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Boron tribromide mediated debenzylation of benzylamino and benzyloxy groups

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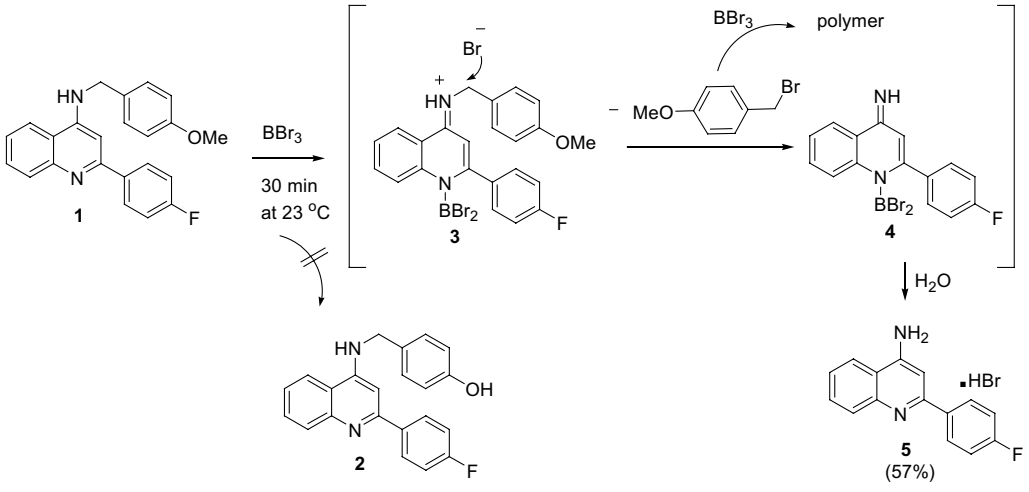
Abstract—The treatment of 2(or 4)-benzylamino substituted quinolines, 9-benzylaminoacridine, 2-benzylaminopyridine, a 4-benzyloxyquinoline, and an *N*-benzyloxyamidine with BBr_3 yields the corresponding amino or hydroxy substituted compounds. The scope and limitations of this novel reaction are discussed.

The benzyl and substituted benzyl moieties are widely used protecting groups for amines, alcohols, phenols, esters, and heterocyclic amides. There is a plethora of reagents for cleavage of such *O*- and *N*-benzyl derivatives.[1,2] In particular, boron tribromide has been successfully used for deprotection of *N*-benzyluracils[3,4] and *N*-benzyl substituted heterocyclic amides.[5] A related cleavage of an *N*-(2-pyrrolylmethyl)-substituted lactam has also been reported.[6] Boron tribromide is best known for its ability to cause selective cleavage of aryl methyl ethers in the presence of other functional groups in the molecule. For example, it has been reported that by using this reagent a methoxy group can be demethylated selectively in the presence of a benzylamino function.[7] In fact, there have been no reports in the literature on boron tribromide mediated cleavage of benzylamines. To our best knowledge, no benzyloxy group has ever been cleaved by this reagent either.

Therefore, it was highly surprising to observe that the attempted removal of a methyl group from *N*-methoxybenzyl substituted quinolin-4-amine **1** (Scheme 1)



Scheme 1.

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by treatment with boron tribromide did not produce the desired phenol derivative **2**.

Quinolin-4-amine **5** was isolated in 57% yield after purification and compared to an authentic sample.[8,9] Moreover, the expected compound **2** was not found by using careful chromatographic separations of crude mixtures obtained under different conditions of the reaction time, temperature, and ratio of **1**/BBr_3.

The mechanism of debenzylation of **1** is proposed in Scheme 1. The initial complexation of the basic quinoline *N***1** atom in **1** (estimated pK_a of about 6.5[10]) by BBr_3 is followed by elimination of bromide from the resultant complex to generate a bromide salt **3**. The boryl-quinolinium cation of **3** is expected to be highly reactive in a nucleophilic displacement reaction at the benzylic position with bromide acting as the nucleophile. This reaction would produce 4-methoxybenzyl bromide and a boryl-quinolinimine **4**. The latter derivative is the suggested direct precursor to the observed product **5**. However, 4-methoxybenzyl bromide could not be found, even by using a highly sensitive GC–MS analysis. 4-Hydroxybenzyl bromide was not found in the crude mixture either. Apparently, these compounds, as highly reactive toward electrophilic substitution, underwent cationic polymerization in the presence of BBr_3.[11] Indeed, the reaction of **1**, in addition to **5**, produced a substantial amount of tar. More importantly, the outcome of additional debenzylation reactions conducted with benzyl substituted compounds is fully consistent with the suggested mechanism.

The benzyl substituted heterocyclic amines **6**–**9** are shown in Chart 1. Benzyloxy substituted quinoline **14** and amidine **15** (Chart 2) were also included in this study. Each of these compounds contains a basic nitrogen atom, the complexation of which by BBr_3 would subsequently result in generation of a bromide salt with a structural feature similar to that of **3** (Scheme 1). As with **1**, compounds **6**–**8** were synthesized by treatment of a 4(or 2)-chloroquinoline or 9-chloroacridine with benzylamine or benzylmethylamine using general procedures.[12–14] *N*-Benzylpyridine-2-amine (**9**) was obtained commercially, and 4-benzyloxy-2-(4-fluorophenyl)quinoline (**14**) was prepared by alkylation of 2-(4-fluorophenyl)-4-hydroxyquinoline[15] with benzyl chloride. The *N*-(benzyloxy)amidine **15** was a gift from Dr. D. W. Boykin, Georgia State University.[16]

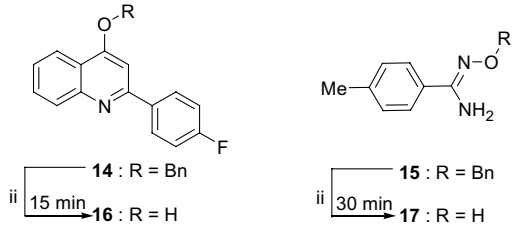

Chart 2. (ii) See Chart 1 for conditions. The mixture was quenched with water and extracted with ether (3 × 4 mL). Compound **16** was isolated as a hydrobromide salt **16**·HBr following concentration of the aqueous solution and crystallization of the residue from 95% EtOH: yield 75%. The free base **17** pure by ^{1}H NMR standard was obtained by treatment of the aqueous solution with $NaHCO_3$ (0.5 g), extraction of the basic mixture with ether (3 × 4 mL), and then concentration of the extract: yield 71%.

As can be seen from Charts 1 and 2, all these benzylamino and benzyloxy derivatives undergo a cleavage of the benzyl group upon treatment with 10 M excess of BBr_3 in CH_2Cl_2 at 23 °C. The high excess of the reagent was used to directly compare the reaction times for consumption of the starting material, which ranged from 15 min for **6** and **14** to 2 weeks for **9** under similar conditions. In the reactions of **6** and **14** conducted with 5 equiv of BBr_3, which is comparable to the amount of the reagent typically used for demethylation of methyl ethers, a complete cleavage was observed in less that 1 h. The yields of the corresponding products **10**–**13**, **16**, **17** after purification were in the range 54–88%. Their structure was established by spectral comparison with authentic samples obtained commercially (**12**, **13**, **17**) and prepared using published chemistry (**10**,[13,14] **11**,[17] **16**[15]). In full agreement with the proposed mechanism (Scheme 1) the presence of benzyl bromide in all crude mixtures was observed by using GC–MS analysis. For the reaction of **15**, the GC analysis was also conducted in the presence of an internal standard (dibenzoylmethane) and gave a 95% yield of benzyl bromide.

As expected, dibenzylamine and *N*-benzylaniline are inert in the presence of BBr_3. *N*-Benzylquinolin-5-amine,[18] *N*-benzylpyrimidine-2-amine,[19] and 2-amino-1-

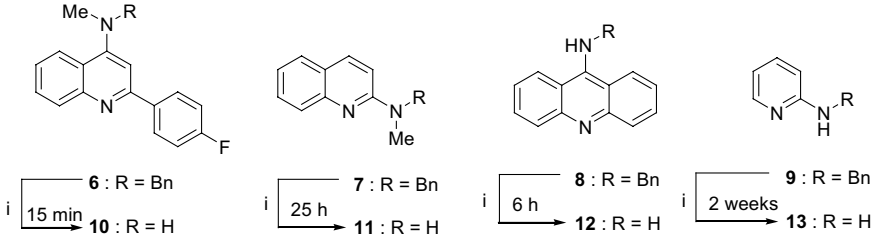

Chart 1. (i) Products **10**–**13** were isolated as hydrobromide salts using the following procedure. A solution of **6**–**9** (0.2 mmol) in CH_2Cl_2 (4 mL) was treated at −10 °C with BBr_3 in CH_2Cl_2 (1 M, 2 mL, 2 mmol), and the mixture was stirred at 23 °C for the indicated period of time. The reaction time refers to consumption of the starting material as shown by GC [a capillary column coated with poly(dimethylsiloxane)] or TLC (silica gel, ether/AcOEt/Et_3N) analysis of aliquots quenched with aqueous $NaHCO_3$. While stirring, the mixture was treated with water (0.2 mL), and the resultant solid material was filtered and crystallized from ether/AcOEt (19:1). Yields: **10**·HBr, 80%; **11**·HBr, 54%; **12**·HBr, 88%; **13**·HBr, 64%.

benzyl-3-cyano-4,5-dimethylpyrrole (a commercial product) also could not be cleaved by treatment with this reagent. These heterocyclic amines are less basic[20] than compounds **1**, **6**–**9**, **14**, and **15** that undergo BBr_3 mediated debenzylation reaction and, apparently, they are only weakly complexed with BBr_3. As a result, bromide salts similar to **3** (Scheme 1) may not be generated.

In conclusion, benzylamines and benzyloxy-substituted compounds that are highly basic for strong complexation with BBr_3 and with structural features that allow for the suggested generation of bromide salts similar to **3** are efficiently cleaved by treatment with BBr_3. Boron tribromide may be considered for deprotection of such compounds. In addition, this report serves as a precaution that the use of BBr_3 for cleavage of various functionalities may also cause undesired debenzylation of benzylamino and benzyloxy moieties.

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16. All new compounds gave satisfactory results of elemental analysis or HRMS data.
    Compound **1**: mp 111–112 °C (from EtOH); ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 4.88 (d, $J = 6$ Hz, 2H), 6.94 (d, $J = 9$ Hz, 2H), 7.09 (s, 1H), 7.43 (d, $J = 9$ Hz, 2H), 7.55 (t, $J = 8$ Hz, 2H), 7.76 (t, $J = 8$ Hz, 1H), 8.04 (m, 3H), 8.12 (d, $J = 8$ Hz, 1H), 8.40 (d, $J = 8$ Hz, 1H), 9.83 (br s, 1H, exchangeable with D_2O).
    Compound **6**·HCl·1/3H_2O: mp 227–228 °C (from EtOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 2.98 (s, 3H), 4.59 (s, 2H), 7.32–7.52 (m, 9H), 7.69 (t, $J = 7$ Hz, 1H), 8.01 (d, $J = 8$ Hz, 1H), 8.08 (d, $J = 8$ Hz, 1H), 8.29 (m, 2H).
    Compound **7**: mp 95–96 °C (from EtOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 3.40 (s, 3H), 5.08 (s, 2H), 7.31–7.48 (m, 7H), 7.55 (t, $J = 8$ Hz, 1H), 7.89 (d, $J = 8$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H), 8.36 (d, $J = 8$ Hz, 1H).
    Compound **10**: mp >210 °C (decomp); ^{1}H NMR (DMSO-d_6) δ 3.04 (s, 3H), 6.89 (s, 1H), 6.35 (t, $J = 9$ Hz, 2H), 6.98 (br d, 1H, exchangeable with D_2O), 7.46 (t, $J = 7$ Hz, 1H), 7.69 (t, $J = 7$ Hz, 1H), 7.92 (d, $J = 8$ Hz, 1H), 8.14 (d, $J = 8$ Hz, 1H), 8.23 (m, 2H).
    Compound **14**·1/4H_2O: mp 116–117 °C (from ether/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.38 (s, 2H), 7.19, (m, 3H), 7.46 (m, 6H), 7.71 (m, 1H), 8.08 (m, 3H), 8.26 (m, 1H).
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