Tetrahedron Letters 45 (2004) 3729–3732

Tetrahedron Letters

Enhanced O-dealkylation activity of $SiCl_4$/LiI with catalytic amount of BF_3

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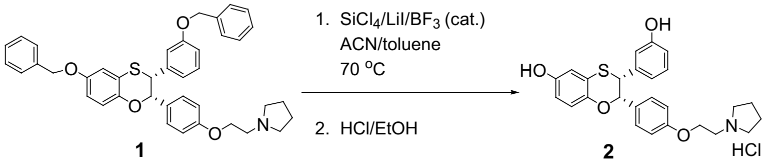
Received 24 February 2004; accepted 16 March 2004

Abstract—Dibenzyloxydihydrobenzoxathiin **1**, which resisted debenzylation with $SiCl_4$/LiI, was effectively debenzylated with $SiCl_4$/LiI in the presence of a catalytic amount of BF_3. The HCl salt of the bis-debenzylated product **2** was isolated in 90% yield and 99% purity. This enhanced dealkylation activity has also been observed with other substrates.

Dihydrobenzoxathiin derivatives are known to function as selective estrogen receptor modulators (SERMs), which are estrogen receptor ligands that act like estrogen in some tissues while blocking estrogen action in others. These molecules are of pharmaceutical interest due to their potential in preventing estrogen related diseases including osteoporosis, hot flashes, increased level of LDL cholesterol, breast cancer, and obesity.[1]

In our recent efforts to synthesize estrogen receptor modulator **2**, a final double debenzylation step of **1** was required (Scheme 1).[1] Due to catalyst poisoning resulting from the presence of sulfur in the molecule, heterogeneous catalytic hydrogenolysis was unsatisfactory. As an alternative, trimethylsilyliodide (TMSI) was initially developed to accomplish the debenzylation. The TMSI reaction was complete in 8–10 h at rt. However, the basic workup resulted in a complex mixture of byproducts including ~40% of the N-benzylated impurity. In addition, three aryl ring-benzylated impurities, probably generated via intramolecular Friedel–Crafts alkylation reactions, were detected from 3% to 4%. Due to their structural similarity to the final product,[1] these impurities were difficult to reject. To minimize these impurities, the use of additives, such as thiourea and *N*-methylimidazole, was explored to scavenge the benzyl iodide and obviate the generation of the byproducts. The resulting debenzylation procedure was highly effective and provided **2** in 81% yield although the cost of the reagents was unacceptably high for large-scale production. Another disadvantage with the use of thiourea was the formation of benzylthiol during the aqueous workup, which gave an unpleasant odor.

We therefore sought to develop a more efficient and cost effective debenzylation procedure that would facilitate the large-scale synthesis of high purity **2**. A variety of reagents have been reported for the cleavage of alkyl ethers including $AlCl_3$,[2] $SnCl_4$,[3] lithium naphthalenide,[4] $Sc(NTf)_3$ (cat.)/anisole,[5] TMSCl/NaI,[6] TMSI,[7] BCl_3/



Scheme 1. Debenzylation of **1**.

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0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.095

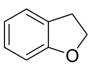
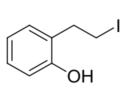
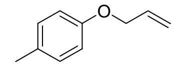
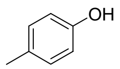
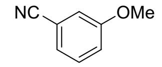
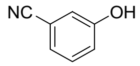
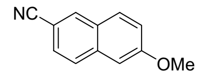
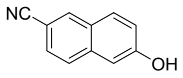
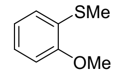
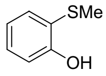
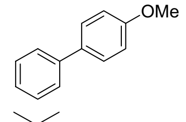
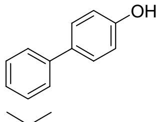
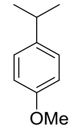
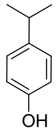
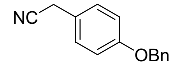
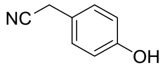
n-Bu_4NI,[8] BBr_3,[9] BF_3/EtSH,[10] and $SiCl_4$/NaI.[11] The use of catalytic scandium(III) triflimide was investigated but, the overnight reaction at 100 °C resulted in no debenzylation of **1** and further reaction resulted in decomposition. The BBr_3/LiI/acetic acid reagent system was more reactive than TMSI, and conversion of **1** to **2** was complete in 2 h at rt giving an improved yield (92%) and impurity profile. The presence of acetic acid during the reaction helped to prevent the N-benzylation reaction. Although thiourea could be replaced by the odorless 2-mercapto-1-methylimidazole or DABCO as effective benzyl iodide scavengers, the requirement of a benzyl iodide scavenger for the process remained undesirable.

Among the reagents reported for O-dealkylation, the $SiCl_4$/NaI[11] system was very attractive in terms of cost and availability of reagents. Unfortunately, minimal debenzylation of **1** was detected after aging the reaction mixture over 2 days at 70 °C. We were however, delighted to find that by adding catalytic amounts of BF_3 (~25 mol% per benzyl site) to the reaction, the debenzylation activity was significantly enhanced giving complete conversion in 45 min.[12] Furthermore, the impurities generated were minimized. A scavenger-free workup procedure was also developed. Experimental results showed that the debenzylation works best in toluene–acetonitrile (3:1). Using optimized reaction conditions, product **2** was obtained in 92% isolated yield and 99% purity. LiI can be replaced by NaI, however, the reaction takes longer (~3 h). While the use of $BF_3{\cdot}AcOH$ is preferred and gives a slightly cleaner reaction profile, BF_3 etherate has also been used successfully. Interestingly the use of excess BF_3/LiI (up to 5 equiv) resulted in decomposition and low yield (~20%).

Encouraged by the enhanced reactivity observed with catalytic amounts of BF_3, we investigated the general application of this reagent system to other substrates. A systematic comparison of $SiCl_4$/LiI with and without catalytic amounts of BF_3 on different substrates highlights the improved reactivity of the former system (Table 1).

It is clear from this table and examples from the literature that the $SiCl_4$/LiI system is sufficiently reactive toward many substrates. Essentially no reaction rate difference is observed for the dealkylation of 4-benzyloxyphenylacetonitrile (entry 8). On the other hand, 2,3-dihydrobenzofuran, allyl tolyl ether, 3-methoxybenzonitrile, and 6-methoxy-2-naphthonitrile all greatly

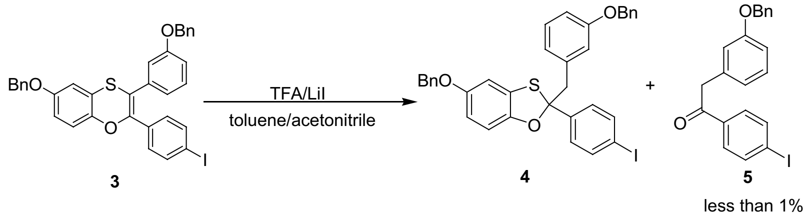
Table 1. $SiCl_4$/LiI dealkylation with and without BF_3[a]

Entry	Substrate	Product	# of equiv $SiCl_4$/LiI/BF_3	Time	Conversion with BF_3 (yield)[b]	Conversion without BF_3
1			1.5/1.5/0.25	45 min	100% (90%)[c]	15%
2			1.2/1.2/0.5	6 h	99.8% (90%)	16%
3			1.5/1.5/0.25	15 h	99.7% (82%)	25%
4			2.0/2.0/0.3	10 h	99.8% (83%)	30%
5			2.0/2.0/0.4	13 h	99.8% (89%)	50%
6			1.5/1.5/0.25	15 h	99.6% (82%)	65%
7			1.2/1.2/0.25	10 h	100% (89%)	65%
8			2.0/2.0/0.3	2 h	99.9% (98%)	90%

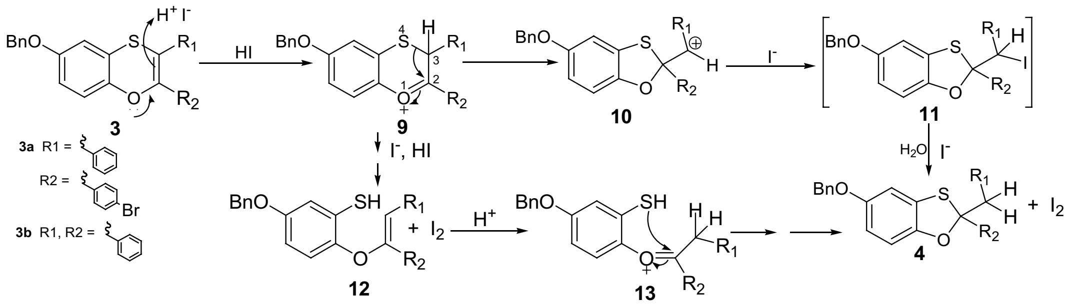
[a] Typical reaction conditions: starting material is dissolved in sieve dried toluene/acetonitrile (0.12 M). LiI is added to the solution and system kept under N_2 while $SiCl_4$ and $BF_3{\cdot}AcOH$ are consecutively added via syringe. Reaction mixture is then aged at 70 °C and progress of reaction is followed by HPLC.

[b] Yields refer to assay yield by HPLC.

[c] Isolated yield of product (entry 1); characterized by ^1H, ^{13}C NMR, HRMS, and elemental analysis data.[13]



Scheme 2.



Scheme 3.

benefited from the presence of the BF_3 (entries 1–4). With 2,3-dihydrobenzofuran the reaction with BF_3 was complete within 45 min whereas only 15% conversion was observed without BF_3. Deallylation of allyl tolyl ether required 6 h in the presence of BF_3 giving 90% yield of 4-methylphenol, but gave only 16% conversion in the absence of BF_3 within this time frame. Similarly, 3-methoxybenzonitrile and 6-methoxy-2-naphthonitrile were dealkylated at a much faster rate with BF_3. Several substrates were found to give marginally accelerated dealkylation rates with BF_3 (entries 5–7). Provided with longer reaction time, these substrates would have been effectively dealkylated even in the absence of BF_3.

The application of the $SiCl_4$/LiI/BF_3 reaction conditions to **3**, an intermediate in the total synthesis of **2**, resulted in no debenzylation. Instead, an interesting reductive rearrangement product **4**, formed via the selective 1,2-migration of the sulfur, was recovered along with a small amount of the ketone **5**. The rearranged product **4** was also obtained when **3** was treated with 4 equiv of $SiCl_4$/LiI. The addition of BF_3 to this reaction only resulted in the accelerated formation of **4**. Use of HCl and HBr did not give **4**.

A similar intramolecular rearrangement under oxidizing conditions has been reported.[14] To rationalize this novel reductive rearrangement, we carried out several investigative NMR experiments. When the reaction was done in the presence of 2–3 equiv of D_2O, ~80% deuterium incorporation was detected at the methylene carbon of **4**, suggesting the reductive rearrangement reaction could be due to the unintentionally generated HI. Further proof was obtained when the reaction was run using in situ generated HI from trifluoroacetic acid and LiI (Scheme 2). The reaction was instantaneous at rt to give **4** in 93% isolated yield. The use of TMSI and H_2O also gave **4** in 86% isolated yield.

Based on these experimental findings, we propose the following mechanisms for the transformation of **3** to **4** (Scheme 3). Thus, the initial protonation of the double bond generates an unstable oxonium ion **9**, which facilitates the migration of the sulfur. The resulting new benzylic carbocation **10** is then trapped by iodide to give **11**, which is subsequently reduced by another iodide[15] to give iodine and the observed product **4**.[16] Alternatively a nucleophilic addition of iodide at C-2 of **9**, followed by its elimination as iodine could form a carbanion resulting in benzoxathiin ring opening and formation of a reactive thiophenol intermediate **12**. Subsequent acid catalyzed ring closure of **13** gives 1,3-benzoxathiol product **4**. This procedure has also been applied to substrates **3a**[17] and **3b**[18] with equal success. In each case the sulfur migrates selectively to give only one product.

In conclusion, catalytic amounts of BF_3 can tremendously enhance the dealkylation power of $SiCl_4$/LiI, a reagent system that is inexpensive and readily available. An interesting novel reductive rearrangement reaction was also observed for the transformation of benzoxathiin **3** to 1,3-bezoxathiol **4**.

Acknowledgements

We thank Dr. P. G. Dormer and R. A. Reamer for NMR support, Dr. T. A. Blizzard for helpful suggestions, Marjorie Waters for providing substrates **3a** and **3b**, and Dr. T. J. Novak for HRMS analysis.

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12. Debenzylation of **1**: To a solution of **1** (2.0 g, 3.2 mmol) in toluene (20 mL) was added LiI (2.2 g, 16 mmol) followed by acetonitrile (7 mL) and reaction mixture was kept under N_2. To the heterogeneous mixture was added $SiCl_4$ (1.83 mL, 16 mmol) followed by $BF_3{\cdot}AcOH$ (0.22 mL, 1.6 mmol). Reaction mixture was then aged at 70 °C over 45 min. Progress of reaction was followed by HPLC. When conversion was complete, the reaction mixture was quenched with 20 mL of EtOH, excess solid $NaHCO_3$ was added, and aged over 20 min at rt. Mixture was filtered (quant assay = 98% yield), and concentrated. The resulting oily material was treated with excess concd HCl and aged at 60 °C over 2 h. The resulting slurry was cooled to rt, seeded, and aged at rt overnight. 1.44 g of **2** was collected as an off white solid after filtration. 90% Isolated yield and 99A% by HPLC.
13. Purification: 1.5 g of crude oily product (entry 1) by silica gel chromatography (CH_2Cl_2–MeOH = 80:1) afforded 1.3 g of solid. Mp 45–47 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22–7.10 (m, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 6.75 (d, $J = 7.9$ Hz, 1H), 3.42 (t, $J = 7.8$ Hz, 2H), 3.23 (t, $J = 7.7$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 130.9, 128.4, 127.3, 121.3, 115.7, 35.3, 5.0. HRMS: Calcd for C_8H_9IO (M−H) = 246.9620, found = 246.9624. Anal. Calcd for C_8H_9IO: C, 38.7; H, 3.7. Found: C, 38.9; H, 3.4.
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16. Representative procedure for compounds **4**, **4a**, and **4b**. To a solution of **3** (1 g, 1.6 mmol) in toluene/acetonitrile (9 mL/3 mL) was added LiI (0.86 g, 6.4 mmol). Reaction mixture was kept under N_2 while TFA (0.49 mL, 6.4 mmol) was added via syringe. Reaction was complete over 10 min at rt as followed by HPLC (96% assay yield). Reaction mixture was diluted with EtOAc (20 mL) and washed with water (2×20 mL) followed by 5% $Na_2S_2O_3$ (10 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated. The light yellow oily material was treated with methyl *tert*-butyl ether and aged at rt overnight affording an off white solid **4** (0.93 g, 93%). Mp 139–141 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62–7.59 (m, 2H), 7.43–7.29 (m, 10H), 7.12–7.08 (om, 3H), 6.83 (d, $J = 8.7$ Hz, 1H), 6.82 (m, 1H), 6.76 (d, $J = 2.6$ Hz, 1H), 6.62 (dd, $J = 8.7$ Hz, 2.6, 1H), 6.55–6.59 (om, 2H), 4.97 (s, 2H), 4.94 (ABq, $\Delta\nu = 5.5$, $J = 12.0$, 2H), 3.64 (d, $J = 13.8$ Hz, 1H), 3.52 (d, $J = 13.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 158.5, 154.8, 149.4, 142.7, 137.2, 137.2, 137.1, 136.4, 129.0, 128.7, 128.1, 128.1, 127.8, 127.6, 127.6, 127.1, 123.6, 117.2, 114.0, 112.1, 111.1, 109.7, 103.0, 94.0, 71.0, 70.1, 49.6. HRMS calcd for $C_{34}H_{27}SO_3I$ (M+H) = 643.0804, found = 643.0809. Anal. Calcd for $C_{34}H_{27}SO_3I$: C, 63.6; H, 4.2. Found: C, 63.6; H, 4.1.
17. Product **4a** crystallized from EtOH–ACN (5:1). Mp 108–110 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.42–7. 32 (m, 7H), δ 7.27–7.15 (m, 5H), 7.00–6.95 (m, 2H), 6.87 (d, 1H, $J = 8.7$ Hz), 6.77 (d, $J = 2.6$ Hz, 1H), 6.63 (dd, $J = 8.7$ Hz, 2.6, 1H), 4.97 (s, 2H), 3.68 (d, $J = 13.8$ Hz, 1H), 3.56 (d, $J = 13.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 149.5, 142.0, 137.2, 134.9, 131.2, 130.9, 128.8, 128.2, 128.1, 127.6_2, 127.5_8, 127.1_9, 127.1_7, 122.2, 112.1, 111.1, 109.7, 103.0, 71.1, 49.6. HRMS calcd for $C_{27}H_{21}SO_2Br$ (M+H) = 489.0524, found = 489.0523. Anal. Calcd for $C_{27}H_{21}SO_2Br$: C, 66.3; H, 4.3. Found: C, 66.2; H, 4.2.
18. Product **4b**, re-crystallized from EtOH. Mp 89–91 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.25 (m, 10H), 7.19–7.13 (m, 3H), 7.00–6.93 (m, 2H), 6.86 (d, $J = 8.7$ Hz, 1H), 6.76 (d, $J = 2.7$ Hz, 1H), 6.61 (dd, $J = 8.7$ Hz, 2.7, 1H), 4.97 (s, 2H), 3.69 (d, $J = 13.8$ Hz, 1H), 3.57 (d, $J = 13.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 149.7, 142.8, 137.3, 135.3, 130.9, 128.8, 128.2, 128.1, 127.9, 127.6, 127.5, 127.0, 125.7, 112.0, 111.0, 109.7, 103.5, 71.1, 49.9. HRMS calcd for $C_{27}H_{22}SO_2$ (M+H) = 411.1419, found = 411.1421. Anal. Calcd for $C_{27}H_{22}SO_2$: C, 78.9; H, 5.4. Found: C, 79.0; H, 5.4.