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Preparation of benzoheterocyclic carbaldeydes ☆

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ABSTRACT

The preparation of benzoheterocyclic carbaldehydes in the 2-amino-substituted benzothiazole, benzoxazole and benzimidazole series is described. Starting with the methyl-substituted 2-aminobenzoheterocycle, the nitrogen is protected as an *N*,*N*-diBoc derivative. Next, free radical halogenation of the methyl group with NBS/AIBN affords the $N(Boc)_2$-protected benzylic dibromide which is directly used in the final step. A mild silver nitrite/dimethylsulfoxide-mediated conversion of the dibromide to the aldehyde functionality completes the process.

Benzoheterocycles such as benzothiazoles, benzimid azoles and benzoxazoles can serve as unique and versatile scaffolds for experimental drug design as exemplified by the structures of riluzole,®[2] dabigatran®[3] and flunoxaprofen,®[4] and the vanillanoid receptor-1 (VR1) antagonist AMG 628[5] (Fig. 1). For structural elaboration in lead optimization, the points of attachment on the benzoheterocycle can be through a number of atoms on either the benzene or heterocyclic rings and can take the form of ether, sulfide, amide, amine or carbon–carbon bonds. In general, the formation of heteroatom linkages between any point on the benzoheterocyclic nucleus and, for example, any aromatic, lipid-like, peptide, heterocyclic or even carbohydrate appendage may take advantage of O, S, N nucleophilicity (see riluzole and AMG 628, Fig. 1). However, the formation of *carbon–carbon* bonds to the benzoheterocyclic nucleus from these appendages may be more involved, particularly in the presence of sensitive heteroatom functionality on the heterocyclic portion of the nucleus. Such structures are exemplified in the benzothiazole series that include the β_2-adrenoceptor agonist S1319[6] and the dual D_2–β_2 receptor agonist, sibenadet (Fig. 1).[7] For example, palladium chemistry may be envisioned to facilitate the formation of a carbon linkage between a suitably halogenated benzo-heterocyclic nucleus and the coupling partners activated via C-organometal (aryl or alkyl) derivatives (Scheme 1). A similar alternative may entail the reaction of a halomethyl derivative of the benzoheterocycle and a C-organometal coupling partner with transition metal mediation. A more involved strategy, albeit with the same end in mind, might be to formylate the appropriately-protected metalated benzoheterocycle followed by submitting the resulting aldehyde to the reliable and vastly numerous carbon–carbon bond forming reactions of aldehydes (Scheme 1). The coupling reaction, of course, would depend on the structure of the coupling partner, the protecting groups present and the synthetic target desired. The main issue to address when pursuing the metalation-formylation approach is the lack of ready availability of a reliable and robust amine protecting group which is compatible with the requisite carbanion chemistry and subsequent C–C bond formation reactions. Our approach to the synthesis of benzoheterocyclic aldehydes is with the ultimate goal of single-step carbon–carbon bond formation so that scaffolds with benzoheterocyclic *C*-aryl and *C*-alkyl cores may be prepared (Scheme 2). Hence, we required aldehyde intermediates since these derivatives may be used in numerous reliable, high-yield and scalable reactions so that the desired carbon-linked core structures may be obtained. Our scheme begins with N-protected benzoheterocycles having a specifically-positioned methyl that is the procarbonyl carbon which will be converted to the aldehyde intermediate via a halo or dihalo intermediate. When viewing the overall transformation of an arylmethyl group to an aldehyde or carboxylic acid, one would immediately surmise that any number of direct oxidants will accomplish the same. However, the presence of oxidant-sensitive heteroatoms such as nitrogen and sulfur that make up the ring system, as well as any additional nitrogen appendages, will complicate the formation of the desired products and render the task far more demanding. Earlier studies by a Wyeth group entailed the benzylic free-radical bromination of an N-protected-2-methylindole nucleus followed by a DMSO-mediated conversion of the resultant dibromide to the desired aldehyde.[8] Another report by a Novartis group encompassed the free-radical benzylic dibromination of a 2-adamantyl-substituted-6-methyl chromenone followed by hydrolysis to the dialdehyde with potassium acetate/acetic acid.[9,10] In both cases the isolated methyl group on the aryl portion of the benzoheterocyclic system was converted to the corresponding aldehydes under conditions which did not require harsh oxidants. Accordingly, we developed a multistep, albeit milder version of the above-cited methods for the preparation of benzoheterocyclic carbaldehydes having two heterocyclic atoms and a protected nitrogen appendage. The method does not employ

☆ See Ref. [1].

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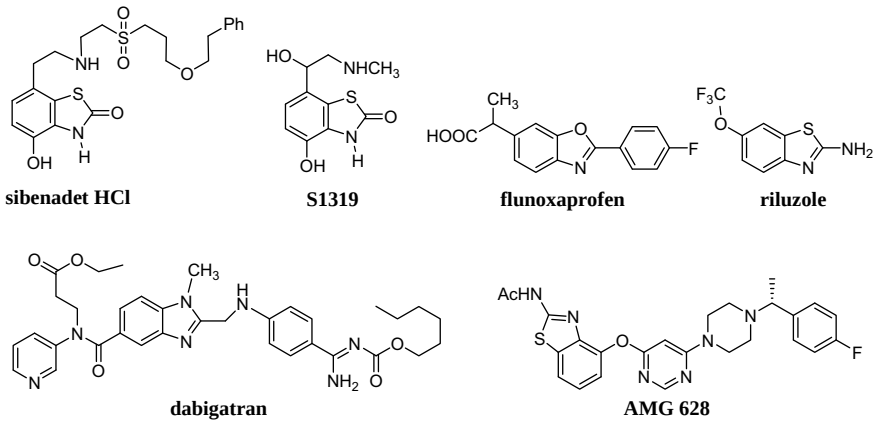
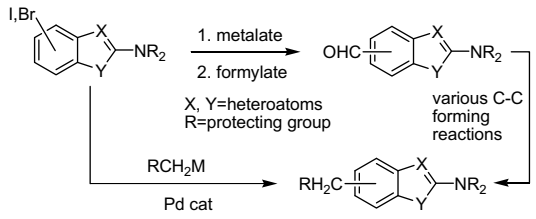
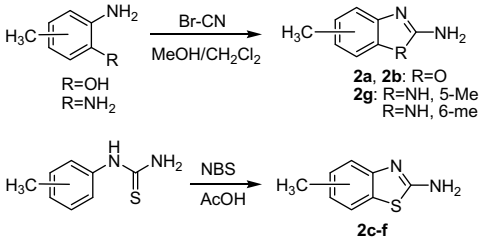


Figure 1.



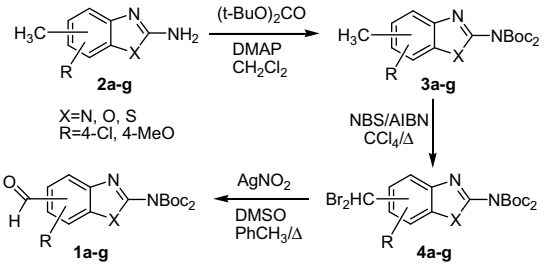
Scheme 1.



Scheme 3.

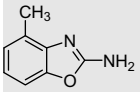
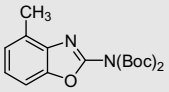
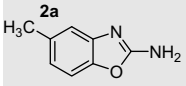
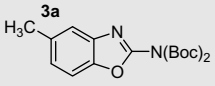
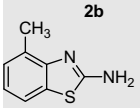
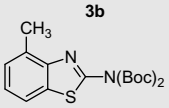
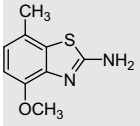
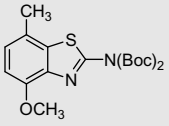
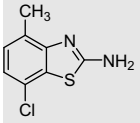
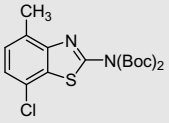
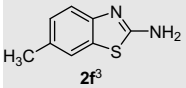
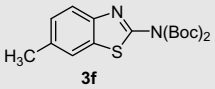
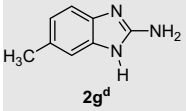
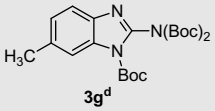
harsh oxidants or high temperatures and is proven to be compatible with amine protection.

The preparation of the starting heterocycles is straightforward and can be accomplished in relatively large scale with commercially-available compounds. 2-Aminomethyl-substituted benzoxazoles or benzimidazoles were prepared by reaction of methyl-substituted *o*-aminophenols or *o*-diamines with cyanogen bromide while the corresponding benzothiazoles can be prepared by halogen-mediated cyclization of methyl-substituted *N*-phenylthioureas (Scheme 3). The relative inertness of the methyl group allows a great many possibilities in generating the starting heterocycle before conversion to the title aldehydes especially in cases where halogenative ring closure of N-substituted thioureas was the only route to the corresponding benzothiazoles. Our synthetic scheme starts with *N*,*N*-diBoc protection of the 2-amino substituent of the heterocycle as depicted in Scheme 2.[11] In reviewing the literature for cases of effective N-protection of substrates which are to undergo subsequent free-radical halogenation, we found that free radical benzylic bromination of amino acids protected as their *N*,*N*-diBoc derivatives was successful.[12] Treatment of the methyl-substituted-2-aminobenzo-heterocycles **2a–g** with Boc carbonate and triethylamine or 4-dimethylaminopyridine (DMAP) provides the *N*,*N*-diBoc compounds **3a–g** (Table 1) as crystalline materials in modest to excellent yields. The lone exception is the benzimidazole **2g** which afforded a mixture of the 5- and 6-methyl tri-Boc derivatives **3g**. The resulting *N*,*N*-diBoc compounds **3a–g** are then converted to the dibromomethyl 2-*N*,*N*-diBoc products **4a–g** by treatment with *N*-bromosuccinimide (NBS) in tetrachloromethane (CCl_4) with initiation by 2, 2′-azobis-isobutyronitrile (AIBN). Although the free radical bromination step to the dibromide is run under relatively mild conditions, it is necessary to fully protect the nitrogen otherwise decomposition and unwanted side products predominated as preliminary experiments revealed.[13] Interestingly, our original plan was to monobrominate the methyl group followed by direct conversion to the aldehyde by a displacement-oxidation protocol using a metal nitrate.[14] However, we found that monobromination to the bromomethyl intermediate was difficult to control thereby giving substantial amounts of dibromide before the starting methyl compounds were consumed. In turn, tribromination of the benzylic methyl group may be minimized or avoided by carefully monitoring the reaction by ^{1}H NMR, and since the brominations are run in CCl_4, the reaction mixture may be directly sampled for spectral analysis without solvent removal or workup. Overall, we found that the dibromide intermediates necessitated minimal separation from the by-products and components of the free-radical reactions. The yields of the intermediate dibromides are listed in Table 2. Next, an efficient protocol for the direct conversion of the more controllable, higher-yielding dibromides **4a–g** to the aldehydes **1a–g** (Table 2) was pursued. A number of factors influenced our choice of the nitrite ion in the conversions of **4a–g** to the title compounds. In practice, a straightforward base-mediated hydrolysis is all that is required for the conversion of a typical aryldibromide to a benzaldehyde.[15] However, any form of base would also work to the detriment of the N(Boc)$_2$ group, present in our compounds, and result in complex product mixtures due to partial N-deprotection. We presumed that the benzylic carbon, with its *gem*-dibromo substitution, would have a high carbonium ion-like reactivity and would be ideal for



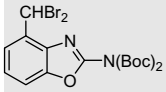
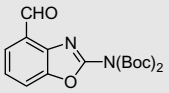
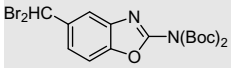
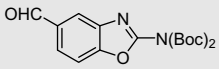
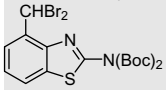
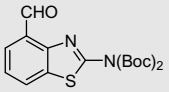
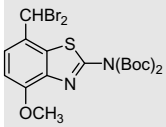
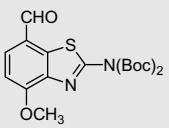
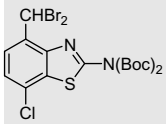
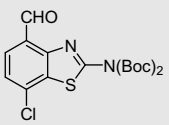
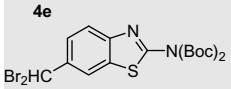
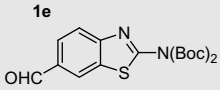
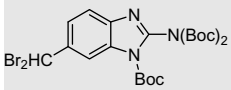
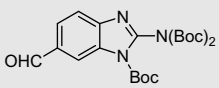
Scheme 2.

Table 1
DiBoc protection of 2-aminobenzoheterocycles

Substrate	DiBOC Product	Yield[a,b] (%)
 **2a**	 **3a**	97
 **2b**	 **3b**	52
 **2c**[c]	 **3c**	94
 **2d**	 **3d**	97
 **2e**	 **3e**	85
 **2f**[3]	 **3f**	75
 **2g**[d]	 **3g**[d]	71

[a]Isolated, purified yield from the corresponding 2-aminobenzoheterocycle.
[b]Compounds were fully characterized by ^{1}H, ^{13}C NMR, IR and HRMS.
[c]Commercially-available starting materials.
[d]Mixture of chromatographically homogeneous 5- and 6-methylbenzo imidazole-2-amine (**2g**) and corresponding N-Boc derivatives (**3g**).

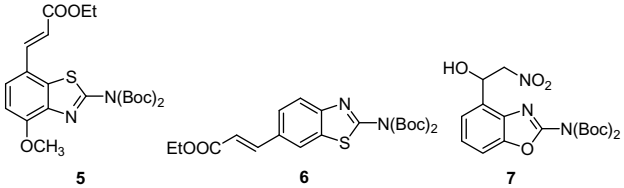
Table 2
Preparation of the benzoheterocyclic aldehydes from the dibromides

Dibromide (%)[a]	Yield (%)	Aldehyde	Yield[b] (%)
 **4a**	77	 **1a**	87
 **4b**	80	 **1b**	52
 **4c**	70	 **1c**	99
 **4d**	74	 **1d**	93
 **4e**	83	 **1e**	95
 **4f**	46	 **1f**	93
 **4g**[c]	49	 **1g**[c]	77

[a]Characterized by ^{1}H and ^{13}C NMR but used directly in the next reaction.
[b]Yields of title compounds are of isolated, purified products.
[c]Mixture of chromatographically homogeneous 5-dibromomethyl (**4g**) and 6-formylbenzoimidazole-2-amine derivatives (**1g**).

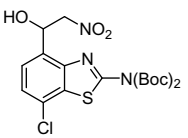
introduction of oxygen through the ambident nitrite ion.[16,17] The decomposition of any intermediate *gem*-dinitrite, formed through the silver-promoted *bis*-substitution, will then result in aldehyde formation. Given that silver nitrite is very difficult to render strictly anhydrous, any adventitious water will play a positive role in the decomposition of intermediate nitrite esters. Furthermore we anticipated that the $N(Boc)_2$ group should be relatively stable to the released nitrous acid thereby ensuring the survival of the title compounds in the final reaction. Hence, direct submission of the 2- *N,N*-diprotected dibromomethyl intermediates **4a–g** to silver nitrite in a two-phase system of dimethylsulfoxide (DMSO)/toluene afforded the corresponding title benzoheterocyclic aldehydes **1a–g** in yields of 52–99% (Table 2).

Some of the $-N(Boc)_2$ heterocyclic aldehydes were probed for their response to several fundamental carbon–carbon forming reactions, in part to evaluate the robustness of the diBoc group, and to introduce new structural motifs bearing the benzoheterocyclic core. Aldehydes **1d** and **1f** were treated with freshly-prepared ethoxycarbonyl methylidenetriphenylphosphorane (19 h, rt) to give olefinic esters **5** and **6** in 85% and 76% yields, respectively after chromatographic purification. En route to the preparation of S1319 (Fig. 1) analogues,[6,18] submission of aldehydes **1a** and **1e** to the Henry reaction using nitromethane (10 equiv, 1–5 h, rt) in THF gave both the corresponding nitroalcohols **7** and **8** in 97% and 75% isolated yield, respectively. Treatment of aldehyde **1d** with freshly-prepared phenylmagnesium bromide (0.68 M, 1.1 equiv, 0 →rt) gave the $-N(Boc)_2$ heterocyclic biarylmethanol **9** in 84% yield after chromatographic purification. Finally, exposure of aldehyde **1d** to *n*-butyllithium (1 equiv, −78 →rt) gave the $-N(Boc)_2$ heterocyclic carbinol **10** in 50% yield accompanied by the –N(Boc) alcohol **10a** (30%) which had suffered partial deprotection.


5

6

7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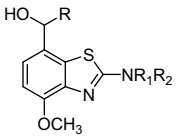
9, R=Ph, R_1=R_2=Boc
10, R=C_4H_9-n, R_1=R_2=Boc
10a, R=C_4H_9-n, R_1=Boc, R_2=H

In summary, we have detailed an efficient synthesis of N-substituted arylcarbaldehydes in the N-protected 2-aminobenzoheterocyclic series using a three-step sequence. The sequence employs methyl-substituted 2-aminobenzo heterocycles effectively protected as their stable *N,N*-diBoc derivatives. Carefully controlled free-radical

benzylic dibromination of the methyl group followed by direct conversion of the reactive product dibromides to the corresponding title compounds with silver nitrite/DMSO completes the overall scheme in modest to high yields. Most notably, only the combination of the $N(Boc)_2$ protection and the nitrite substitution allowed the overall scheme to be successful with the substrates at hand. The multi-step route was the best immediate alternative to the use of harsh oxidants which are historically used to prepare arylaldehydes from relatively robust arylmethyl compounds. In considering the overall utility of the sequence in carbon–carbon bond formation using aldehydes, the route proves to be an excellent, reliable alternative to transition metal and organometal coupling reactions. Application of the scheme to the synthesis of novel pharmacophores and natural products is underway and the results will be reported in due course.

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A. Supplementary data

Experimental procedures, product characterization and 1H and 13C spectra for compounds **1a**–**g** and **3a**–**g**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.066.

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18. The preparation of S1319 analogues, using the scheme described herein will be communicated separately.