Use of the Kaiser Oxime Resin in the Solid-Phase Synthesis of 3-Aminobenzisoxazoles

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In connection with our efforts to identify ligands for a variety of biological targets, we have been interested in the synthesis of 3-aminobenzisoxazoles.[1] To take advantage of parallel synthesis techniques,[2] we sought to develop a method for the solid-phase synthesis of these interesting heterocycles. Two methods for the preparation of 3-aminobenzisoxazoles have been reported. Palermo describes a one-pot procedure involving an S_NAr reaction of an activated *ortho*-halobenzonitrile with hydroxamate ion.[3] Alternatively, Shutske uses a two-step process involving acetone oxime addition to 2-fluorobenzonitrile followed by a subsequent acid-mediated cyclization (Figure 1).[4] We found the two-step approach using polymer-bound oxime particularly attractive, because in theory, one could use the aryl oxime intermediate as a linker. Acid-mediated cyclization would then effect a cyclorelease[5] from the resin, leaving no apparent residual functionality from linkage to the solid phase.

To implement this strategy, we obtained the oxime-containing resin **1** (Scheme 1), which was originally developed by Kaiser and Degrado for solid-phase peptide synthesis[6] and subsequently used in the synthesis of cyclic peptides,[7] ureas,[8] and hydroxamic acids.[9] An attractive feature of the Kaiser resin is the incorporation of the nitro substituent on the benzophenone oxime, which enhances the stability of acylated intermediates to anhydrous acid. We hypothesized that aryl oxime adducts (**3**) would be at least as stable as acylated oxime intermediates, providing chemical compatibility of this linkage for library generation. Therefore, we sought to demonstrate that the Kaiser resin could serve as a nucleophile in S_NAr reactions and that the resulting aryl oxime could be used as a linking group in the solid-phase synthesis of 3-aminobenzisoxazoles.

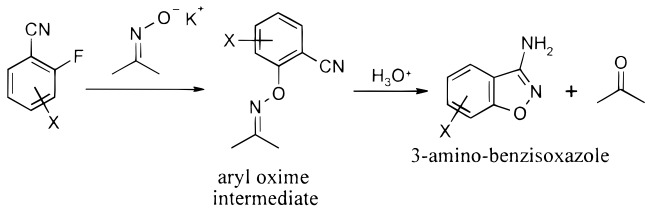
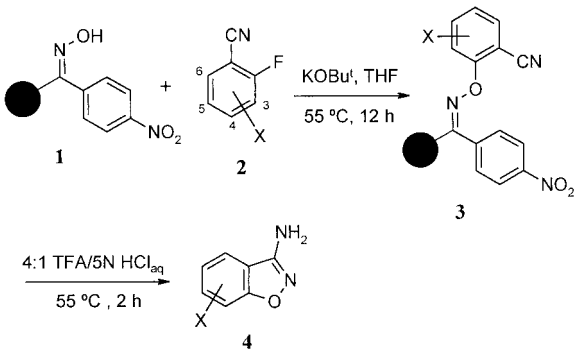


Figure 1. Shutske's Synthesis of 3-Aminobenzisoxazoles.

Scheme 1. Reaction of 2-Fluorobenzonitriles with Oxime Resin 1 Followed by Cyclitive Removal



In preliminary solution-phase studies, the oxime derived from *p*-nitrobenzophenone was treated with 2-fluorobenzonitrile and potassium *tert*-butoxide in DMF to give the S_NAr product in quantitative yield. Treatment of this intermediate with anhydrous trifluoroacetic acid (TFA) for 24 h showed no reaction, whereas the addition of 20% water gave 50% conversion to 3-aminobenzisoxazole (**4a**) after 24 h.

Although these conditions for acid-promoted cyclization are not optimized, the stability of the intermediate to anhydrous acid and the lability under aqueous conditions suggested that the desired transformations could be achieved on resin. Therefore, we moved on to optimize the conditions for these reactions on the solid phase, where we examined the influence of both steric and electronic factors on the loading and cyclitive removal steps.

The effect of solvent on the loading reaction was explored in the case of 4-bromo-2-fluorobenzonitrile (**2e**, Table 1), with DMF, *N*-methylpyrrolidinone, DMSO, and THF giving 58%, 58%, 52%, and 90% yield, respectively.[10] Although DMF is the solvent of choice for the solution phase reaction, THF is preferred on solid phase, presumably as a result of its superior resin-swelling ability. Column 3 of Table 1 gives loading yields for a variety of 2-fluorobenzonitriles. The presence of an electron-withdrawing group facilitates loading at room temperature. These electron-poor aryl fluorides can also be loaded equally well at 55 °C, except in the case of **2f**, which

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(10) The % loading determinations of entries **a**−**h** in Table 1 are an average of 3 experiments and were calculated on the basis of weight difference. IR spectra for these loaded resins showed the requisite nitrile absorptions from 2225 to 2235 cm^{-1}. In addition, % loading was also calculated for entries **a** and **c**−**f** on the basis of nitrogen combustion analysis (n = 12) and were found to be in close correspondence with yield determinations based on weight. See ref 8 for discussion of weight versus elemental analysis for yield determination.

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Table 1. Loading Yields of Oxime Adducts 3; HPLC Purity and % Isolated Yields of 3-Aminobenzisoxazoles 4

entry	**2** (X =)	% yield of **3**[a]	purity of crude **4**[b]	% isolated yield of **4**[c]
a	H	64	>96	76
b	3-CF_3	83	>96	62
c	4-MeO	80	>96	85
d	4-CF_3	90	>96	86
e	4-Br	90	>96	78
f	4-CN	83	84[d]	55
g	5-NO_2	95	79	70
h	6-CF_3	69	>96	75

[a] Determined by resin weight difference (av of 3 experiments, see ref 8). [b] As determined by reverse-phase HPLC. [c] Compounds **4a**−**h** were purified by silica gel chomatography. Yields based on loading yield of **3**. [d] Major impurity was 7-carboxy-3-aminobenzisoxazole (hydrolysis of the nitrile group).

required room temperature for optimal loading (83% vs 69%). Substrates bearing electronically neutral or donating groups require heating to 55 °C in order to load in a reasonable time frame (12 h). As shown by entry **b**, the loading reaction is not sensitive to steric hindrance around the site of nucleophilic substitution.

We observed facile cyclitive removal of compounds **4a**−**c** and **4h**, with reasonable crude purity and high isolated yield using 99:1 TFA/H_2O at 55 °C for 12 h. However, application of the same conditions to **3d**−**f** and **3g** gave much lower isolated yields (crude purity of 60−80%) after 12 h and required several days to reach completion. After we explored a variety of acidic conditions, 4:1 TFA/aqueous 5 N HCl was found to give markedly better results at much shorter reaction times. Column 5 (Table 1) gives the isolated yield of benzisoxazoles **4a**−**h** using these conditions, based on percent loading. As shown in column 4 (Table 1), crude cyclization products (**4**) were generally quite pure. A noticeable exception was entry **f** (Table 1). When **3f** was subjected to cyclitive removal conditions for 2 h, the crude purity of the corresponding product (**4f**) was 72% (isolated yield 68%), with the major impurity arising from hydrolysis of the 4-nitrile group. This purity can be improved to 84% by reducing the cyclitive removal time to 1 h with a modest drop in yield.

Having identified acceptable conditions for loading and cyclitive removal of a variety of substrates, we moved on to confirm the compatibility of the aryl oxime linker with the anhydrous acidic conditions suggested by the solution-phase model study. Thus, the BOC-protected amine **5** (Scheme 2) was prepared and loaded onto the Kaiser resin in 53% yield. The resin was then treated with 25% TFA/CH_2Cl_2 for 2 h, rinsed, and vacuum-dried to give **7** (quantitative) as determined by resin weight difference. The resin washing solutions from this reaction were concentrated and provided no UV-active material by TLC. Resin **7** was then treated with a variety of electrophiles

Scheme 2. On-Resin BOC Removal Followed by Treatment with Electrophiles

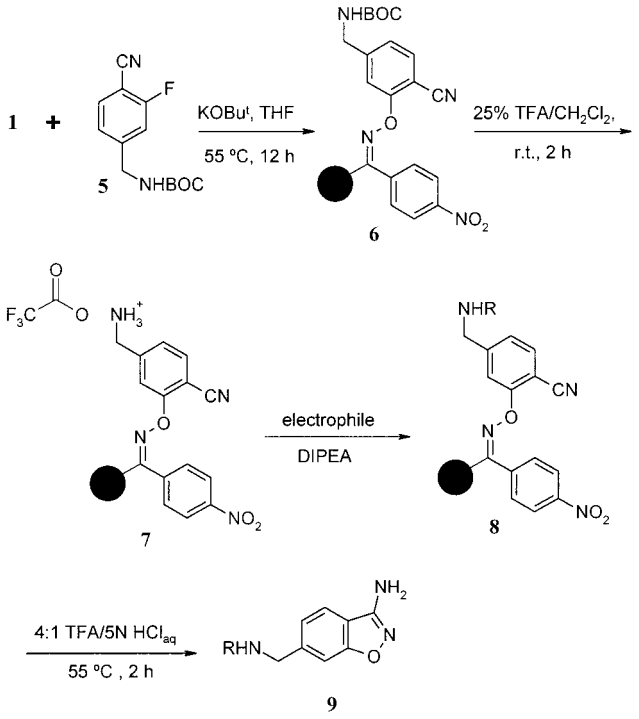
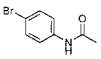
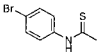


Table 2. Product Yield and Purity of 9

entry	electrophile	R	purity of crude **9**[a]	% isolated yield of **9**[b]
a	acetic anhydride		95	79
b	4-bromo-benzoyl chloride		93	70
c	4-bromo-phenyliso-cyanate		93	72
d	4-bromo-phenylthio-isocyanate		94	70

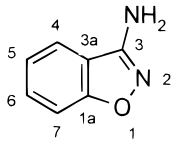
[a] As determined by reverse-phase HPLC. [b] Compounds **9a**−**d** were purified by silica gel chomatography. Yields based on loading yield of **5**.

(as shown in entries **a**−**d** in Table 2) to give **8**. Table 2 gives the crude purities and isolated yields of **9a**−**d** after cyclitive removal.

In conclusion, we have developed an efficient method for the solid-phase synthesis of 3-aminobenzisoxazoles. Our approach involves the first application of the Kaiser oxime resin to S_NAr reactions and can be used successfully with 2-fluorobenzonitriles containing a variety of electron-withdrawing/-donating groups. The intermediate aryl oxime linkage is stable to anhydrous acid and can support BOC-deprotection and amidation reactions, holding promise for compatibility with a broader variety of organic transformations. Progress toward the expansion of this methodology, as well as its application to the synthesis of directed libraries, will be reported in due course.

Experimental Section

General. Except for compound **2c** and **2f**, all reagents used were obtained from commercial sources. Reagents were used without further purification. Kaiser oxime resin **1** was purchased from Novabiochem with a loading capacity of 1.07 mmol/g. All NMR spectra (400 MHz) were recorded on a Varian Gemini-400 spectrometer. Mass spectra were obtained with either ESI or FAB as the ionization method. All purifications were carried out by radial chromatography (Chromatotron model 8924, Harrison Research) using 1 mm silica gel plates (Analtech). Crude purities were estimated from integrated peak areas of HPLC chromatographs with the UV detector monitoring at λ = 215 nm. Analytical HPLC setup: C_{18} Vydac column with solvent gradient A = acetonitrile (0.1% TFA) and B = water (0.1% TFA) at 1 mL/min flow rate. Unless otherwise noted, all HPLC t_R are given for an eluent gradient of 10% A to 60% A over 40 min. The nomenclature for compounds **4a**−**h** and **9a**−**d** is based on the numbering system given in ref 4a and reproduced here:



General Synthesis of 3-Amino-1,2-benzisoxazoles 4a−h. Formation of 3-Amino-1,2-benzisoxazole (4a). To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel was added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluorobenzonitrile (1.07 mmol, 214 mg), and the reaction vessel was rotated at 55 °C in a Robbins oven for 12 h, removed from the oven, and allowed to cool for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of 5% TFA/CH_2Cl_2, 2 × 5 mL of 2-propanol, and 4 × 5 mL of MeOH and then dried in a 35 °C vacuum oven for 12 h to give a Δwt of 36.5 mg (66% loading yield). TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, followed by rotation for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated in vacuo to give the crude product **4a** (>96% purity by reverse-phase HPLC), which was purified by radial chromatography using a 2 mm plate and eluting with 25% EtOAc/hexanes. Concentration of the product-containing fractions gave pure **4a** (35 mg; 2 step yield, 49% based on theoretical equivalents of oxime in the starting resin or 74% based on loading yield). **3-Amino-1,2-benzisoxazole (4a).** HPLC t_R = 12.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 6.38 (bs, 2H). MS (ESI) m/z 135 $(M + H)^+$. Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.61; H, 4.46; N, 20.83.

7-Trifluormethyl-3-amino-1,2-benzisoxazole (4b). HPLC t_R = 21.9 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 8.4 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 5.82 (bs, 2H). MS (ESI) m/z 203 $(M + H)^+$. Anal. Calcd for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86; F, 28.20. Found: C, 47.71; H, 2.60; N, 13.85; F, 28.37.

6-Methoxy-3-amino-1,2-benzisoxazole (4c). HPLC t_R = 14.2 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H), 6.23 (bs, 2H). MS (ESI) m/z 165 $(M + H)^+$. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.78; H, 4.99; N, 17.10.

6-Trifluormethyl-3-amino-1,2-benzisoxazole (4d). HPLC t_R = 24.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.64 (bs, 2H). MS (ESI) m/z 203 $(M + H)^+$. Anal. Calcd for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86; F, 28.20. Found: C, 47.47; H, 2.50; N, 13.59; F, 27.96.

6-Bromo-3-amino-1,2-benzisoxazole (4e). HPLC t_R = 22.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 6.44 (bs, 2H). MS (ESI) m/z 213 [^{79}Br, $(M + H)^+$], 215 [^{81}Br, $(M + H)^+$]. Anal. Calcd for $C_7H_5BrN_2O$: C, 39.47; H, 2.37; N, 13.15; Br, 37.51. Found: C, 39.30; H, 2.26; N, 13.09; Br, 37.58.

6-Cyano-3-amino-1,2-benzisoxazole (4f). HPLC t_R (eluent gradient 5% A to 40% A over 40 min) 17.2 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.67 (bs, 2H). MS (ESI) m/z 160 $(M + H)^+$. Anal. Calcd for $C_8H_8N_2O_2$: C, 60.38; H, 3.17; N, 26.40. Found: C, 60.17; H, 3.46; N, 24.82.

5-Nitro-3-amino-1,2-benzisoxazole (4g). HPLC t_R = 15.9 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 2.8 Hz, 1H), 8.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 6.82 (bs, 2H). MS (ESI) m/z 180 $(M + H)^+$. Anal. Calcd for $C_7H_5N_3O_3$: C, 46.94; H, 2.81; N, 23.46. Found: C, 46.85; H, 2.80; N, 23.26.

4-Trifluoromethyl-3-amino-1,2-benzisoxazole (4h). HPLC t_R = 21.5 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 8.4 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 5.81 (bs, 2H). MS (ESI) m/z 203 $(M + H)^+$. Anal. Calcd for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86; F, 28.20. Found: C, 47.32; H, 2.62; N, 13.92; F, 27.96.

General Synthesis of 3-Aminobenzisoxazoles 9a−d. Formation of 6-(Acetylaminomethyl)-3-amino-1,2-benzisoxazole (9a). To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel was added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 4-(*tert*-butoxycarbonylaminomethyl)-2-fluorobenzonitrile (1.07 mmol, 268 mg). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h and allowed to cool for 1 h. The resin was then rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of 5% TFA/CH_2Cl_2, 2 × 5 mL of 2-propanol, and 4 × 5 mL of MeOH. The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt of 65.0 mg (53% loading yield). To effect BOC-deprotection, the resin was then suspended in 25% TFA/CH_2Cl_2 (7 mL) and rotated for 2 h. The resin was again rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of 2-propanol, and 4 × 5 mL of MeOH. The resin was then suspended in DMF (7 mL), followed by addition of acetic anhydride (505 μL, 6.42 mmol) and *N*,*N*-diisopropylethylamine (930 μL, 6.42 mmol). After the reaction vessel rotated for another 12 h, the resin was rinsed with 2 × 5 mL of CH_2Cl_2, 2 × 5 mL of 2-propanol, and 4 × 5 mL of MeOH. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with 2 × 5 mL of CH_2Cl_2. These washings were combined and concentrated in vacuo to give the crude product **9a** (95% purity by reverse-phase HPLC), which was purified by radial chromatography on a 2 mm plate, eluting with 50% EtOAc/hexanes. Concentration of the product-containing fractions gave pure **9a** (45 mg; 4 step yield, 41% based on 1.07 mmol/g given by the manufacturer or 79% yield based on loading yield).

6-(Acetylaminomethyl)-3-amino-1,2-benzisoxazole (9a). HPLC t_R = 10.5 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (bs, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.32 (bs, 1H), 4.32 (d, J = 6.4 Hz, 2H), 1.86 (s, 3H). MS (ESI) m/z 206 $(M + H)^+$. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N,20.48. Found: C, 57.77; H, 5.45; N, 19.92.

6-[(*p*-Bromophenylcarbonyl)aminomethyl]-3-amino-1,2-benzisoxazole (9b). HPLC t_R = 21.5 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (bs, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.31 (s, 1H), 7.18 (d, J = 8.1 Hz, 1H), 6.34 (bs, 2H), 4.55 (d, J = 5.9 Hz, 2H). MS (ESI) m/z 346 [^{79}Br, $(M + H)^+$], 348 [^{81}Br, $(M + H)^+$]. Anal. Calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.05; H, 3.49; N, 12.14. Found: C, 51.80; H, 3.54; N, 11.67.

6-[(*p*-Bromophenylaminocarbonyl)aminomethyl]-3-amino-1,2-benzisoxazole (9c). HPLC t_R = 28.2 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (bs, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.35 (s, 4H), 7.29 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.76 (t, J = 6.2 Hz, 1H), 6.33 (bs, 2H), 4.38 (d, J = 6.2 Hz, 2H). MS (ESI) m/z 361 [^{79}Br, $(M + H)^+$], 363 [^{81}Br, $(M + H)^+$]. Anal. Calcd for $C_{15}H_{13}BrN_4O_2$: C, 49.88; H, 3.63; N, 15.51. Found: C, 49.78; H, 3.93; N, 15.10.

6-[(*p*-Bromophenylaminothiocarbonyl)aminomethyl]-3-amino-1,2-benzisoxazole (9d). HPLC $t_R = 30.5$ min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (bs, 1H), 8.32 (bs, 1H), 7.72 (d, $J =$ 8.1 Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H), 7.32 (s, 1H), 7.19 (d, $J = 8.1$ Hz, 1H), 6.34 (bs, 2H), 4.81 (s, $J =$ 5.5 Hz, 2H). MS (FAB) m/z 377 [^{79}Br, $(M + H)^+$], 379 [^{81}Br, $(M + H)^+$]. Anal. Calcd for $C_{15}H_{13}BrN_4OS$: C, 47.76; H, 3.47; N, 14.85. Found: C, 47.79; H, 3.29; N, 14.68.

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