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Heterocycle Synthesis

Concise and Diversity-Oriented Route toward Polysubstituted 2-Aminoimidazole Alkaloids and Their Analogues

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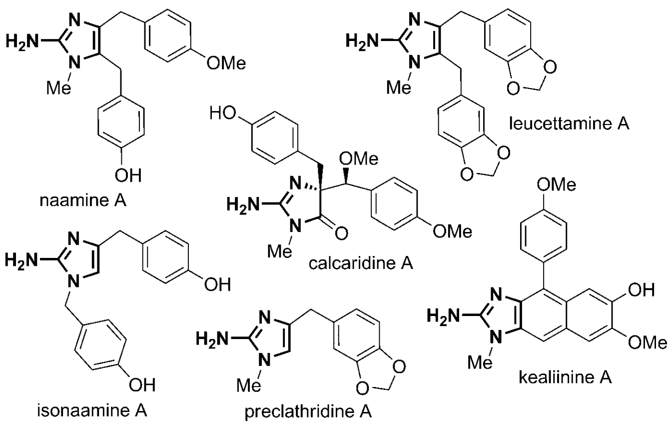
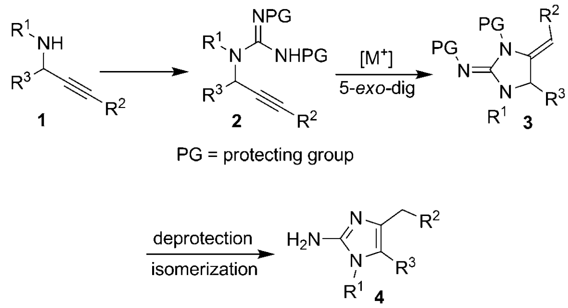
2-Aminoimidazole is emerging as an important pharmacophore. It is widely found in biologically active marine-sponge alkaloids (Scheme 1).[1] In particular, polysubstituted 2-aminoimidazoles have recently been reported as potent modulators of the formation and dispersion of bacterial biofilms,[2] human β-secretase (BACE1) inhibitors,[3] and tubulin-binding agents.[4] Although a variety of synthetic methods[1,5,6] for the preparation of highly functionalized 2-aminoimidazole core structures have been developed owing to the rising demand in natural product synthesis and medicinal chemistry, most of them involve long experimental procedures with many protection/deprotection steps and the use of unstable precursors, such as α-aminoketones,[6a] α-bromoaldehydes,[6b] and organomagnesium[6c] and organolithium[6d] compounds.



Scheme 1. Examples of polysubstituted 2-aminoimidazole marine-sponge alkaloids.

A recently reported synthesis of polysubstituted 2-dialkylaminoimidazoles through the lanthanide-mediated hydroamination of propargylic cyanamides is rather limited by the diversity and availability of the starting electron-rich secondary benzylamines as well as by the harsh reaction conditions.[7] Accordingly, the development of straightforward and general procedures for the synthesis of diversely substituted 2-aminoimidazoles from readily available precursors is highly warranted. Herein, we report a rapid and highly efficient silver(I)-mediated synthesis of 1,4,5-trisubstituted 2-aminoimidazoles from secondary propargylamines.

We envisioned that propargylguanidine **2** could be assembled from propargylamine **1** by using modern guanylation procedures (Scheme 2).[8] The subsequent intramolecular π-philic metal-catalyzed 5-*exo*-dig heterocyclization[9] of propargylguanidine **2** into the protected 2-iminoimidazoline **3** followed by deprotection and isomerization would provide the target 1,4,5-trisubstituted 2-aminoimidazole **4**.



Scheme 2. Synthesis of 1,4,5-substituted 2-aminoimidazoles from secondary propargylamines.

To the best of our knowledge, there is only one reported example of the formation of a 2-iminoimidazole from a secondary propargylamine and a thiourea.[10] It was obtained from a secondary propargylamine and a thiourea in the presence of HgO. Importantly, as we reported recently, the microwave-assisted copper(I)-catalyzed three-component coupling of an aldehyde, an alkyne, and a primary amine (A^3 coupling) provides direct access to diversely functionalized secondary propargylamines **1**.[11]

Initially, we focused on the guanylation of the sterically hindered propargylamines **1a–h** (Table 1, entries 1–8) with *N,N'*-bis-Boc-protected thiourea[12] **5** (1.35 equiv) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI; 2 equiv) and the Hünig base (3 equiv; Table 1, route A). The resulting propargylguanidines **2a–h** underwent cyclization in the presence of various catalysts. The desired Boc-protected 2-iminoimidazolines **3a–h** were formed in

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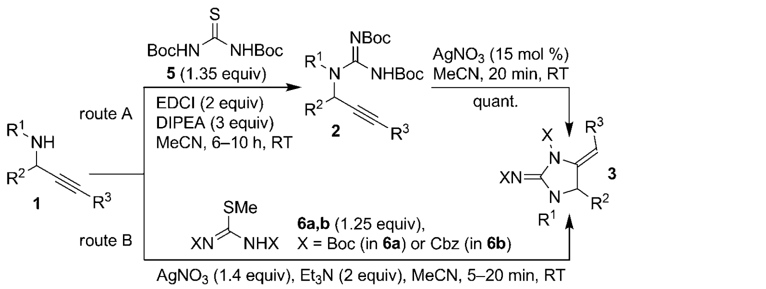
Table 1: Synthesis of the protected 2-iminoimidazolines from secondary propargylamines.[12]



Entry	3	X	R1	R2	R3	Yield [%][a]
1	**3a**	Boc	Me	H	H	100 (98)[b]
2	**3b**	Boc	Bn	*c*Pr	Ph	98 (94)[b]
3	**3c**	Boc	Bn	*n*Pr	Ph	86 (87)[b]
4	**3d**	Boc	Bn	*i*Pr	*p*-Tol	97 (91)[b]
5	**3e**	Boc	PMB	*p*-FC_6H_4	*t*BuC_6H_4	84 (81)[b]
6	**3f**	Boc	*c*-C_8H_{15}	*n*Am	Ph	88 (87)[b]
7	**3g**	Boc	*c*-$C_{12}H_{23}$	*i*Bu	Ph	77 (68)[b]
8	**3h**	Boc	*n*Bu	*i*Bu	*p*-Tol	98 (79)[b]
9	**3i**	Cbz	3,4-DMB	H	Me	84
10	**3j**	Cbz	Bn	*c*-C_6H_{11}	Ph	99
11	**3k**	Boc	Bn	Ph	*c*Pent	82
12	**3l**	Boc	Bn	*p*-Tol	*p*-$PentOC_6H_4$	80
13	**3m**	Boc	Bn	Ph	Bn	85
14	**3n**	Boc	(*S*)-1-$CHMeC_6H_5$	*c*-C_6H_{11}	PMP	79[c]
15	**3o**	Boc	*c*Bu	*c*Pr	*c*$PentCH_2$	83
16	**3p**	Cbz	Me	*p*-$BnOC_6H_4CH_2$	PMP	87
17	**3q**	Boc	*t*Bu	*i*Bu	Ph	86
18	**3r**	Boc	*c*-C_7H_{13}	*i*Bu	Ph	78
19	**3s**	Cbz	Bn	*n*Pr	Ph	95
20	**3t**	Boc	3-$MeOC_6H_4CH_2CH_2$	*i*Bu	Ph	99
21	**3u**	Cbz	Bn	*i*Pr	*p*-Tol	98
22	**3v**	Boc	*p*-Tol	*p*-FC_6H_4	Ph	84

[a] Yield of the isolated product prepared by route B. [b] Yield of the isolated product prepared by route A after two steps. [c] The yield was determined by ^1H NMR spectroscopy; d.r. 65:35. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy, DIPEA = *N*,*N*′-diisopropylethylamine, DMB = dimethoxybenzyl, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl.

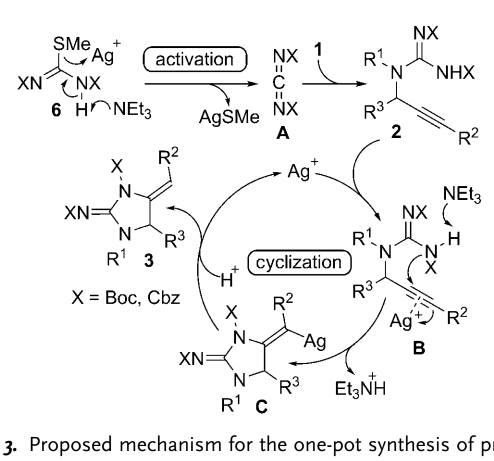
quantitative yield within 20 min when $AgNO_3$ (15 mol%) in MeCN was used. Comparable results were obtained with AgOTf or $Hg(OTf)_2$ (5–10 mol%), whereas other catalysts, such as $AuCl_3$, CuCl, CuBr, and $Cu(OTf)_2$ (Tf = trifluoromethanesulfonyl) were not efficient.[13] Our attempts to carry out guanylation and cyclization simultaneously with the Ag^I catalyst (15 mol%) failed, probably as a result of the formation of insoluble silver sulfide in the presence of **5**.

Surprisingly, when we attempted the guanylation[14] of propargylamines **1** with protected *S*-methylisothioureas **6** (1.25 equiv) in the presence of $AgNO_3$ (1.4 equiv) and Et_3N (2 equiv) in MeCN, the corresponding Boc- and Cbz-protected 2-iminoimidazolines **3a**–**v** were obtained in high yields in a single step within 5–20 minutes at room temperature (Table 1, route B). Remarkably, sterically hindered propargylamines underwent efficient cyclization (Table 1, entries 6, 7, 14, 17, and 18) as did an *N*-aryl propargylamine (entry 22).

We presumed that the reaction proceeds through a carbodiimide mechanism (Scheme 3).[15] In the first step, the protected *S*-methylisothiourea **6** undergoes silver(I)-promoted methylsulfide elimination in the presence of a base to form a reactive carbodiimide intermediate **A**. The addition of propargylamine **1** to carbodiimide **A** then gives the protected propargylguanidine intermediate **2**. Silver(I)-catalyzed cyclization and subsequent proton transfer to intermediate **C** finally provides the protected 2-iminoimidazoline **3**. The resulting insoluble AgSMe can be converted readily into $AgNO_3$ and reused.[13] Remarkably, the presence of Boc or Cbz protecting groups facilitates the key steps of the process: 1) the activation of thiourea toward methylsulfide elimination; 2) the activation of the carbodiimide toward the addition of the propargylamine; 3) the activation of the guanidine functionality toward the intramolecular hydroamination of the alkyne.

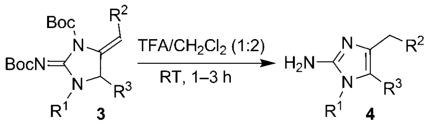
The Boc groups were removed by treatment with TFA/CH_2Cl_2 (1:2) at room temperature, and the desired 2-aminoimidazoles **4a**–**f** were isolated as the free bases in high yields (Table 2). 2-Aminoimidazoles **4a**–**f** were found to effectively inhibit biofilm formation by pathogenic *Salmonella* Typhimurium and *Pseudomonas aeruginosa* bacteria without a significant influence on planktonic growth (Table 2, entries 3, 5, and 6).[13] These results provide the first evidence of anti-biofilm activity[2] of N-substituted 2-aminoimidazoles against Gram-negative bacteria.

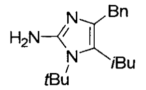
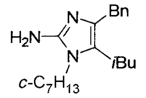
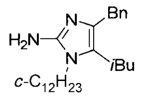
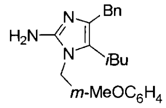
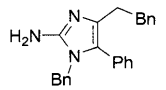
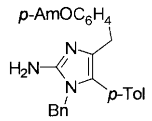
Next, we applied our protocol to the total synthesis of 1,4,5-trisubstituted 2-aminoimidazole alkaloids of the naamine family (Scheme 4). The starting *N*-methylpropargylamines **11a**–**f** were readily accessed through a microwave-assisted copper(I)-catalyzed A^3-coupling reaction[11] followed



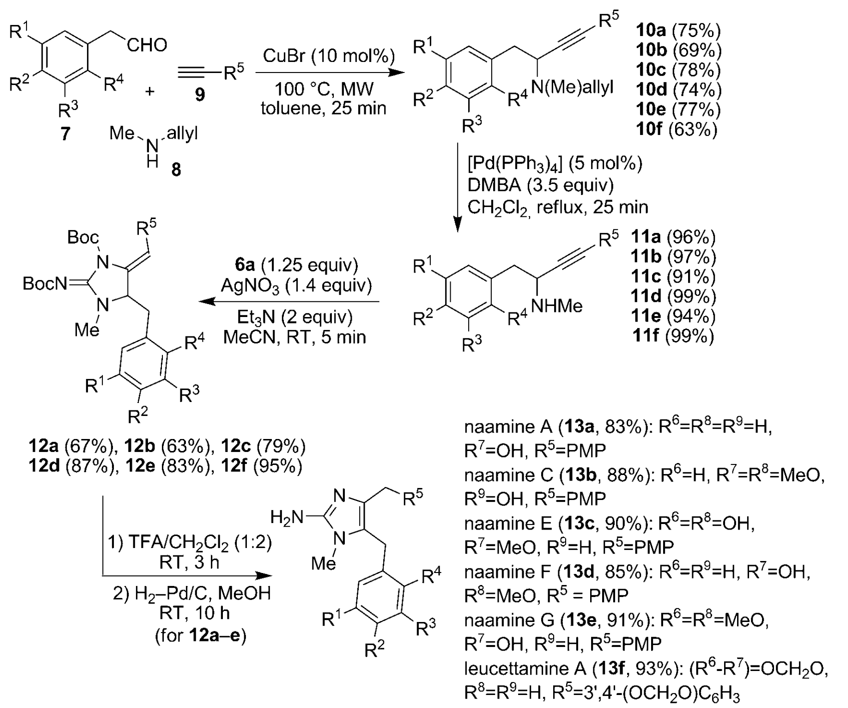
Scheme 3. Proposed mechanism for the one-pot synthesis of protected 2-iminoimidazolines **3** from propargylamines **1**.

Table 2: Deprotection[a] of bis-Boc-protected 2-iminoimidazolines **3** and inhibitory activity of the products against bacterial biofilm formation.



Entry	4		Yield [%][b]	IC50 [μM] S. Typhimurium ATCC14028	PA14
1		**4a**	85	42.4	377.1
2		**4b**	95	74.4	109.0
3		**4c**	78	18.3	17.4
4		**4d**	80	100.3	85.6
5		**4e**	75	20.1	19.8
6		**4f**	92	10.3	27.4

[a] Reaction conditions: **3** (0.2 mmol), TFA (2.0 mL), CH_2Cl_2 (4.0 mL), 1–3 h, room temperature. [b] Yield of the isolated product. TFA = trifluoroacetic acid.



Scheme 4. Short total synthesis of alkaloids of the naamine family. MW = microwave irradiation. See the Supporting Information for groups corresponding to R^{1-4}.

by palladium(0)-catalyzed deallylation in the presence of 1,3-dimethylbarbituric acid (DMBA). Silver(I)-promoted cycloguanylation of the propargylamines and subsequent removal of the Boc and Bn protecting groups (see the Supporting Information) provided the target naamines A, C, E–G (**13a**–**e**) and leucettamine A (**13f**) in high overall yields (Scheme 4).

In summary, we have described a novel short and efficient synthesis of diverse 2-aminoimidazoles from readily available polysubstituted secondary propargylamines and thioureas. Both the guanylation and the cyclization steps can be carried out either in a stepwise manner with a carbodiimide activator and an Ag^I catalyst or in a one-pot process with a recoverable Ag^I salt as a promoter and catalyst. This protocol was successfully applied to the total synthesis of all trisubstituted 2-aminoimidazole naamine alkaloids. Furthermore, we demonstrated the potential of polysubstituted 2-aminoimidazoles as inhibitors of bacterial biofilm formation. The synthesis of other 2-aminoimidazole alkaloids is currently under development.

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