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A novel synthetic approach towards 2-guanidinomethyl-4(5)-sulfamoylimidazoles

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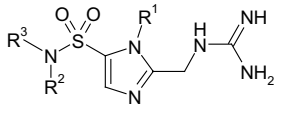
Abstract—A library of 2-guanidinomethyl-4(5)-sulfamoylimidazoles was synthesised in a convergent manner by introducing a sulfonyl chloride group via a trianion electrophilic sulfinylation of suitably protected 2-guanidinomethyl imidazoles.

As part of a collaborative effort to discover new inhibitors of certain serine proteases, an in silico design exercise has been carried out using the bespoke SKELGEN® software[1] to design molecules that should interact competitively at the target enzyme active sites. The nature of the SKELGEN® derived molecules was a combination of an imidazole template, a guanidine warhead and a sulfamoyl substituent suitable for diversity creation, which presented novel challenges to the synthetic chemist. Thus, whereas 4(5)-sulfamoylimidazoles have been reported on a limited number of occasions, when combined with substitution at the 2-position few examples have been described.[2] Herein, we can now describe the synthesis of a library of 2-guanidinomethyl-4(5)-sulfamoylimidazoles **1** in quantities and purities suitable for biological evaluation against the target enzymes.



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To synthesise a library of such sulfonamides **1** in an efficient fashion it was desirable to use a convergent approach and introduce the diversity at the latest possible stage to avoid multiple synthetic repetitions. It was envisaged that the best way to achieve this would be condensation of suitably protected 2-guanidinomethyl-5-sulfonyl chlorides with a number of diverse amines.

It was also envisaged that the sulfonyl chlorides would be synthesised from 2-guanidinomethylimidazoles, but that the ring nitrogen and exocyclic guanidine nitrogens would require protection. The protecting group selected for the guanidine nitrogens was *tert*-butoxycarbonyl (Boc).[3] 2-(Trimethylsilyl)ethoxymethyl (SEM)[4] was selected as a protecting group for the imidazole ring nitrogen when required. These were chosen primarily due to their expected ease of removal under mild acidic conditions as a final synthetic stage.

Conventional approaches for the introduction of a sulfonyl chloride group at the 4- or 5-position of an imidazole have involved the use of strongly acidic conditions, with chlorosulfonic acid being the reagent of choice.[2,5] Evidently, this methodology would not be compatible with either Boc or SEM protecting groups. An alternative method for the introduction of a sulfonyl chloride group into aryl and heteroaryl systems involves the reaction of a suitable Grignard reagent or lithium reagent with a suitable electrophile, such as sulfuryl chloride or sulfur dioxide followed by chlorination.[6,7] The use of lithium anion chemistry has been previously described

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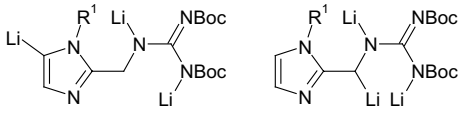
to capture electrophiles at the 5-position of *N*-substituted imidazoles, albeit only on simplified systems.[8] Thus it was decided to determine whether a trianion **2a** (which might be in equilibrium with **2b**) could be generated and captured by a suitable electrophile[6,7] at the 5-position of the *N*-substituted 2-(bis(Boc)-guanidino)methylimidazoles to provide the desired sulfonyl chlorides.



2a **2b**

Synthesis of suitably protected 2-guanidinomethyl imidazoles commenced from the known 2-formyl imidazoles **3a**,**b** (Scheme 1).[4a,9] Reaction of **3a**,**b** with hydroxylamine hydrochloride and pyridine in ethanol (v/v 85%), followed by reduction of the resultant oximes (which could be effected by reducing agents such as Raney Ni, H_2 or Zn in acetic acid) gave the desired amines (80–90%). These were subsequently reacted with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea[10] to give the protected 2-guanidinomethylimidazoles **4a**,**b** (40–45%). Treatment of the protected 2-guanidinomethylimidazole **4a** with 3 equiv of *n*-butyllithium was expected to provide the trianion **2a** and/or **2b**. Unfortunately, quenching with the electrophile dimethyl disulfide yielded the undesired regioisomer **5a** (27%) showing that the obtained trianion had, in fact, a structure better depicted as **2b**.

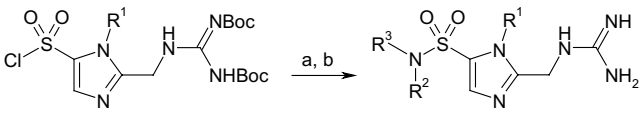
To prevent the capture of an electrophile at the methylene position, trimethylsilyl chloride (TMSCl) was added as a sacrificial electrophile to block derivatisation at this position.[8b,11] Thus, treatment of **4a** with *n*-butyllithium (3.5 equiv) followed by TMSCl (1 equiv), addition of *sec*-butyllithium,[8c,11] (1 equiv to deprotonate at the 5-position of the imidazole), and finally introduction of dimethyl disulfide to the desired trianion indeed gave the 5-substituted protected 2-guanidinomethylimidazole **6c** (20%).

These (unoptimised) reaction conditions were then applied to the suitably protected imidazoles **4a**,**b** with sulfur dioxide as the final electrophile, to generate the lithium salts of the respective 5-sulfinic acids. These sulfinic acids were oxidised in situ using sulfuryl chloride to give the desired sulfonyl chlorides, which were purified by silica gel column chromatography, thus providing the desired sulfonyl chlorides **6a** and **6b** in unoptimised yields (7% and 10%, respectively).

With the sulfonyl chlorides **6a**,**b** in hand, synthesis of the final library products was completed using the appropriate amines in the presence of triethylamine to give the desired protected sulfonamides.

Deprotection of the protected sulfonamides using hydrogen chloride in dioxane (4 M solution) gave the final products **1** as their corresponding HCl salts (Scheme 2). Table 1 shows yields and purities over the two final steps.

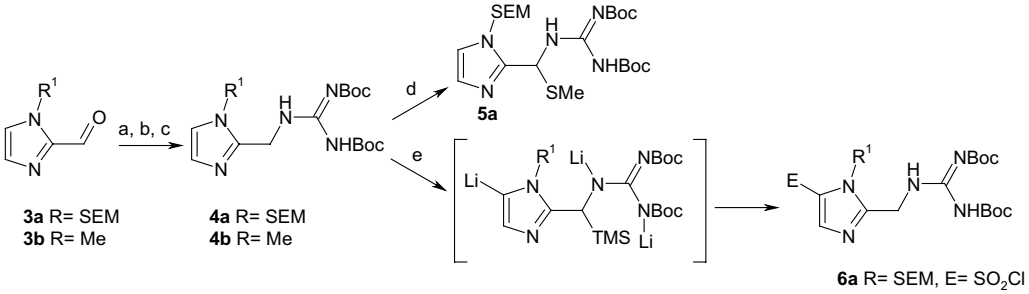
In summary, novel trianions of suitably protected 2-guanidinomethylimidazoles have been generated. These undergo electrophilic sulfinylation at the 5-position. These trianions have a trimethylsilyl group at the methylene position to prevent regioisomeric electrophile capture. The desired 5-sulfinic acids generated have been oxidised in situ to the corresponding sulfonyl chlorides. A library of 2-guanidinomethyl-4(5)-sulfamoylimidazoles, prospective serine protease inhibitors, has been synthesised.



6a R = SEM
6b R = Me

1

Scheme 2. Reagents and conditions: (a) $R^2R^3NH_2$, Et_3N, THF; (b) HCl, dioxane.



3a R= SEM
3b R= Me

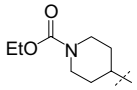
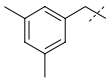
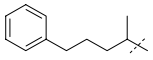
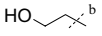
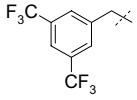
4a R= SEM
4b R= Me

5a

6a R= SEM, E= SO_2Cl
6b R= Me, E= SO_2Cl
6c R= SEM, E= SMe

Scheme 1. Reagents and conditions: (a) Py, NH_2OH, EtOH, 50 °C; (b) Zn, AcOH or Raney Ni, H_2, EtOH; (c) MSC(=NBoc)NHBoc, THF; (d) (i) 3 equiv *n*-BuLi, THF, (ii) MeSSMe; (e) (i) 3.5 equiv *n*-BuLi, THF, (ii) 1 equiv TMSCl, (iii) 1 equiv *sec*-BuLi, THF, (iv) MeSSMe or SO_2/H_2O, (v) SO_2Cl_2.

Table 1. 2-Guanidinomethyl-4-sulfamoylimidazoles **1**

Entry	R^1	R^2	R^3	Purity (%)	Yield[a]
1a	H	H	Me	95	46
1b	H	Me	Me	95	30
1c	H	Me		85	15
1d	H	H		95	51
1e	H	H		90	51
1f	H	H		85	38
1g	H	H		90	34
1h	H			90	19
1i	H			90	45
1j	Me	H		80	4
1k	Me	H		95	13

[a] Yields calculated assuming the products to be trihydrochloride salts.
[b] Structural integrity confirmed by HMBC and HMQC NMR experiments.

Acknowledgements

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