A Novel Synthesis of 3-Amino-1,2-benzisoxazoles - an Entry into the Isoxazolo[3,4,5-*ef*][1,4]benzoxazepine Ring System

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

A novel synthesis of 3-amino-1,2-benzisoxazole (**3**) from 2-[(isopropylideneamino)oxy]benzonitrile (**2**) is described. This methodology was used to synthesize 3-amino-4-hydroxy-1,2-benzisoxazole (**10**), which served as an intermediate for a number of isoxazolo[3,4,5-*ef*][1,4]benzoxazepines.

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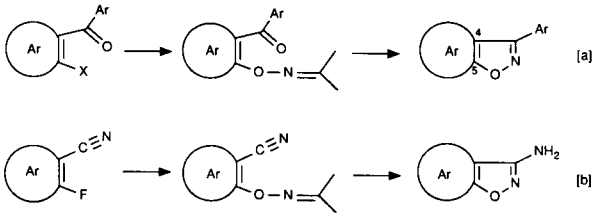
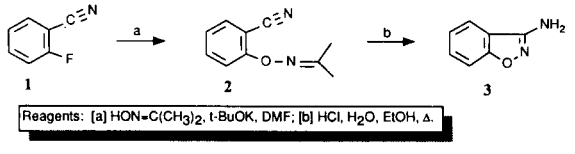
We recently described a new synthesis of isoxazoles fused to an aromatic group along the 4,5-bond [1,2]. This method consists of the intramolecular ring closure of an *O*-(*o*-keto)arylacetone oxime derived from the S_NAr reaction of a suitably activated *o*-halo ketone with the potassium anion of acetone oxime (Figure 1a). Using this reaction sequence, 3-aryl-1,2-benzisoxazoles [1] and 3-aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines [2] were synthesized. In this paper we describe a further application of this methodology, in which the cyclization of an *O*-(*o*-cyano)-arylacetone oxime, derived from an *o*-fluorobenzonitrile, yields a 3-amino-1,2-benzisoxazole (Figure 1b). In particular, we describe how this chemistry was used to construct 3-amino-4-hydroxy-1,2-benzisoxazole, which served as the precursor of the heretofore unknown isoxazolo[3,4,5-*ef*]-[1,4]benzoxazepine ring.

Figure 1



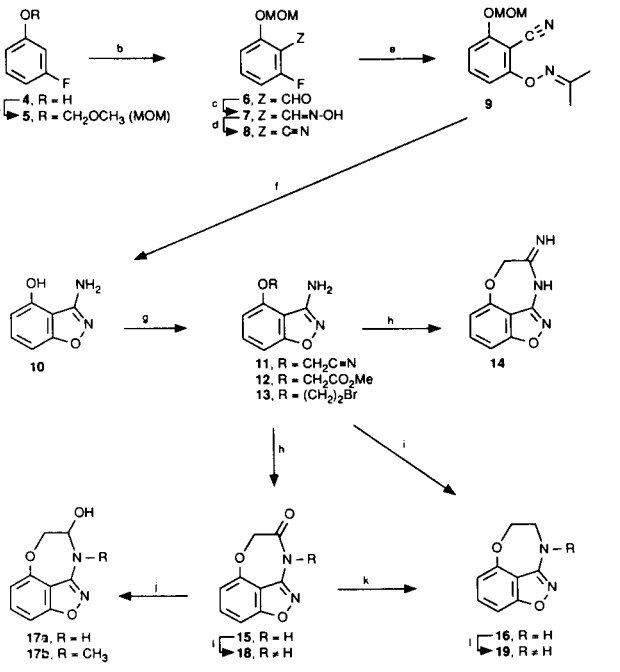
3-Amino-1,2-benzisoxazoles have previously been synthesized by the cyclization of *O*-ethoxycarbonyl derivatives of salicylamidoximes [3]. This methodology entails three steps, starting from an *o*-cyanophenol: formation of the salicylamidoxime, synthesis of the *O*-ethoxycarbonyl derivative, and cyclization by heating. In contrast, the new method involves only two steps from an *o*-fluorobenzonitrile: formation of the *O*-(*o*-cyano)arylacetone oxime and cyclization by acid catalyzed transoximation. The synthesis of 3-amino-1,2-benzisoxazole (**3**) by this method is depicted in Scheme 1. The reaction of *o*-fluorobenzonitrile (**1**) with the potassium anion of acetone oxime in *N*,*N*-dimethylformamide gave the intermediate *O*-(*o*-cyano)-phenylacetone oxime (**2**), which cyclized to give the known **3** [3] in refluxing 1:1 ethanol:5% aqueous hydrochloric acid, conditions that were previously described [1].

Scheme 1



The synthesis of 3-amino-4-hydroxy-1,2-benzisoxazole (**10**) and its subsequent elaboration to a number of isoxazolo[3,4,5-*ef*][1,4]benzoxazepines is described in Scheme 2. Compound **10** was obtained in one step from the key intermediate *O*-(*o*-cyano)arylacetone oxime (**9**), which was constructed from 3-fluorophenol (**4**) by using the following *o*-directed lithiation strategy. Compound **4** was protected as its methoxymethyl (MOM) ether (**5**), using a method that employed dimethoxymethane instead of the carcinogenic chloromethyl methyl ether [4]. Low temperature lithiation of **5** with *n*-butyllithium was directed by both the alkoxy group and the fluorine [5], so that treatment with *N*,*N*-dimethylformamide gave exclusively aldehyde **6**. Compound **6** was an oil, so the crude **6** was treated with hydroxylamine hydrochloride in pyridine to give the oxime **7** in 79% total yield from **5**. Dehydration of **7** using 1,1'-carbonyldiimidazole in dichloromethane [6] gave the nitrile **8** (87% yield) which, upon treatment with the potassium anion of acetone oxime as described above, provided 2-[[(isopropylidene)amino]oxy]-6-methoxymethoxybenzonitrile (**9**) in 69% yield. Treatment of **9** with aqueous hydrochloric acid in refluxing alcohol as described above for **2** gave a mixture of products and was not a suitable method for the conversion of **9** to **10**. Alternatively, treatment of **9** with methanolic hydrogen chloride simultaneously accomplished ring closure of the *O*-(*o*-cyano)arylacetone oxime and removal of the MOM protecting group to give the desired **10** in 89% recrystallized yield.

Scheme 2



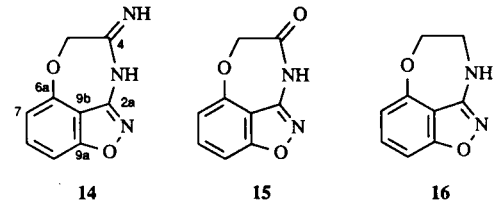
Reagents: [a] $(CH_3O)_2CH_2$, TsOH, CH_2Cl_2, Δ; [b] n-BuLi, -78°, DMF; [c] H_2NOH•HCl, pyridine, Δ; [d] Im_2CO, CH_2Cl_2; [e] $HON=C(CH_3)_2$, t-BuOK, DMF; [f] HCl, MeOH; [g] K_2CO_3, RX, acetone; [h] NaH, DMF; [i] NaH, THF; [j] $LiAlH_4$, THF; [k] BH_3, THF; [l] NaH, RX, DMF.

The hydroxy group of **10** could be selectively alkylated by using potassium carbonate in acetone. Employing chloroacetonitrile or methyl bromoacetate as the alkylating agent gave, respectivley, the acetonitrile derivative **11** in 41% yield and the methyl acetate derivative **12** in 43% yield; the use of a tenfold excess of 1,2-dibromoethane as the alkylating agent gave the bromoethyl compound **13** in 60% yield. In each case, it was apparent from the proton nmr spectrum that alkylation had occurred on oxygen: the hydroxyl group, distinct in the proton spectum of **10** in dimethylsulfoxide-d_6 (1H, 10.7 ppm), was absent in each case and the amino group was still present (2H, *ca.* 6 ppm in DMSO). The chemical shift of the methylene group adjacent to the heteroatom was also consistent with alkylation on oxygen (see Experimental).

Treating **11**, **12** or **13** with sodium hydride accomplished intramolecular alkylation/acylation and formation of the respective isoxazolo[3,4,5-*ef*][1,4]benzoxazepines, **14**, **15** or **16** (64%, 58% and 29%, respectively). The structures of **14-16** were confirmed by mass spectra and proton nmr (see Experimental section). In addition, the carbon-13 spectra of **15** and **16** were completely assigned and are tabulated in Table 1. Interestingly, while lactam **15** could be converted to compound **16** by reduction with diborane/-tetrahydrofuran, an initial attempt to reduce **15** to **16** with lithium aluminum hydride in tetrahydrofuran gave the hemiaminal **17a**. It may be that the steric constraints of the isoxazolo[3,4,5-*ef*][1,4]benzoxazepine ring system do not favor alkoxide elimination from the initially formed hemiaminal complex, thus hindering the pathway that leads to **16** and making possible the isolation of the hemiaminal **17a** (Figure 2) [7].

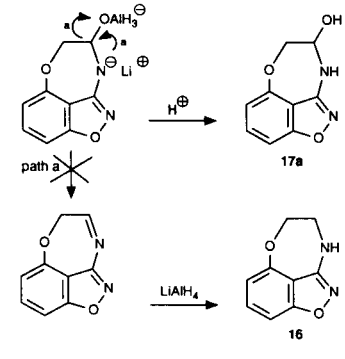
Table 1

^{13}C Chemical Shifts of Some Isoxazolo[3,4,5-*ef*][1,4]benzoxazepines



Carbon	14	15	16
2a	161.6	152.1	160.1
4	164.3	168.3	47.1
5	72.0	75.1	73.2
6a	155.0	153.6	154.3
7	108.1	109.2	108.9
8	131.4	132.7	131.9
9	103.6	103.9	102.3
9a	164.7	164.4	165.2
9b	110.0	107.8	106.5

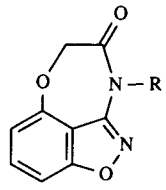
Figure 2

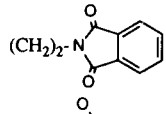
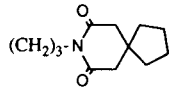


Lactam **15** could be alkylated in *N,N*-dimethylformamide with sodium hydride and an appropriate alkyl halide to give the *N*-alkylisoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4(5*H*)-ones (**18**) described in Table 2. A number of *N*-alkyl-4,5-dihydroisoxazolo[3,4,5-*ef*][1,4]benzoxazepines (**19**), described in Table 3, were also prepared. Where R = methyl (**19a**) and R = 3-dimethylaminopropyl (**19d**), these compounds were synthesized by reduction of the corresponding lactams, **18a** and **18d**, with diborane/tetrahydrofuran. It is interesting to note that attempted reduction of the *N*-methyl lactam **18a** with lithium aluminum hydride again gave a hemiaminal, **17b**. The other compounds of Table 3 (**19b-c**, **19e-f**) were prepared by the direct alkylation of **16**, again with sodium hydride in *N,N*-dimethylformamide.

Table 2

Isoxazolo[3,4,5-ef][1,4]benzoxazepin-4(5H)-ones

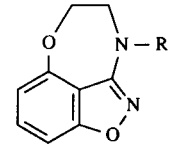


Compound	R	Mp°C	Yield[a] %	Molecular Formula	Analysis % Calcd. (Found) C	H	N
18a	CH_3	159-161	48 [b]	$C_{10}H_8N_2O_3$	58.82 (58.71	3.95 3.97	13.72 13.73)
18b	$CH_2C_6H_5$	105-107	35 [c]	$C_{16}H_{12}N_2O_3$	68.56 (68.69	4.32 4.23	10.00 10.09)
18c	$CH_2C{\equiv}CH$	143-145	42 [b]	$C_{12}H_8N_2O_3$	63.16 (63.23	3.53 3.64	12.28 12.26)
18d	$(CH_2)_3N(CH_3)_2$	147-149	51 [d]	$C_{14}H_{17}N_3O_3{\cdot}C_4H_4O_4$ [e]	55.24 (55.53	5.41 5.47	10.74 10.53)
18e		197-199	54 [f]	$C_{19}H_{13}N_3O_5$	62.81 (62.74	3.61 3.60	11.57 11.42)
18f		116-118	44 [g]	$C_{22}H_{25}N_3O_5$	64.22 (64.44	6.12 6.25	10.21 10.29)

[a] Yields were not optimized. [b] Recrystallized from methanol. [c] Recrystallized from i-propyl ether. [d] Recrystallized from i-propanol. [e] Fumarate. [f] Recrystallized from N,N-dimethylformamide/water. [g] Recrystallized from methanol/water.

Table 3

4,5-Dihydroisoxazolo[3,4,5-ef][1,4]benzoxazepines



Compound	Method[a]	R	Mp°C	Yield[b] %	Molecular Formula	Analysis % Calcd. (Found) C	H	N
19a	A	CH_3	98-100	62 [c]	$C_{10}H_{10}N_2O_2$	63.15 (63.15	5.30 5.36	14.73 14.73)
19b	B	$(CH_2)_3CH(C_6H_5)_2$	99-102	52 [d]	$C_{25}H_{24}N_2O_2$	78.10 (78.26	6.29 6.38	7.29 7.36)
19c	B	$CH_2C{\equiv}CH$	143-145	42 [e]	$C_{12}H_8N_2O_3$	63.16 (63.23	3.53 3.64	12.28 12.26)
19d	A	$(CH_2)_3N(CH_3)_2$	107-109	30 [e]	$C_{14}H_{19}N_3O_2{\cdot}1.5C_4H_4O_4$ [f]	55.17 (54.80	5.79 5.72	9.65 9.63)
19e	B	$(CH_2)_2N(CH_3)_2$	104-106	42 [g]	$C_{13}H_{17}N_3O_2{\cdot}1.5C_4H_4O_4$ [f]	54.15 (54.54	5.50 5.80	9.97 9.97)
19f	B	$CONHCH_3$	177-179	49 [h]	$C_{11}H_{11}N_3O_3$	56.65 (56.27	4.76 4.79	18.02 18.20)

[a] Method A = reduction of corresponding lactam with borane/tetrahydrofuran. Method B = alkylation of **16** with appropriate alkylating agent (see experimental section). [b] Yields were not optimized. [c] Recrystallized from methanol/water. [d] Recrystallized from methanol. [e] Recrystallized from i-propanol. [f] Sesquifumarate. [g] Recrystallized from ethyl acetate/ethanol. [h] Purified by trituration with pentane.

The biological activity of this series of compounds is under investigation.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra

were recorded on a Perkin-Elmer 547 and nuclear magnetic resonance spectra were taken on a Varian XL-200. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. The ^1H and ^{13}C assignment were made on the basis of single frequency homonuclear decoupling experiments, APT, HETCOR and fully proton coupled experiments. Mass spectra data were determined by direct insertion at 70 eV with a Finnigan 4000 GC-MS equipped with a INCOS data system. E. Merck 230-400 mesh silica gel was used for flash chromatography. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

Benzyl bromide, propargyl bromide, *N*-(2-bromoethyl)phthalimide, and methyl isocyanate were commercially available (Aldrich). Dimethylaminopropyl chloride and dimethylaminoethyl chloride were released from their commercially available hydrochlorides immediately before use by treatment with 50% sodium hydroxide solution. 4,4-Diphenylbutanol methanesulfonate was made by a literature procedure [8] and 8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione *p*-toluenesulfonate was synthesized from 8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione [9] by the standard method [10].

2-[[(Isopropylidene)amino]oxy]benzonitrile (**2**).

In 100 ml of dry *N,N*-dimethylformamide was dissolved 8.04 g (0.11 mole) of acetone oxime, followed by 12.33 g (0.11 mole) of potassium *t*-butoxide. After this mixture had stirred for 30 minutes, *o*-fluorobenzonitrile (**1**) (12.1 g, 0.10 mole) was added. After an additional 1 hour the reaction mixture was poured into a mixture of saturated ammonium chloride solution and ether, and then the organic phase was separated, washed with water, dried, and evaporated under reduced pressure to give 16.42 g (86%) of **2** as an oil; ^1H nmr (deuteriochloroform): δ 2.08, 2.12 (2 x s, 3H, N=C(CH_3)$_2$), 7.02 (m, 1H, H-3), 7.57 (m, 3H, H-4,5,6); ms: m/e 174 (M^+). The compound suffered extensive decomposition upon attempted distillation, but a few mg for an analytical sample were obtained by distillation through a micro short path apparatus.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 68.90; H, 5.59; N, 15.57.

3-Amino-1,2-benzisoxazole (**3**).

Compound **2** (12.0 g, 0.069 mole) was brought to reflux in a mixture of 150 ml of ethanol and 150 ml of 5% aqueous hydrochloric acid. After 45 minutes the ethanol was evaporated under reduced pressure, and the remaining aqueous phase was made basic with potassium carbonate solution and extracted three times with ethyl acetate. The combined organic phase was washed with water, dried and evaporated to give a residue that was purified by flash chromatography (10% ethyl acetate/dichloromethane). Combination of the product-containing fractions and recrystallization from dichloromethane/pentane gave 6.36 g of **3** (69%), mp 108-109° (lit [3] mp 111°); ^1H nmr (DMSO-d_6): δ 6.56 (broad s, 2H, exchanges with deuterium oxide, NH_2), 7.25 (m, 1H, H-5), 7.48 (m, 2H, H-6,7), 7.95 (d, 1H, J = 9 Hz, H-4); ms: m/e 134 (M^+).

2-Fluoro-6-methoxymethoxybenzaldehyde Oxime (**7**).

3-Fluoromethoxymethoxybenzene (**5**) was prepared from 3-fluorophenol (**4**) according to a literature procedure [4], using dimethoxymethane in refluxing dichloromethane with catalysis by *p*-toluenesulfonic acid and water removal by molecular seives. A 63% yield of **5** was obtained after distillation, (0.1 mm Hg, kugelrohr oven temperature 110°); ^1H nmr (deuteriochloroform): δ 3.48 (s, 3H, OCH_3), 5.16 (s, 2H, OCH_2O), 6.81 (m, 3H, H-4,5 and 6), 7.23 (m, 1H, H-2).

A solution of **5** (46.85 g, 0.30 mole) in 400 ml of tetrahydrofuran was chilled to −75°. *n*-Butyllithium (140 ml of 2.5 *M*, 0.35 mole) was added at such a rate that the internal reaction temperature did not rise above −65°, and the reaction was allowed to stir for 30 minutes in the cold. At the end of this time, *N,N*-dimethylformamide (27.0 ml, 0.35 mole) was added and the reaction was stirred for an additional 30 minutes after which the reaction was poured into water and extracted with ethyl ether. The organic phase was dried and evaporated to give 2-fluoro-6-methoxymethoxybenzaldehyde (**6**) as an oil which was used without further purification; ^1H nmr (deuteriochloroform): δ 3.53 (s, 3H, OCH_3), 5.32 (s, 2H, OCH_2O), 6.80 (m, 1H, H-4), 7.03 (m, 1H, H-5), 7.51 (m, 1H, H-3), 10.02 (s, 1H, C*H*O); ms: m/e 184 (M^+).

The compound **6** thus obtained was heated on a steam bath in 200 ml pyridine containing 24.3 g of hydroxylamine hydrochloride (0.35 mole). At the end of 30 minutes the solvent was evaporated and the residue was triturated with water. The crystalline product was filtered, rinsed well with water, dissolved in dichloromethane and dried. After evaporation of the solvent and recrystallization from cyclohexane, 47.5 g (79% from **5**) of **7** was obtained, mp 102-104°; ir (chloroform): ν cm^{-1}, 1615 (C=N); ^1H nmr (deuteriochloroform): δ 3.52 (s, 3H, OCH_3), 5.31 (s, 2H, OCH_2O), 6.83 (m, 1H, H-4), 7.05 (m, 1H, H-5), 7.31 (m, 1H, H-3), 8.50 (s, 1H, C*H*=N-OH), 10.36 (broad s, 1H, exchanges with deuterium oxide, =N-O*H*); ms: m/e 199 (M^+).

Anal. Calcd. for $C_9H_{10}FO_3$: C, 54.27; H, 5.06; N, 7.03. Found: C, 54.33; H, 5.12; N, 6.95.

2-Fluoro-6-methoxymethoxybenzonitrile (**8**).

Compound **7** (65.0 g, 0.326 mole) was dissolved in 450 ml of dichloromethane and treated with 1,1'-carbonyldiimidazole (58.2 g, 0.359 mole) in small portions. At the end of the addition, the organic phase was washed with water, dried, and evaporated, and the residue was purified by flash chromatography(dichloromethane) giving 51.4 g of **8** (87%), mp 48-52°. An analytical sample was obtained by recrystallization from pentane, mp: 53-55°; ir (chloroform): ν cm^{-1}, 2255 (C≡N); ^1H nmr (deuteriochloroform): δ 3.56 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2O), 6.87 (m, 1H, H-4), 7.07 (m, 1H, H-5), 7.52 (m, 1H, H-3); ms: m/e 181 (M^+).

Anal. Calcd. for $C_9H_8FNO_2$: C, 59.66; H, 4.45; N, 7.73. Found: C, 59.55; H, 4.47; N, 7.87.

2-[[(Isopropylidene)amino]oxy]-6-methoxymethoxybenzonitrile (**9**).

In 300 ml of dry *N,N*-dimethylformamide was dissolved 11.14 g (0.152 mole) of acetone oxime, followed by 17.0 g (0.152 mole) of potassium *t*-butoxide. After this mixture had stirred for 30 minutes, **8** (23.0 g, 0.127 mole) was added as a solution in 150 ml of *N,N*-dimethylformamide. After an additional 30 minutes the reaction was poured into 1 liter of water and stirred well as the product crystallized. The precipitate was filtered off, washed well with water, dissolved in dichloromethane and dried. Concentration of the solvent and recrystallization from methanol/water gave 20.5 g (69%) of **9**, mp 62-64°; ir (chloroform): ν cm^{-1}, 2235 (C≡N); ^1H nmr (deuteriochloroform): δ 2.02, 2.08 (2 x s, 3H, N=C(CH_3)$_2$), 3.53 (s, 3H, OCH_3), 5.29 (s, 2H, OCH_2O), 6.81 (d, J = 9 Hz, 1H, H-3), 7.19 (d, J = 9 Hz, 1H, H-5), 7.42 (dd, J = 9 Hz, 1H, H-4); ms: m/e 234 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.03; N, 11.96.

Found: C, 61.29; H, 6.07; N, 11.49.

3-Amino-4-hydroxy-1,2-benzisoxazole (**10**).

Compound **9** (9.91 g, 0.0423 mole) was dissolved in 100 ml of methanol. To this was added 100 ml of a freshly prepared saturated ethereal hydrochloric acid solution. The reaction was stirred for 20 hours, the solvent was evaporated and the residue was triturated with dichloromethane. Recrystallization of the resulting solid from methanol/water gave 5.62 g (89%) of **10**, mp 255° dec; ^{1}H nmr (DMSO-d_6): δ 5.88 (broad s, 2H, exchanges with deuterium oxide, NH_2), 6.57 (d, J = 9 Hz, 1H, H-5), 6.85 (d, J = 9 Hz, 1H, H-7), 7.30 (dd, J = 9 Hz, 1H, H-6), 10.70 (broad s, 1H, exchanges with deuterium oxide, OH), ms: m/e 150 (M^+).

Anal. Calcd. for $C_7H_6N_2O_2$: C, 55.99; H, 4.03; N, 18.66. Found: C, 55.93; H, 4.01; N, 18.51.

[(3-Amino-1,2-benzisoxazol-4-yl)oxy]acetonitrile (**11**).

Compound **10** (4.2 g, 0.0279 mole) was refluxed for 5 hours in a mixture of 4.6 g of potassium carbonate (0.0335 mole) and 1.9 ml of chloroacetonitrile (0.030 mole) in 80 ml of acetone. The reaction was then quenched with dilute hydrochloric acid solution and extracted with ethyl acetate. The organics were washed with water, dried and evaporated. The residue was passed though a column of florisil (ethyl acetate) giving a solid which was recrystallized from methanol to give 2.17 g (41%) of **11**, mp 133-136°; ^{1}H nmr (DMSO-d_6): δ 5.33 (s, 2H, OCH_2C≡N), 6.09 (broad s, 2H, exchanges with deuterium oxide, NH_2), 6.94 (d, J = 9 Hz, 1H, H-5), 7.18 (d, J = 9 Hz, 1H, H-7), 7.55 (dd, J = 9 Hz, 1H, H-6); ms: m/e 189 (M^+).

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 56.96; H, 3.64; N, 22.14.

Methyl[3-Amino-1,2-benzisoxazol-4-yl)oxy]acetate (**12**).

This compound was prepared from 17.5 g (0.117 mole) of **10** and 13.2 ml (0.140 mole) of methyl bromoacetate in a manner analogous to that described for the preparation of **11**. The crude product was purified *via* flash chromatography (10% ethyl acetate/dichloromethane) giving a solid, mp 133-139°, which was recrystallized from methanol/water to give **12** in 43% yield, mp 133-136°; ir (potassium bromide): ν cm^{-1}, 1745 (C=O); ^{1}H nmr (DMSO-d_6): δ 3.75 (s, 3H, CO_2CH_3), 4.98 (s, 2H, OC$H_2CO_2CH_3$), 6.01 (broad s, 2H, exchanges with deuterium oxide, NH_2), 6.70 (d, J = 9 Hz, 1H, H-5), 7.07 (d, J = 9 Hz, 1H, H-7), 7.45 (dd, J = 9 Hz, 1H, H-6); ms: m/e 222 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.13; H, 4.61; N, 12.61.

3-Amino-4-[(2-bromoethyl)oxy]-1,2-benzisoxazole (**13**).

This compound was prepared from 1.50 g (0.010 mole) of **10** and 21.8 g (0.116 mole) of ethylene dibromide in a manner analogous to that described for the preparation of **11**. The crude product was purified *via* flash chromatography (10% ethyl acetate/dichloromethane) to give **13** in 60% yield. An analytical sample was obtained by recrystallization from benzene, mp 105-107°; ^{1}H nmr (deuteriochloroform): δ 3.76 (t, J = 6 Hz, 2H, OCH_2CH_2Br), 4.45 (t, J = 6 Hz, 2H, OCH_2CH_2Br), 4.68 (broad s, 2H, exchanges with deuterium oxide, NH_2), 6.51 (d, J = 9 Hz, 1H, H-5), 7.02 (d, J = 9 Hz, 1H, H-7), 7.37 (dd, J = 9 Hz, 1H, H-6); ms: m/e 256 (M^+).

Anal. Calcd. for $C_9H_9BrN_2O_2$: C, 42.04; H, 3.53; N, 10.90. Found: C, 42.01; H, 3.53; N, 10.95.

Isoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4(5*H*)-imine (**14**).

A solution of compound **11** (4.44 g, 0.0235 mole) in 40 ml of *N,N*-dimethylformamide was added to a suspension of sodium hydride (0.0282 mole) in *N,N*-dimethylformamide. After stirring for 15 minutes, the mixture was added to water. The resulting solid was filtered, washed with water and dried to give 3.4 g of crude **14**. This was recrystallized from dimethylsulfoxide/water to give 2.85 g (64%) of **14**, mp 273-276°; ir (potassium bromide): ν cm^{-1}, 1685 (C=N); ^{1}H nmr (DMSO-d_6): δ 4.92 (s, 2H, OCH_2), 6.79 (d, J = 9 Hz, 1H, H-7), 7.21 (d, J = 9 Hz, 1H, H-9), 7.47 (dd, J = 9 Hz, 1H, H-8), 7.87, 7.97 (2 x broad s, 2H, exchanges with deuterium oxide, H-3 and C=N*H*); ms: m/e 189 (M^+).

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.07; H, 3.90; N, 21.77.

Isoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4(5*H*)-one (**15**).

A solution of compound **12** (7.2 g, 0.0323 mole) in 60 ml of *N,N*-dimethylformamide was added to a suspension of sodium hydride (0.0387 mole) in *N,N*-dimethylformamide. After stirring for 20 minutes, the mixture was added to a dilute hydrochloric acid solution. The resulting solid was filtered and dried to give 5.7 g (93%) of crude **15**, mp 188-190°. Recrystallization from methanol gave pure **15** in 58% yield, mp 187-189°; ir (potassium bromide): ν cm^{-1}, 1690 (C=O); ^{1}H nmr (DMSO-d_6): δ 5.96 (s, 2H, H-5), 6.94 (d, J = 9 Hz, 1H, H-7), 7.35 (d, J = 9 Hz, 1H, H-9), 7.62 (dd, J = 9 Hz, 1H, H-8), 11.90 (broad s, 1H, exchanges with deuterium oxide, N*H*); ms: m/e 190 (M^+).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.54; H, 3.01; N, 14.79.

4,5-Dihydroisoxazolo[3,4,5-*ef*][1,4]benzoxazepine (**16**).

Compound **13** (10.86 g, 0.0428 mole) was dissolved in 200 ml of tetrahydrofuran. To this was added 5.0 g of sodium hydride (50 % oil dispersion, 0.10 mole). After stirring for 30 minutes at reflux, the reaction was cooled and an additional 1.0 g of sodium hydride was added. After 30 minutes of continued reflux, the reaction was poured into water, the aqueous phase was acidified with concentrated hydrochloric acid and the product was extracted into ethyl ether. Concentration of the dried organic phase gave a residue which was purified by flash chromatography (10% ethyl acetate/dichloromethane). The isolated product was then passed through a short column of alumina (dichloromethane). The product thus obtained was recrystallized from dichloromethane/pentane to give 2.20 g (29%) of pure **16**, mp 165-166°; ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 3.68 (m, 2H, H-4), 4.50 (m, 2H, H-5), 6.32 (broad s, 1H, exchanges with deuterium oxide, N*H*), 6.69 (d, J = 9 Hz, 1H, H-7), 6.98 (d, J = 9 Hz, 1H, H-9), 7.40 (dd, J = 9 Hz, 1H, H-8); ms: m/e 176 (M^+).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.90. Found: C, 60.84; H, 4.89; N, 16.04.

4,5-Dihydroisoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4-ol (**17a**).

Compound **15** (4.54 g, 0.0239 mole) was dissolved in 90 ml of tetrahydrofuran and chilled to 0° in an ice bath. To this was slowly added 17 ml of a 1 molar solution of lithium aluminum hydride in tetrahydrofuran. The reaction was stirred for 15 minutes and then quenched with 10 ml of a saturated ammonium chloride solution. The mixture was diluted with ethyl acetate, filtered and the filtrate was dried. Concentration of the solvent gave a solid which was purified *via* flash chromatography (15% ethyl ace-

tate/dichloromethane) to give 2.50 g (54%) of crude **17a**, mp 143-147°. This was recrystallized from ethyl acetate/hexane to give 1.94 g (42%) of pure **17a**, mp 142.5-144.5°; ^{1}H nmr (DMSO-d_6): δ 4.20 (d, J_{gem} = 14 Hz, 1H, H-5), 4.55 (dd, J_{gem} = 14 Hz, $J_{4,5}$ = 4 Hz, 1H, H-5), 5.07 (m, 1H, H-4), 6.08 (d, $J_{4,OH}$ = 4 Hz, 1H, exchanges with deuterium oxide, O*H*), 6.72 (d, J = 9 Hz, 1H, H-7), 7.04 (d, J = 9 Hz, 1H, H-9), 7.44 (dd, J = 9 Hz, 1H, H-8), 8.07 (d, $J_{4,NH}$ = 4 Hz, 1H, exchanges with deuterium oxide, N*H*); ms: m/e 192 (M^+).

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.10; H, 4.24; N, 14.51.

3-Methylisoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4(5*H*)-one (**18a**).

A solution of 4.0 g (0.0210 mole) of **15** in 30 ml of *N,N*-dimethylformamide was added to a suspension of sodium hydride (1.2 g of 50% in oil). After 15 minutes, iodomethane (1.4 ml, 0.0231 mole) was added. After this addition, the reaction was quenched into a dilute hydrochloric acid solution and the resulting precipitate was filtered, washed with water and dried to give 3.34 g (78%) of crude product, mp 156-159°. This was recrystallized from methanol to give 2.1 g (48%) of pure **18a**, mp 159-161°; ir (chloroform): ν cm^{-1}, 1685 (C=O); ^{1}H nmr (DMSO-d_6): δ 3.42 (s, 3H, N-C*H*$_3$), 5.01 (s, 2H, H-5), 6.95 (d, J = 9 Hz, 1H, H-7), 7.39 (d, J = 9 Hz, 1H, H-9), 7.62 (dd, J = 9 Hz, 1H, H-8); ms: m/e 204 (M^+).

Compounds **18b-f** were prepared in an analogous manner, using benzyl bromide, propargyl bromide, dimethylaminopropyl chloride, *N*-(2-bromoethyl)phthalimide, and 8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione *p*-toluenesulfonate, respectively. Melting points and combustion analysis data for compounds **18a-f** are tabulated in Table 2.

4,5-Dihydro-3-methylisoxazolo[3,4,5-*ef*][1,4]benzoxazepin-4-ol (**17b**).

This compound was prepared from 5.54 g (0.0271 mole) of **18a** in a manner analogous to that described for **17a**. The crude product was passed through a column of florisil (ethyl acetate) to give 3.95 g of product, mp 116-119°, which was recrystallized from ethyl acetate/hexane to give 2.95 g (53%) of pure **17b**, mp 118-120°; ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3H, N-C*H*$_3$), 4.27 (d, J_{gem} = 14 Hz, 1H, H-5), 4.58 (dd, J_{gem} = 14 Hz, $J_{4,5}$ = 4 Hz, 1H, H-5), 5.06 (m, 1H, H-4), 6.44 (m, 1H, exchanges with deuterium oxide, O*H*), 6.72 (d, J = 9 Hz, 1H, H-7), 7.06 (d, J = 9 Hz, 1H, H-9), 7.46 (dd, J = 9 Hz, 1H, H-8); ms: m/e 206 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.05; H, 4.74; N, 13.40.

Preparation of 4,5-Dihydroisoxazolo[3,4,5-*ef*][1,4]benzoxazepines.

Method A.

4,5-Dihydro-3-methylisoxazolo[3,4,5-*ef*][1,4]benzoxazepine (**19a**).

To a solution of 4.84 g (0.0237 mole) of compound **18a** in 200 ml of tetrahydrofuran was added 72 ml of a 1 molar solution of borane/tetrahydrofuran. This was stirred for 3.5 hours at which time an additional 24 ml of borane was added. The reaction was stirred at ambient temperature for 15 hours and was then quenched with 40 ml of a 10% sodium hydroxide solution. The aqueous layer was separated and extracted with ethyl acetate and the combined organics were washed with water and dried. The compound was purified *via* flash chromatography (4% ethyl acetate/dichloromethane) to give 3.35 g (74%) of crude product, mp 95-100°. This was recrystallized from methanol/water to give 2.80 g (62%) of pure **19a**, mp 98-100°; ^{1}H nmr (DMSO-d_6): δ 3.67 (m, 2H, H-4), 4.51 (m, 2H, H-5), 6.71 (d, J = 9 Hz, 1H, H-7), 7.07 (d, J = 9 Hz, 1H, H-9), 7.46 (dd, J = 9 Hz, 1H, H-8); ms: m/e 190 (M^+).

Compound **19d** was prepared in an analogous manner. Melting points and combustion analysis data for compounds **19a** and **19d** are tabulated in Table 3.

Method B.

4,5-Dihydro-3-(4,4-diphenylbutyl)isoxazolo[3,4,5-*ef*][1,4]benzoxazepine (**19b**).

A solution of 3.17 g (0.018 mole) of compound **16** in 100 ml of *N,N*-dimethylformamide was added to a suspension of 1.1 g of sodium hydride (50% in oil, 0.0216 mole) in *N,N*-dimethylformamide. This was followed by the addition of 6.1 g (0.0198 mole) of 4,4-diphenylbutanol methanesulfonate. The reaction was heated at 90° for 4 hours, quenched into water and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with water and dried. Purification by flash chromatography (dichloromethane) gave 5.13 g (74%) of crude product, mp 88-93°, which was recrystallized from methanol to give 3.60 g (52%) of pure **19b**, mp 99-102°; ^{1}H nmr (deuteriochloroform): δ 2.70 (m, 2H, NCH$_2$C*H*$_2$CH$_2$CH), 2.14 (m, 2H, NCH$_2$CH$_2$C*H*$_2$CH), 3.54 (m, 4H, H-4, NC*H*$_2$CH$_2$CH$_2$CH), 3.98 (t, J = 7 Hz, 1H, NCH$_2$CH$_2$CH$_2$C*H*), 4.42 (m, 2H, H-5), 6.67 (d, J = 9 Hz, 1H, H-7), 7.00 (d, J = 9 Hz, 1H, H-9), 7.26 (m, 10H, phenyl), 7.38 (dd, J = 9 Hz, 1H, H-8); ms: m/e 384 (M^+).

Compounds **19c**, **19e** and **19f** were prepared in an analogous manner, using propargyl bromide, dimethylaminoethyl chloride, and methyl isocyanate, respectively. Melting points and combustion analysis data for compounds **19b-c** and **19e-f** are tabulated in Table 3.

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