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Novel Borane Reduction of Ether-Protected Aromatic Lactams†

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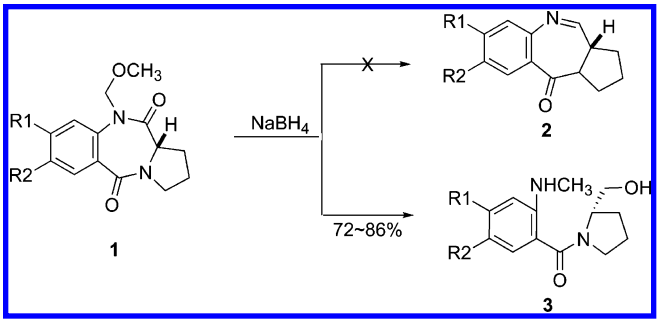
Abstract: Borane reduction of ether-protected aromatic lactams produces 1-alkyl-1,2,3,4-tetrahydroquinolines (**5** and **6**) in excellent yields. This reaction provides a novel one-pot tandem process for reduction of amide group and *N*-protected groups. Experimental results demonstrate that the reaction proceeds through two consecutive elimination and reductions via two C−O bond cleavages to form the foresaid products.

The reduction of tertiary lactams to their respective amines has been approached with various hydrides such as lithium aluminum hydride, sodium borohydride, and lithium borohydride.[1,2] In a previous article, we described an unusual amide bond cleavage of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**1**) by complex hydride reduction. Rather than simple deoxygenation products (**2**), ring-opening secondary amines (**3**) were formed, as detailed in Scheme 1.[3] On the basis of the products obtained, we proposed that this reaction proceeds via 3-aza-Grob fragmentation, as shown in Scheme 2.[3]

We subsequently extended our studies to a variety of ether-protected aromatic lactams. The results showed that hydride reduction of MOM-, MEM-, SEM-, and BOM-protected oxindole analogues afforded ring-opening products via the same path as seven-membered ring lactams (**1**) in excellent yields.[4] More recently, we demonstrated the first example to directly support 3-aza-Grob fragmentation with evidence that the nucleofuges stay with the parent molecules after fragmentation. Further examination by stable isotope studies corroborates our original observations.[5]

Boranes have been used as reducing agents for application in organic synthesis for six decades. Their reactions on reduction of functionalities, such as alkenes, aldehydes, ketones, amides, and lactams etc., have been extensively studied.[1,2,6] For instance, ϵ-carprolactam is rapidly and quantitatively reduced to the corresponding amine by borane−dimethyl sulfide complex.[7] In the class of tertiary lactams, 1-benzyl-3-methoxycarbonyl-5-pyrolidone is selectively reduced to methyl 1-benzyl-3-pyrolidinecarboxylate in moderate yield by borane.[8] We decided to explore whether ether-protected aromatic lactams would be deoxygenated to the corresponding amines by borane. The present note documents the results of our studies.

SCHEME 1. Hydride Reduction of *N*-Methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazeoine-5-11-diones (1)



SCHEME 2. 3-Aza-Grob Fragmentation

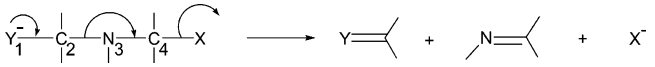


TABLE 1. Products of Boranes Reduction of Ether-Protected Aromatic Lactams

entry	substrate	reaction conditions[a]	product	yield (%)
1	**4a**	a	**5**	92
2	**4a**	b	**5**	85
3	**4b**	a	**5**	85
4	**4b**	b	**5**	90
5	**4c**	a	**5**	94
6	**4c**	b	**5**	81
7	**4d**	a	**5**	91
8	**4d**	b	**5**	89
9	**4e**	a	**5**	94
10	**4e**	b	**5**	79
11	**4f**	a	**5**	70
12	**4f**	b	**5**	78
13	**4g**	a	**6a**	95
14	**4g**	b	**6a**	98
15	**4h**	a	**6b**	89
16	**4h**	b	**6b**	75

[a] a: 15 equiv of BH_3−THF; b: 15 equiv of BH_3−$S(CH_3)_2$.

A variety of ether-protecting groups such as EOM (ethoxymethyl) (**a**, Figure 1), MOM (methoxymethyl) (**b**), MEM (2-methoxyethoxymethyl) (**c**), MTM (thiomethoxymethyl) (**d**), SEM (2-(trimethylsilyl)ethoxymethyl) (**e**), BOM (benzyloxymethyl) (**f**), THF (tetrahydrofuranyl) (**g**), and THT (tetrahydrothienyl) (**h**) were introduced to 3,4-dihydro-2(1*H*)-quinolinones (**4**) as previously reported.[2−4] The results of borane reduction of ether-protected 3,4-dihydro-2(1*H*)-quinolinones are shown in Table 1. In the examples of protecting groups possessing open chain systems such as the EOM analogues (**a**−**f**), the reductive

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† Dedicated to Professor Heinz G. Floss on the occasion of his 70th birthday.

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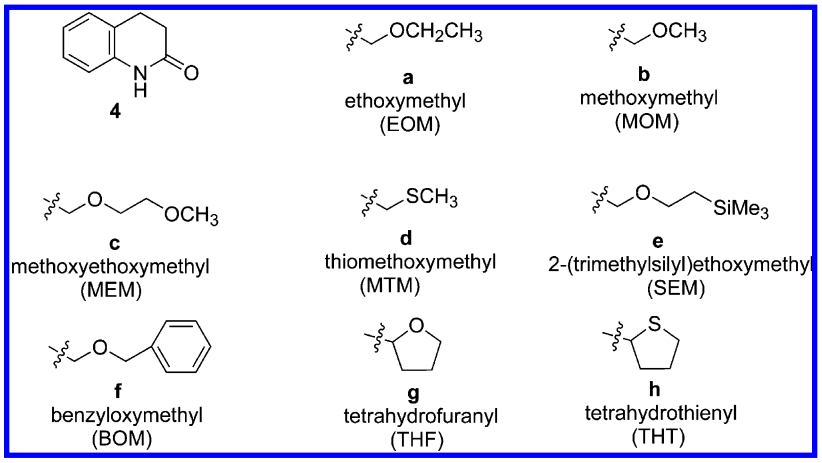
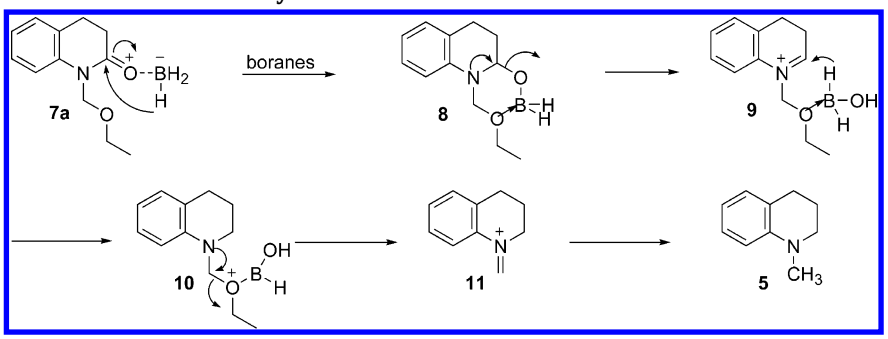
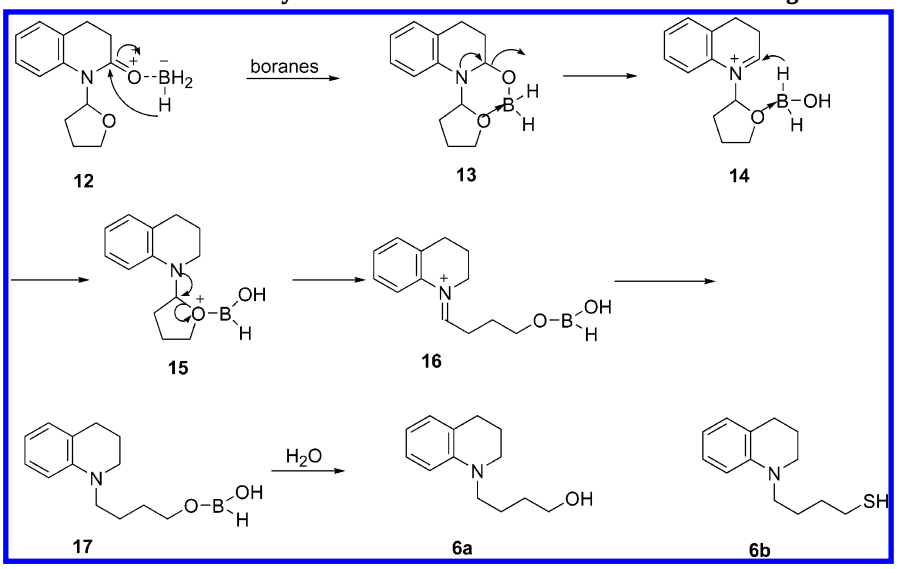


FIGURE 1. Structures of 3,4-dihydro-2(1*H*)-quinolinone (**4**) and other protective groups: EOM, MOM, MEM, MTM, SEM, BOM, THF, THT.

SCHEME 3. Plausible Reaction Pathway for the Conversion of EOM-Protected 4 into 5



SCHEME 4. Plausible Reaction Pathway for the Conversion of THF-Protected 4g into 6a



reactions were completed with addition of 15 equiv of borane−tetrahydrofuran or borane−dimethyl sulfide at room temperature for 24 h to form 1-methyl-1,2,3,4-tetrahydroquinoline (**5**) in excellent yields (Table 1, entries 1−12). Similar results were observed for ring-bearing protecting groups, producing 4-(3,4-dihydro-2*H*-quinolin-l-yl)-butan-1-ol (**6a**) (Table 1, entries 13−14) and 4-(3,4-dihydro-2*H*-quinolin-l-yl)-butane-1-thiol (**6b**) (Table 1, entries 15−16).

A plausible mechanistic interpretation of this intriguing reaction is shown in Scheme 3. Since boranes are electron-deficient agents they behave as Lewis acids. Reduction proceeds with an electrophilic attack on the center of highest electron density, the carbonyl oxygen, to form complex **7**. After a hydride transfer, a six-membered ring of dioxyborane complex **8** is generated, followed by consecutive elimination (**9**), reduction (**10**), elimination (**11**), and another reduction to give 1-methyl-1,2,3,4-tetrahydroquinoline (**5**). The aforementioned reduction process involves two C−O bond cleavages. We propose that THF- and THT-protecting groups undergo a similar reaction as shown in Scheme 4. The ring

systems of tetrahydrofuranyl and tetrahydrothienyl moieties are reductively cleaved to amino alcohol (**6a** and **6b**) in excellent yields under mild conditions.

To examine the proposed mechanism, the key intermediate 1-(ethoxymethyl)-1,2,3,4-tetrahydroquinoline (**10**) was synthesized by reaction of 1,2,3,4-tetrahydroquinoline with ethoxymethyl chloride in 63% yield. The reduction of compound **10** using 1 equiv of borane−tetrahydrofuran proceeded at room temperature for 2 h to form 1-methyl-1,2,3,4-tetrahydroquinoline (**5**) in excellent yields (98%). A similar result was observed with borane−dimethyl sulfide. This evidence suggests that the schemes proposed here offer practical routes leading to tertiary amine and amino alcohols in aromatic series.

In conclusion, we have examined borane reduction of ether-protected aromatic lactams. The mechanism is distinct from that of complex hydrides previously reported. This reaction provides a novel one-pot tandem process for reduction of amide and *N*-protected groups. The results are consistent with a reaction that proceeds through two consecutive eliminations and reductions via two C−O bond cleavages with excellent product yields.

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Supporting Information Available: Experimental procedures for borane reduction of ether-protected aromatic lactams and spectra data for compounds **5**, **6a**, **6b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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