated THF and D₂O in a sealed tube. tert-Butanol (4b), di-tert-butyl thiosulfonate (5b) and di-tert-butyl thiosulfinate (6b) were identified (based on NMR and ESI-MS analyses of the reaction mixture) in the reaction system. These compounds might be the by-products obtained from further oxidation of tert-butylsulfinic acid.⁶ Di-tert-butyl thiosulfonate (5b) was isolated and fully characterized by NMR and HRMS. Deprotection of the p-toluenesulfinyl unit with compound 1y was also conducted (Scheme 3), formation of p-toluenesulfate 3c was confirmed by NMR and ESI-MS analyses. To make sure that tert-butanesulfonyl amine 1z was not involved as an intermediate in this deprotection process, a control experiment with 1z, obtained by oxidation of 1b with m-CPBA, was also carried out. No deprotection of the tert-butanesulfonyl group occurred under the identical reaction conditions (Scheme 3).

Deprotection in the presence of excess sodium carbonate (3.0 eq.) was conducted to exclude the possible hydrolysis of acids (HI acid, which might be generated in the reaction process). Although more iodine (2.5 eq.) was required, amine **2b** was obtained in 81% yield together with compound **7b** (Scheme 4).⁷ It could be concluded that iodine, rather than acids generated *in situ*, plays the key role in this deprotection process.

We next conducted the reaction in the presence of a stable oxyl radical, 2,2,6,6-tetramethyl-1-oxylpiperidine (TEMPO),⁸ and found that the deprotections were significantly inhibited (Scheme 4). It was noteworthy that no reaction was observed upon treatment of *tert*-butanesulfinyl amine **1b** with *n*-Bu₃SnH, a radical initiator. Based on collected evidence, a single electron transfer initiated pathway was

| Table 2 Screening of optimal reaction conditions for the deprotection of tert-butanesulfinyl amines ^a | | | | | | |
|--|---|---------------------------------|------------------------|--|--|--|
| | MOMO 1b H H N Solvents 2, NaHCO ₃ | | | | | |
| Entry | Iodine, additive | Solvent, temperature | Time; yields | | | |
| 1 | I ₂ (2.5 eq.), Na ₂ CO ₃ (3.0 eq.), DMAP (0.2 eq.) | THF/H ₂ O, rt | 16 h, 81% ^b | | | |
| 2 | I_2 (2 eq.), DMAP (0.2 eq.) | THF/H_2O , rt | 12 h, 95% ^b | | | |
| 3 | I_2 (2 eq.), none | THF/H_2O , rt | 12 h, 95% ^b | | | |
| 4 | I_2 (0.2 eq.), DMAP (0.1 eq.), CuSO ₄ (0.1 eq.) | THF/H ₂ O, rt | 72 h, 87% ^b | | | |
| 5 | I_2 (0.2 eq.), none | THF/H_2O , rt | 72 h, 70% ^c | | | |
| 6 | I_2 (0.2 eq.), none | MeCN/H ₂ O, 50 °C | 12 h, 69% ^d | | | |
| 7 | I_2 (0.2 eq.), none | EtOH/H ₂ O, 50 °C | 12 h, $63\%^d$ | | | |
| 8 | I_2 (0.2 eq.), none | Acetone/H ₂ O, 50 °C | 12 h, $82\%^d$ | | | |
| 9 | I_2 (0.2 eq.), none | THF/H ₂ O, 50 °C | 12 h, $97\%^d$ | | | |
| 10 | None | THF/H ₂ O, 50 °C | 96 h, 0% ^d | | | |

^{*a*} Yields represent isolated yields at 0.25 mmol scale of **1b**, and the reactions could be conducted either under air or nitrogen in solvents (5 mL). ^{*b*} THF/H₂O = 1/1. ^{*c*} THF/H₂O = 3/1. ^{*d*} Organic solvents/H₂O = 5/1.







^{*a*} Yields represent isolated yields at 0.5 mmol scale. ^{*b*} **1w** and **1x** (acid sensitive substrates): Na₂CO₃ (3.0 eq.), I₂ (2.5 eq.), DMAP (0.2 eq.), THF-H₂O (1:1, 10 mL) at room temperature, see ESI.



a: I_2 (0.2 eq.), THF/H₂O (5:1), 50 °C; or I_2 (2.5 eq.), Na₂CO₃ (3.0 eq.), THF/H₂O (1:1) Scheme 3 Some reactions to elaborate the reaction pathway.



proposed for this iodine mediated deprotection of sulfinyl units (Scheme 5).

In summary, we have developed an iodine mediated single electron transfer process for the deprotection of *tert*butanesulfinyl and *p*-toluenesulfinyl units. For most substrates used in this research, the yields are good to excellent using only catalytic amounts of iodine. Our new methods are especially



Scheme 5 Proposed pathway for iodine mediated deprotection of *tert*-butanesulfinyl units.

useful for the deprotection of *N-tert*-butanesulfinyl amines with acid sensitive structure motifs and should find more applications in the synthesis of complex natural products.

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