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Preparation of 3-(4-Pyridinylamino)-1,2-Benzisoxazoles *via* a Nucleophilic Aromatic Substitution Reaction

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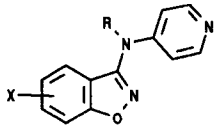
Abstract: *An efficient three step process for the preparation of secondary 3-amino-1,2-benzisoxazoles is described. The key step is the isomerization/cyclization of an ortho halo or nitro amidoxime. The nucleophilic substitution reaction is successful with a wide variety of substituents on the aromatic ring, including an electron donating substituent para to the site of attack.*

In our program directed at the discovery of new Alzheimer's Disease therapeutics, we became interested in the preparation of the 3-amino-benzisoxazoles exemplified by **1**. Several strategies exist for the preparation of primary 3-amino-1,2-benzisoxazoles.[1-3] Secondary and tertiary amines are available only



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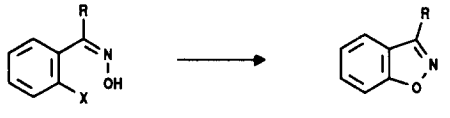
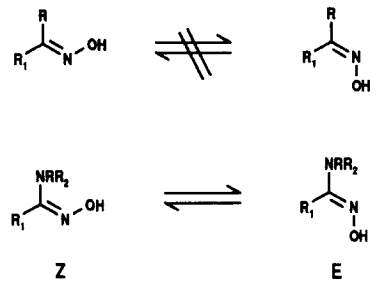
via the alkylation of primary 3-amino benzisoxazoles or *via* the nucleophilic displacement of chlorine from 3-chloro-benzisoxazoles with amines. [4]

A further survey of the literature revealed no satisfactory methods for the preparation of 3-arylaminobenzisoxazoles. For example, treatment of 3-chlorobenzisoxazole with aniline afforded none of the addition product.[4,5] An attractive strategy for the preparation of 1,2-benzisoxazoles is the S_NAr nucleophilic displacement of a fluorine, chlorine or nitro group by an oxime. (eqn.1) The major limitation of this method is that only the E oxime isomer will cyclize, and thus the success of these reactions depends on the availability of the E oxime isomer.[6] Surprisingly, we were unable to find any application of this



Eqn. 1

method for the preparation of 3-aminobenzisoxazoles via an amidoxime (eqn. 1, R=amino) cyclization. We anticipated that the cyclization of amidoximes would be more general than the reaction of keto-oximes, since unlike keto-oximes, amidoximes are configurationally labile. (eqn. 2)[7-9]This is particularly important since amidoximes which are monosubstituted on the amide nitrogen generally form oximes with the Z configuration. Thus isomerization to the E isomer is crucial to the success of the reaction.[9]

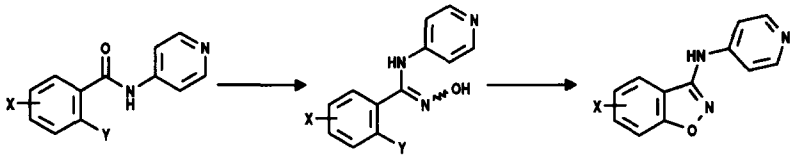


Eqn. 2

Z E

The required amidoximes were prepared by a modification of standard procedures in which O-trimethylsilylhydroxylamine was used as a source of anhydrous hydroxylamine. Treatment of the amides **2** with either thionyl chloride or phosphorus pentachloride,[10] followed by treatment of the crude imidoyl chlorides with O-trimethylsilylhydroxylamine led to the O-trimethylsilyl amidoximes, which subsequently

Scheme 1



2 3 4

desilylated under the reaction conditions to provide the desired amidoximes as mixtures of E and Z isomers. Although the identity of the major isomer was not rigorously proven, the NMR spectra of the two component systems were consistent with the expected Z isomer as the major component of the reactions.[11] Cyclization of the amidoximes proceeded smoothly as shown in Table 1.[12] The conditions for the cyclization were determined by the substituents on the aromatic ring. Both the parent system and fluoro-substituted compounds (examples 1-5) cyclized upon treatment with potassium-*tert*-butoxide in refluxing THF. Introduction of an electron withdrawing group (examples 6-8) allowed the reaction to proceed at room temperature. It was also possible to replace the *ortho* fluoro leaving group with a nitro group (example 9).[13] Treatment of substrates containing an electron donating group under reflux conditions failed to provide any of the desired product. Initial experiments were performed with the 4-methoxy substituted compound (example 11). It was found that switching the solvent from THF to the dipolar aprotic solvent DMF and maintaining the temperature at 60°C afforded the cyclized product in 50% yield. Unfortunately, application of these conditions to the 5-methoxy case (example 12) in which the donating substituent is *para* to the electrophilic site failed to provide the desired benzisoxazole. Upon further experimentation it was found that treatment of this substrate with potassium-tert-butoxide in N-methylpyrrolidinone at 100°C for 1 hr. followed by addition of water to the hot mixture gave the product in 78% yield upon cooling.

Table 1 ***Preparation of 3-(4-Pyridinylamino)-1,2-Benzisoxazoles***

example	amidoxime 3	yield %[a] of 3	conditions[b]	benzisoxazole 4	yield %[c] of 4
1	X=H, Y=F	65	A	X=H	69
2	X=3-F, Y=F	56	A	X=7-F	61
3	X=4-F, Y=F	54	A	X=6-F	81
4	X=5-F, Y=F	58	A	X=5-F	69
5	X=6-F, Y=F	65	A	X=4-F	43[a]
6	X=3- CF_3, Y=F	66	B	X=7-CF_3	76
7	X=4- CF_3, Y=F	52	B	X=6- CF_3	63[a]
8	X=5- CF_3, Y=F	67	B	X=5- CF_3	70[a]
9	X=4-NO_2, Y= NO_2	39	A	X=6- NO_2	74
10	X=3-OMe, Y=F	64	D	X=7-OMe	86
11	X=4-OMe, Y=F	79	C	X=6-OMe	50
12	X=5-OMe, Y=F	71	D	X=5-OMe	78

a) Yields reflect purification by trituration of the crude reaction mixtures. b) A. ^{t}BuOK, THF reflux; B. ^{t}BuOK, THF, room temperature; C. ^{t}BuOK, DMF 60°C; D. ^{t}BuOK, N- methylpyrrolidinone, 100°C. c.Yields reflect purification by recrystallization unless otherwise noted.

In conclusion, we have developed an efficient three step process for the preparation of secondary 3-amino-1,2-benzisoxazoles. The key step is the isomerization/cyclization of an *ortho* halo or nitro amidoxime. The nucleophilic substitution reaction is successful with a wide variety of substituents on the aromatic ring, including an electron donating substituent *para* to the site of attack. Although we did not prepare any secondary alkyl or tertiary amino compounds, we expect that these reactions will work as well, making this a general procedure for the preparation of 3-amino-1,2-benzisoxazoles.

Experimental: **7-Methoxy-3-[4-(pyridinyl)amino]-1,2-benzisoxazole:** A mixture of 2-fluoro-3-methoxy-N-4-pyridinylbenzamide (25 g, 102 mmol) and phosphorus pentachloride (27.5 g, 132 mmol) in 200 mL of dichloroethane was heated at reflux for 5 hr. The reaction mixture was allowed to cool to room temperature, diethyl ether was added, and the precipitated imidoyl chloride was collected by filtration.

O-Trimethylsilylhydroxyl amine (24.7 g, 235 mmol) was added rapidly to a suspension of the imidoyl chloride formed above in 500 mL of tetrahydrofuran, and the resulting mixture was stirred at room temperature for 20 hr.[14] The reaction was diluted with ethyl acetate and basified with saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and

concentrated. The solid that precipitated upon reducing the volume of solvent was collected to give 17.1 g (64%) of amidoxime, which was used below without further purification.

Potassium-t-butoxide (2.36 g, 21 mmol) was added to a portion of the amidoxime (5.0 g, 19.1 mmol) in 95 mL of N-methylpyrrolidinone, and the mixture was heated at 100°C for 3 hr. Subsequently, the mixture was diluted with water and allowed to cool to room temperature. The precipitated solid was collected (3.42 g). The filtrate was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to leave an additional 0.9 g of crude product. Recrystallization of the product from acetonitrile provided 3.0 g (65%) of product as a yellow solid, m.p.=226-227°C. ^{1}HNMR (200 MHz, DMSO-d6) δ 10.05 (s, 1H), 8.46 (d, 2H, J=6.5Hz), 7.62-7.70 (m, 3H), 7.34 (t, 1H, J=7.8Hz), 7.23 (d, 2H, J=6.5Hz), 3.98 (s, 3H). EIMS *m/e* (rel intensity) 241 (M^+, 100). IR(KBr) 1712, 1700 cm^{-1}. Calculated for $C_{13}H_{11}CN_3O_2$: 64.72%C, 4.60%H, 17.42%N; Found: 64.34%C, 4.77%H, 17.50%N

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10) Phosphorus pentachloride was the reagent of choice and was necessary for substrates containing an electron withdrawing group on the aromatic ring (examples 6-9).
11) The Z:E ratio of isomers in the isolated material was generally >10:1. The structure assignment was based on the observation that the hydroxyl proton of the Z isomer was downfield from the hydroxyl proton of the E isomer. [6]
12) The amidoximes exhibited satisfactory ^{1}H NMR and MS. The benzisoxazoles had satisfactory ^{1}H NMR, mass and IR spectra.
13) This example was not run at ambient temperature, although based on the results with the trifluoromethyl substituent it may have worked at this temperature.
14) In some cases the trimethylsilyl group was not fully removed under the reaction conditions. Stirring the reaction mixture with 10% HCl completed the desilylation in these cases.

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