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Synthesis of 2-Aminoimidazolones and Imidazolones by (3+2) Annulation of Azaoxyallyl Cations

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Abstract

The first examples of (3+2) annulations between azaoxyallyl cations and cyanamides and nitriles to give the corresponding 2-aminoimidazolones and imidazolones is reported. Based on the isolation of unexpected imidate products with certain substrates, it is proposed that the reaction proceeds via fast kinetic *O*-alkylation followed by rearrangement to the thermo-dynamically favored 2-aminoimidazolones and imidazolones. The method was applied to the formal synthesis of the antihypertensive drug irbesartan (Figure 1).

Graphical Abstract

Both 2-aminoimidazolones and imidazolones are featured in important biologically active compounds, such as irbesartan (antihypertensive drug),¹ leucettamine B (DYRK and CLK kinase inhibitor),^{2,3} diphenylimidazolone **3** (human neuropeptide Y5 receptor antagonist, NPY5),⁴ and 2-amino-diphenylimidazolone **4** (β -secretase inhibitor).⁵ Some of these compounds are quite potent and are active at nanomolar concentrations.

Many of the existing methods for preparing these types of compounds rely on condensation reactions of α -amino amide derivatives such as **5** to give bonds **b** and **c** depicted in Scheme 1.^{6–9} Zhu reported a process for making bonds **c** and **d**.¹⁰ Retrosynthetically, we envisioned a complementary method that targets bonds **a** and **c** for preparing these important heterocycles. Such a disconnection would require synthons represented by dipole **6** whose electronic criteria are satisfied by azaoxyallyl cations.

Azaoxyallyl cations are a unique class of reactive intermediates that have been shown to engage in (4+3) annulation reactions with furan.^{11,12} Recently, our group and Jeffrey's,^{13,14}

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, full optimization table, and characterization of all new compounds, including ¹H, ¹³C NMR spectra, IR, and high-resolution mass spectrometry.

followed by Liao's,¹⁵ published a novel method for the dearomative (3+2) annulation reaction between 3-substituted indoles and azaoxyallyl cations to give pyrroloindolines. In the intervening time, others have expanded upon our initial work, thus reporting the (3+3), (3+2), and (3+1) reactions of azaoxyallyl cations with nitrones,^{16–19} carbonyls,^{20–24} isothiocyanates,^{25,26} alkynes,²⁷ sulfur ylides,²⁸ thiocyanates,²⁹ and other coupling partners.³⁰ In this manuscript, *we report for the first time annulation reactions between azaoxyallyl cations and nitriles and cyanamides to give imidazolones and 2-aminoimidazolones* (Scheme 1).

We began our studies by examining the reaction between dimethylcyanamide (**7a**) and α -bromoamide **9a**. We found that in the presence of carbonate and amine bases, several Lewis acids promoted the transformation to give the desired product **10a** with a range of yields (Table 1; entries 1–4). Control experiments reveal that Lewis acids were not necessary, and that Na₂CO₃ alone was able to induce formation of the product. A brief solvent survey demonstrated that the annulation proceeds well in both *i*PrOH and 1,1,1,3,3,3-hexaisopropanol (HFIP) (entries 5 and 6). We were encouraged by the success of *i*PrOH as a suitable solvent because it was believed that powerful hydrogen bond donor solvents such as HFIP were required for the formation of the azaoxyallyl cation intermediate. But because subsequent reactions proved to be less efficient in *i*PrOH, we adopted HFIP as the solvent of choice (entry 5).

With optimized conditions in hand, we proceeded to examine the scope of the reaction (Scheme 2). The synthesis of 2-aminoimidazolones was amenable to the use of a monosubstituted α -haloamide to give **10b**, while starting with *t*-butyl cyanamide lead to efficient formation of **10c**. We next explored annulation reactions of nitriles **8** which we expected would lead to the formation of the corresponding imidazolone products. Indeed, this reaction worked well with a wide range of substituent types on the nitrile, including: methyl, ethyl, *i*Pr, halogen, alkenyl, heterocyclic, and aryl. Although imidazolone **11a** was produced using MeCN as the nitrile component, a reaction carried out entirely in MeCN as solvent, failed.^{16,26} As a final note, it was necessary to vary the relative amounts of haloamide versus nitrile or cyanamide to further optimize yields.

Curiously, in the reaction between nitrile **8a** and α -haloamide **9a** (eq 1), we isolated an unexpected product in which the amide ¹³C resonance was shifted upfield by approximately 20 ppm. These data are consistent with the presence of an imidate, leading to our structural assignment of **12** as shown below. This result is likewise consistent with experimental and computational studies from our group of related oxyallyl cation intermediates that implicate *O*-alkylation as the kinetically preferred product.³¹ Others have also observed similar phenomena.^{17,21,23,30} Subsequent rearrangement is postulated to deliver the lower energy *N*-alkylated product; although in this case, treatment of **12** with 2 equiv of TFA at room temperature for 1 h did not result in any rearrangement. At the moment, it is unclear why this is the only substrate that results in *O*-alkylation.

(1)

We then applied the methodology to the formal synthesis of the antihypertensive drug, irbesartan (**2**) (Scheme 3). The (3+2) annulation reaction between α -bromoamide **9b** and valeronitrile **8b** proceeded as expected to provide imidazolone **11o**. This was followed by cleavage of the N–O bond with SmI_2 to give an **13**, an intermediate which was used by Bernhart en route to the synthesis of irbesartan (**2**).³²

In conclusion, we have reported the first examples of (3+2) annulation reactions between nitriles and cyanamides to give imidazolones and 2-aminoimidazolone products. The isolation of imide products under certain conditions suggest that the mechanism may proceed via fast *O*-alkylation followed by subsequent rearrangement to the thermodynamically favored *N*-alkylated product. This method was applied to the formal synthesis of irbesartan (**2**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biologically-active compounds that contain the imidazolone and 2-aminoimidazolone core

Scheme 1.
 Synthesis of Imidazolones and 2-Aminoimidazolones

Scheme 2.
Reaction Scope

Scheme 3.
Formal Synthesis of Irbesartan (2)

Table 1

Optimization Studies

Entry	Base	Catalyst	Mol (%)	Solvent	Time (h)	Yield (%)
1	Na ₂ CO ₃	ZnBr ₂	10	HFIP	24	53
2	Na ₂ CO ₃	Cu(OAc) ₂	10	HFIP	24	95
3	Na ₂ CO ₃	NiBr ₂	10	HFIP	24	20
4	DIPEA	LiClO ₄	5	MeOH	24	94
5	Na ₂ CO ₃	—	—	HFIP	18	92
6	Na ₂ CO ₃	—	—	pPOH	18	95
7	Na ₂ CO ₃	—	—	MeOH	24	67