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Novel One-Pot Cyclization of *Ortho* Substituted Benzonitriles to 3-Amino-1,2-benzisoxazoles

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Abstract: A novel one-pot synthesis of 3-amino-1,2-benzisoxazoles (iii), from *ortho* substituted benzonitriles (i), is described. The synthesis likely involves a S_NAr reaction of an activated *ortho* halo or nitro group by a hydroxamate anion, followed by an intra-molecular ring closure. 3-Amino-1,2-benzisoxazoles (iii) can be generated quickly in comparable or superior yields via this one-pot procedure when compared to other methods.^{1,2} Reaction parameters and conditions are presented.

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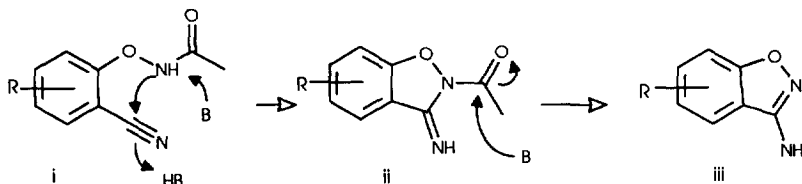
The compounds in Table 1 were prepared as intermediates for the synthesis of a series of 3-[[2-(4-morpholinyl)-ethyl]amino]-1,2-benzisoxazol-yl carbamates. These carbamates are potential therapeutic agents for the treatment of Senile Dementia of the Alzheimer type (SDAT), and exhibit dual inhibition of acetylcholinesterase (AChE) and monoamine-oxidase (MAO).³

One of the first syntheses of 3-amino-1,2-benzisoxazoles was reported by Böshagen and Schraufstätter¹. Their methodology involves formation of a salicylamidoxime from a salicylonitrile, conversion to the *O*-ethoxycarbonyl derivative, and cyclization upon heating to the product. Generally <5% yield is obtained.

Also, the cyclization of *ortho* substituted benzonitriles is a useful reaction for the preparation of 3-amino-1,2-benzisoxazoles, as demonstrated by Shutske and Kapples.² This methodology entails a two-pot procedure involving formation and isolation of a 2-[(isopropylidene-amino)oxy]benzonitrile (as a protected hydroxylamine) from an *o*-halobenzonitrile, and cyclization with accompanying hydrolysis to afford the 3-amino-1,2-benzisoxazole.

In contrast, this new method involves a convenient one step procedure where an *o*-halo or *o*-nitrobenzonitrile is treated with a hydroxamate anion [formation of the *N*-(2-cyano-phenoxy)acetamide (i) is postulated as an intermediate] and followed by *in situ* base-catalyzed intramolecular cyclization. The synthesis of 3-amino-1,2-benzisoxazole and nuclear substituted analogs by this method is depicted in Table 1 and a possible mechanism for this transformation is shown in Scheme 1. A variety of functionalized 3-amino-1,2-benzisoxazoles were synthesized by this method (Table 1).

Scheme 1.



Certain trends are observed with the compounds in Table 1, such as increased yield as the halogen (R) in the 6-position increases in size. This may be attributed to subsequent halogen displacement from the product (iii), resulting in overall bis-hydroxamylation, and lower yields of the desired product. Experiments using a *o*-nitro group (7) versus a *o*-fluorine atom (8) show negligible differences in yield. Displacement of a chlorine atom (10) under normal reaction conditions was not possible. However, upon addition of 1.5 eq. of Cs_2CO_3 displacement and cyclization was achieved in 43% yield (11). Surprisingly, all attempts at forming the 5-methoxy derivative (6) resulted in phenol formation ($X=OH$). Presumably, electron donating R-groups, such as

Table 1.

Example	X	R	Yield(%)	Mp(°C)
1	F	H	55	107-9
lit. ²	F	H	59	108-9
2	F	6-F	25	143-4
3	NO ₂	6-Cl	60	125-6
4	F	6-Br	70	129-30
5	F	4-MeO	94	129-30
6	NO ₂	5-MeO	not det.	-----
7	NO ₂	6-MeO	55	150-1
8	F	6-MeO	56	151-2
9	Cl	6-MeO	n.r.	-----
10	Cl	6-BnS	n.r.	-----
11	Cl	6-BnS	43	154-5
12	F	4-MOMO	not det.	-----
13	F	6-MOMO	80	88-9
14	NO ₂	5-Cl, 6-MeO	not det.	-----

Addition of 1.5 eq. of Cs₂CO₃

methoxy, *para* to the leaving group, add electron density to the possible intermediate N-(2-cyano-phenoxy)-acetamide (i) and facilitate the formation of the corresponding salicylonitrile. Electron donating groups *meta* to the leaving group, however do not appear to significantly affect formation of the desired product. No product was obtained in example 12, suggesting that steric bulk of the MOM group ortho to the nitrile may influence the desired course of the reaction.

The one-pot procedure for this transformation makes the synthesis of many 3-amino-1,2-benzisoxazoles, which previously required two or three steps, a convenient procedure. The general conditions make it a versatile transformation; however, alkoxy groups in the *para* position to the leaving group do not appear to be tolerated.

6-Methoxy-3-amino-1,2-benzisoxazole (8)

A general procedure for this reaction : In 400 mL of dry N,N-dimethylformamide (DMF) was dissolved acetohydroxamic acid (24.6 g, 328 mmol), followed by potassium *t*-butoxide (36.8 g, 328 mmol) at ambient temperature. After this mixture had been mechanically stirred for 30 minutes, 2-fluoro-4-methoxybenzonitrile (33.0 g, 218 mmol) was added. After an additional 5 hours of stirring, the reaction mixture was poured into a mixture of brine and ethyl acetate. The organic phase was separated, washed with brine (5X), dried, filtered, and evaporated under reduced pressure. The remaining solid was recrystallized from dichloromethane/petroleum ether to give 20.0 g (56%, mp= 151-2°C) of **8** as a white solid; ¹H NMR (CDCl₃): δ 3.88 (s, 3), 4.38 (bd s, 2, exchanges with deuterium oxide, NH₂), 6.84 (m, 2, H-4, H-5), 7.38 (m, 1, H-7); MS: m/e 164 (M⁺).

References

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