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New methods for the preparation of aryl 2-iminoimidazolidines

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ABSTRACT

A divergent strategy for the synthesis of 1-aryl- and 2-aryl-2-iminoimidazolidines is presented. Cyclization of *N*-Boc-*N*′-aryl-*N*″-(2-hydroxyethyl)guanidines in the presence of methanesulfonyl chloride and triethylamine or sodium hydride at 0 °C affords the corresponding 2-iminoimidazolidines in good yields.

During a recent series of biological studies, our group became interested in aryl 2-iminoimidazolidines as DNA minor groove binders for the potential treatment of cancer,[1] and as ligands of α-adrenergic receptors for the treatment of central nervous system disorders.[2] The aryl 2-iminoimidazolidine motif is often employed as an analogue of the guanidine functional group with increased steric bulk and hydrophobicity, and is found in several clinical adrenergic drugs including brimonidine (antiglaucoma) and clonidine (antihypertensive/anaesthetic). This heterocycle is also found in numerous natural products including the neurotoxic sodium channel blocker saxitoxin[3] and the closely-related analogues gonyautoxin[4] and zetekitotoxin AB.[5]

Several approaches to the synthesis of aryl 2-iminoimidazolidines have been reported, including a two-step method for simple unsubstituted compounds previously reported by our group.[6] Several other methods[7,8] construct the 2-iminoimidazolidine heterocycle via the reaction of a 1,2-diamine with an imine bearing two suitable leaving groups, or with cyanogen bromide.[9] Although this approach is often used for the preparation of optically active derivatives,[10] the introduction of the requisite functionality on the 1,2-diamine and imine components often necessitates a lengthy sequence of five or more synthetic steps from commercial starting materials.

We have previously described the preparation of unsubstituted aryl 2-iminoimidazolidines by the reaction of *N,N*′-*bis*-Boc protected imidazolidine-2-thione with an aromatic amine in the presence of $HgCl_2$ and a mild base.[6]

In the present work, we have expanded this procedure to the synthesis of 4-substituted-2-iminoimidazolidines through the use of 4-substituted imidazolidine-2-thiones **3**, which were prepared by two different procedures. Thus, 4-methylimidazolidin-2-thione (**3a**) was prepared via the 2-thiohydantoin derivative **1** of L-alanine following Scheme 1 (i),[11] while 4-(2-furyl)imidazolidin-2-thione (**3b**) was ultimately synthesized from 2-furfural according to literature procedures [see Scheme 1 (ii)].[12]

Compounds **3a** and **3b** were *bis*-Boc protected under standard conditions to afford the corresponding protected imidazolidin-2-thiones **4** (see Scheme in Table 1). In the presence of $HgCl_2$ and Et_3N, these substrates reacted readily with several aromatic amines to afford the expected *N,N*′-*bis*-Boc protected 2-iminoimidazolidines **5** in good yields, which were deprotected using 4 M HCl/1,4-dioxane to produce the desired 2-aryliminoimidazolidine hydrochloride salts **6**.

We initially hoped to incorporate the chirality of the parent amino acid, L-alanine into the final 2-iminoimidazolidine **6** as per Scheme 1 (i). However, preparation of the (*S*)-Mosher's acid derivative of **3a** revealed that epimerization had occurred during the reaction sequence and, therefore, the product 2-iminoimidazolidines were racemic (see Supplementary data). Moreover, the preparation of the requisite imidazolidine-2-thiones **3** remains an impediment to the expedient synthesis of the desired compounds **6**. Thus, we examined an alternative approach via the cyclization of (2-hydroxyethyl)guanidines **9**. The requisite guanidine was prepared by the reaction of *N*-Boc-*N*′-phenylthiourea (**7**) and 2-substituted-2-aminoethanol derivatives **8a–c** using our standard guanidylation procedure (Scheme 2).[13]

Many 2-aminoethanol derivatives **8** are available in high optical purity from commercial sources; alternatively, these compounds may be prepared via reduction of the corresponding amino acid

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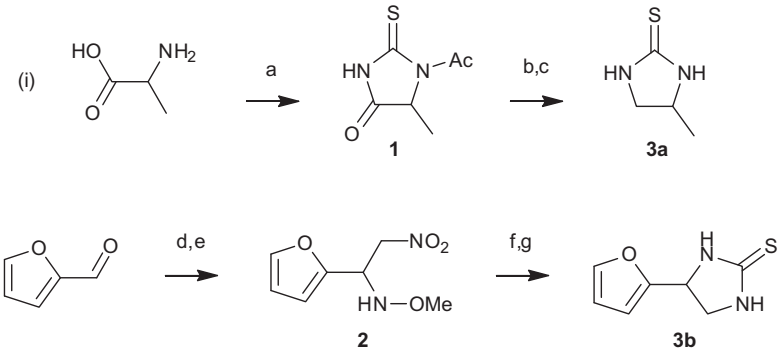
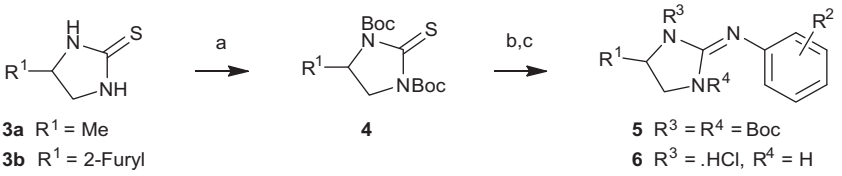


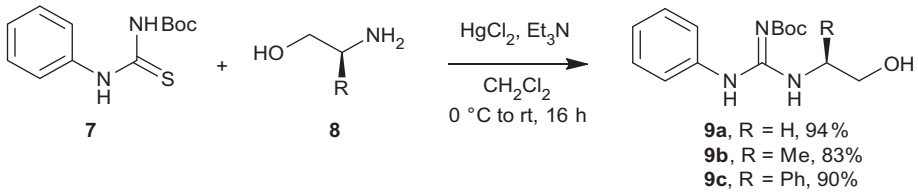
Scheme 1. Reagents and conditions: Preparation of imidazolidin-2-thiones **3a** (i) and **3b** (ii). (a) KNCS, Ac_2O, 75 °C, 1 h, 68%, (b) 4 M aq. HCl, μW 150 °C, 5 min, 99%, (c) $Me_2S.BH_3$, THF, 60 °C, 3.5 h, 53%, (d) 1. $MeNO_2$, NaOH, 2. HCl, MeOH/H_2O, 0 °C to rt, 0.5 h, 65%, (e) $MeONH_2$.HCl, $NaHCO_3$, THF/H_2O, rt, 16 h, 88%. (f) Zn/AcOH, 55 °C, 2 h, 78%. (g) 1,1′-thiocarbonyldiimidazole, Et_3N, CH_2Cl_2, rt, 1 h, 44%.

Table 1
Preparation of 2-aryliminoimidazolidines **6** from imidazolidine-2-thiones **3**



Entry	Product	R^1	R^2	Yield (%) (**5**)	Yield (%) (**6**)	Overall yield (%)
1	**6a**	2-Furyl	4-EtO	62	70	43
2	**6b**	2-Furyl	4-$N(CH_3)_2$	72	58	42
3	**6c**	2-Furyl	3,4-$(CH_2)_4$	74	60	44
4	**6d**	CH_3	4-EtO	65	76	49
5	**6e**	CH_3	4-$N(CH_3)_2$	78	71	55
6	**6f**	CH_3	3,4-$(CH_2)_4$	88	73	64

(a) NaH, Boc_2O, THF, 0 °C to rt, 3 h, 81% (**3a**), 84% (**3b**). (b) R2PhNH_2, $HgCl_2$, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h, 62–88%. (c) 4 M HCl/1,4-dioxane, CH_2Cl_2, 55 °C, 3.5 h, 58–76%.



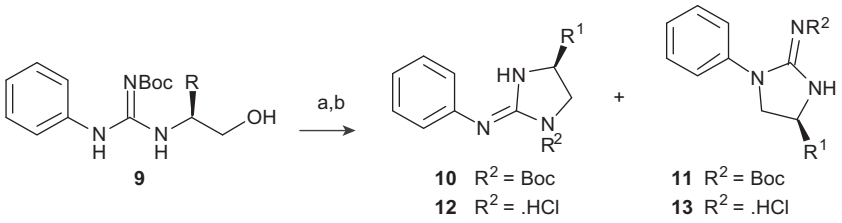
Scheme 2. Preparation of *N*-(2-hydroxyethyl)-*N′*-arylguanidines **9**.

with lithium aluminium hydride.[14] Exposure of **9** to MsCl in the presence of Et_3N at 0 °C led to the complete consumption of starting material within 0.5 h and the formation of two isomeric 2-iminoimidazolidine products, presumably via an unobserved *O*-mesylate intermediate. The two products could be readily separated using strongly basic chromatography (see Supplementary data). Using Et_3N as the base, 2-aryliminoimidazolidine product **10** was typically obtained as the major isomer, while the minor product corresponded to the 1-aryl-2-iminoimidazolidine isomer **11**. This assignment was confirmed by deprotection of the Boc groups using 4 M HCl in 1,4-dioxane followed by a comparison of their characterization data with values previously reported in the literature (Table 2, compounds **12a** and **13a**).

Notably, under these conditions the major isomer **10a** corresponds to the product of nucleophilic attack by the Boc protected nitrogen N2, while the minor isomer **11a** is formed through attack by the unprotected nitrogen N1 (numbering as per Fig. 1). This counterintuitive result can be explained by closely examining the lowest energy conformation of the starting material **9a**. For electronic reasons, the preferred tautomer of **9a** places the C=N double bond in conjugation with the electron-withdrawing Boc substituent.[15] This tautomer allows the formation of a strong intramolecular hydrogen bond (IMHB) between the Boc carbonyl oxygen O1 and the NH proton at N1, which is made slightly acidic by the adjoining phenyl group. This IMHB prevents N1 from readily attaining the correct angle of approach for nucleophilic attack, while N2 is now ideally positioned to react with the adjacent leaving group-bearing C1′ (Fig. 1); the prevalence of this conformation was supported by DFT calculations (B3LYP/6-31+G**). Similar IMHBs have also been observed in *bis*-Boc protected aryl guanidines, and their effects upon reactivity and conformation are an on-going subject of research within our group.[16]

It was speculated that the use of a much stronger base might negate the influence of the IMHB upon the outcome of this reaction

Table 2
Preparation of 2-aryl iminoimidazolidines **12** and 1-aryl-2-iminoimidazolidines **13** *via* the cyclization of (2-hydroxyethyl)guanidines **9**



Entry	Product	R^1	Base/solvent Step (a)	Yield (%) (**10**)	Yield (%) (**11**)	Ratio (**10**:**11**) step (a)	Yield (%) (**12**/**13**)	Overall yield (%)
1	**12a**	H	Et_3N/CH_2Cl_2	64	24	2.7:1	83	53
2	**12b**	Me	Et_3N/CH_2Cl_2	66	19	3.5:1	84	55
3	**12c**	Ph	Et_3N/CH_2Cl_2	61	21	2.9:1	87	53
4	**13a**	H	NaH/THF	13	52	1:4	80	42
5	**13b**	Me	NaH/THF	22	61	1:2.9	90	55
6	**13c**	Ph	NaH/THF	49	30[a]	1.6:1	96	29

(a) Et_3N/CH_2Cl_2 or NaH/THF, MsCl, 0 °C to rt, 0.5 h, 30– 66%. (b) 4 M HCl/1,4-dioxane, 55 °C, 3.5 h, 83–96%.
For entry 6, **11c** was the intended product of step (a), but **10c** remained as the major product of the reaction.

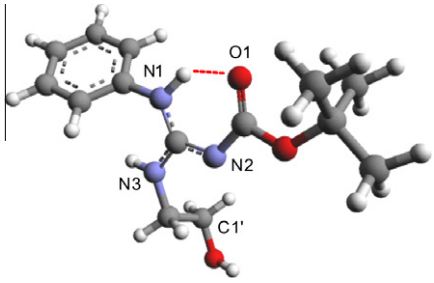


Figure 1. Optimized DFT structure of **9a** (B3LYP/6-31+G**) with intramolecular hydrogen bonding shown in red.[17]

through deprotonation of N1. In the event, carrying out the cyclization reaction with sodium hydride as the base typically led to an inversion of the ratio of product isomers (Table 2, entry 4). Interestingly, the use of the slightly weaker base NaHMDS afforded 47% of the 1-aryl isomer **10a** and 31% of **11a**. The reaction was also attempted with the very strong base, lithium diisopropylamide, however, using this reagent only led to a very poor conversion into the 2-aryl isomer **11a** and the majority of the starting material underwent decomposition to a complex mixture of side-products (TLC).

In the synthesis of 4-methyl-2-iminoimidazolidines **10b** and **11b**, the reactivity closely resembles that of unsubstituted species **10a** and **11a**. Using triethylamine in the cyclization reaction afforded the 2-aryl isomer **10b** as the major product, while switching to sodium hydride provided a 61% yield of the 1-aryl isomer **11b** (Table 2). Nevertheless, the synthesis of 4-phenyl-2-iminoimidazolidines proved less amenable to this type of control. In this instance, using triethylamine provided a 61% yield of the expected 2-aryl isomer **10c**, however, changing to sodium hydride afforded only a 30% yield of the 1-aryl isomer **11c** and **10c** remained the major product. This discrepancy might be attributable to the bulky phenyl substituent preventing the approach of the unprotected nitrogen N1, and, hence, attack by the less hindered nitrogen N2 remains preferred.

The cyclization products were readily deprotected in good to quantitative yields using 4 M HCl in 1,4-dioxane and the resulting hydrochloride salts were generally obtained in >95% purity (HPLC). The optical purity of the hydrochloride salt **13c** was examined by the preparation of the corresponding (*S*)-Mosher's acid derivative, which was confirmed to exist as a single diastereoisomer by comparison with its epimer, indicating that the chiral centre does not undergo racemization during this sequence of reactions (see Supplementary data).

In summary, we have developed new and expedient methods for the synthesis of 4-substituted aryl-2-iminoimidazolidines, including a divergent strategy for the synthesis of 1-aryl and 2-aryl-2-iminoimidazolidines. The cyclization of (2-hydroxyethyl)guanidines **9** also provides concise access to optically active 4-substituted derivatives, although the preparation of sterically hindered 1-aryl-2-iminoimidazolidines may be more difficult to control. The pharmacological activities of the product 2-iminoimidazolidine hydrochloride salts are currently under investigation and will be reported in subsequent publications.

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Supplementary data

Supplementary data (characterisation data and HPLC analysis of the final hydrochloride salts) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.042.

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