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A Divergent Synthesis of Substituted 2-Aminoimidazoles from 2-Aminopyrimidines

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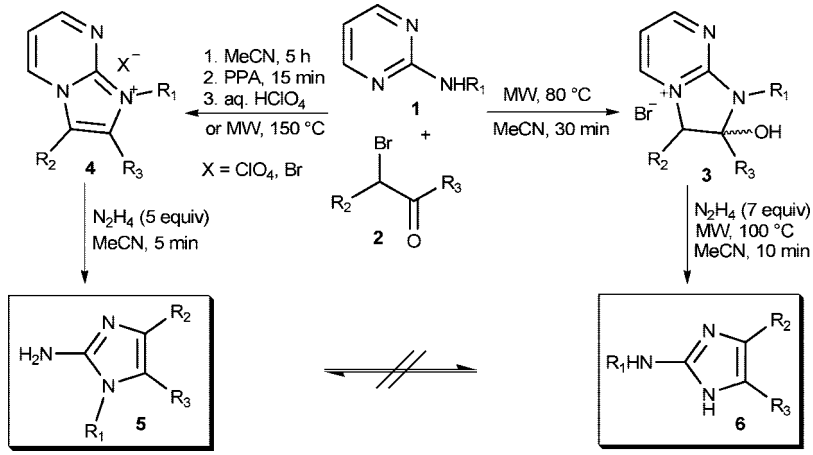

A new divergent and efficient synthesis of substituted 2-aminoimidazoles **5** and **6** has been developed starting from the readily available 2-aminopyrimidines **1** and α-bromocarbonyl compounds **2**, using conventional heating or microwave irradiation. Thus, the cleavage of 1,2,3-substituted imidazo[1,2-*a*]pyrimidin-1-ium salts **4** with hydrazine or secondary amines led to 1,4,5-trisubstituted 2-aminoimidazoles **5**, when the hydrazinolysis of 2-hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium salts **3**, followed by a novel Dimroth-type rearrangement, resulted in formation of 2-amino-1*H*-imidazoles **6**. The relevant pathway of transformations was identified by characterization of the intermediates.

Introduction

The class of 2-aminoimidazoles has recently been given particular interest due to various biological properties of these compounds and can be divided into 1-unsubstituted and 1-substituted 2-aminoimidazole scaffolds. 1-Unsubstituted 2-amino-1*H*-imidazole alkaloids and their metabolites, isolated from marine sponge *Hymeniacidon* sp., have been reported as potent antagonists of serotonergic[1] and histaminergic[2] receptors. Naamine and isonaamine alkaloids from the marine sponge *Leucetta* sp., as examples of 1-substituted 2-aminoimidazoles, have been reported to possess antiviral and anticancer activity.[3,4] Because of these interesting biological activities, numerous synthetic routes to 2-aminoimidazoles have been reported.

Modern synthetic methods of accessing 1-unsubstituted 2-amino-1*H*-imidazoles can be roughly classified as heterocyclization of substituted or protected guanidines with 1,2-

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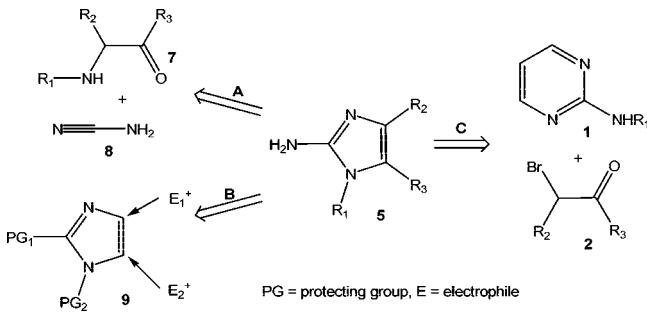
SCHEME 1



dielectrophiles,[5] heteroaromatic nucleophilic substitution,[5c,6] and recyclization of 2-aminooxazoles.[7] Although different substituted guanidines are readily available and can be prepared in situ (e.g., from cyanamines[8]), the high basicity of guanidines together with nonregioselectivity often leads to multiple products.[9] Protection by acetyl[5a] and Boc groups[5c] requires, in turn, acidic deprotection conditions. Another procedure is the cyclocondensation of aldehydes and guanidine nitrate using sodium cyanide and supported aluminum oxide, which provides 2-aminoimidazoles with identical substituents on positions 4 and 5 of the ring structure.[10] However, only a few approaches describe the direct synthesis of 1-substituted 2-aminoimidazoles, in particular, 1,4,5-trisubstituted 2-aminoimidazoles **5** (Scheme 1). The earliest method involves condensation of α-aminocarbonyl compounds **7** with cyanamide **8**, isothioureas, or their synthetic equivalents (route A) and appears to be the most popular method for the direct construction of the 2-aminoimidazole ring.[11,12] However, this reaction is strongly pH-sensitive and can lead to the self-condensation of α-amino aldehydes or ketones **7** resulting in the formation of symmetrical pyrazines.[13] Other general applicable strategies related to route A are the iminophosphorane-mediated cyclization of α-azido esters[14] and the ammonolysis of 2-amino-1,3-oxazol-3-ium salts.[15] Route B involves sequential functionalization of 1,2-diprotected imidazole ring **9** with different electrophiles and was realized by Ohta and co-workers in the total synthesis of marine sponge alkaloids.[16]

In a preliminary report,[17] we described the microwave-assisted procedure for the synthesis of 1,4,5-substituted 2-aminoimidazoles **5** (Scheme 1, route C). This one-pot, two-step protocol is based on the cyclocondensation of 2-aminopyrimidines **1** and α-bromocarbonyl compounds **2** at 130−150 °C, followed by the cleavage of the intermediary imidazo[1,2-*a*]pyrimidin-1-ium salts with an excess of hydrazine. We have recently re-examined this chemistry and present here a full account that addresses (1) the isolation and characterization of the intermediates in the synthesis of 1-substituted 2-aminoimidazoles, (2) the evaluation of the scope and limitations of the microwave-assisted protocol to a series of substrates related to the reported[18] marine sponge alkaloids, and (3) the development of a new approach for the synthesis of 2-amino-1*H*-imidazoles via a novel Dimroth-type rearrangement.

Results and Discussion

We found that the cyclocondensation of 2-aminopyrimidines **1** with α-bromoacetophenones **2** first led to stable 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyrimidin-4-ium bromides **3** (Table 1). The bicyclic nature of the structures **3** clearly followed from ^{1}H NMR data clearly indicating the multiplet of the methylene fragments, as well as from ^{13}C NMR spectra. Simultaneous ring closure to bicyclic hydrates was previously observed in other similar cases, e.g., for the cyclocondensation between α-bromo ketones and 2-alkylaminopyridines.[19] Remarkably, we never observed the formation of monocyclic *N*-phenacylpyrimidin-1-ium salts,[20] and our attempts to quaternize 2-dialkylaminopyrimidines (e.g., 2-(dimethylamino)pyrimidine and 2-(pyrrolidin-1-yl)pyrimidine) with different α-bromoacetophenones were not successful.

The salts **3a**−**g** were obtained in good and high yields (Table 1), and only for sterically hindered 2-aminopyrimidines did the yields slightly decrease (entries 4, 6, and 7). Dehydration of the salts **3a**−**g** was successfully achieved by short (15 min) heating in polyphosphoric acid at 150 °C. The corresponding imidazo[1,2-*a*]pyrimidin-1-ium salts **4a**−**g** were isolated and characterized as perchlorates, and in most cases, the yields were almost quantitative (Table 1).

The structures of aromatic salts **4** were completely consistent with their ^{1}H, ^{13}C, and DEPT NMR data. The cleavage of the imidazo[1,2-*a*]pyrimidin-1-ium salts **4a**−**g** was successfully performed using 3.5 equiv of piperidine in refluxing acetonitrile (Table 1). The reaction was completed in 45 min, and the resulting 2-aminoimidazoles **5a**−**g** were isolated after flash chromatography (CH_2Cl_2−MeOH, 9:1 v/v) in good yields (Table 1, entries 1−7).

Careful investigation of the pyrimidine ring cleavage in salts **4** along with isolation and characterization of the intermediates have been performed using piperidine or morpholine as nucleophiles. It was found that imidazo[1,2-*a*]pyrimidin-1-ium salts **4a**−**g** undergo ring-opening reaction at room temperature within 3 min in the presence of 3.5 equiv of secondary amine, giving new deeply colored azabutadienes **10a**−**g** in high yields (Table 1, entries 1−7). The imidazo[1,2-*a*]pyrimidin-1-ium salts **4**, bearing bulky substituents R_1 at the N-1 position, were found to be much more reactive toward nucleophilic attack and are thermally unstable (Table 1, entries **10d**−**g**).

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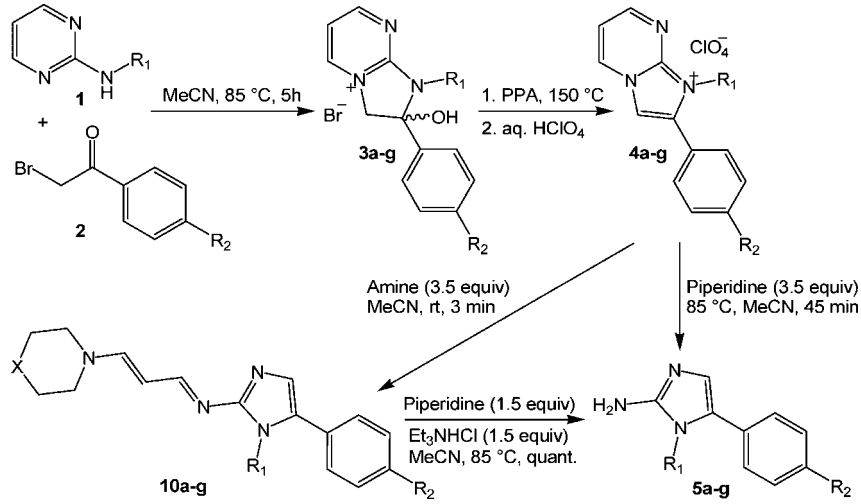
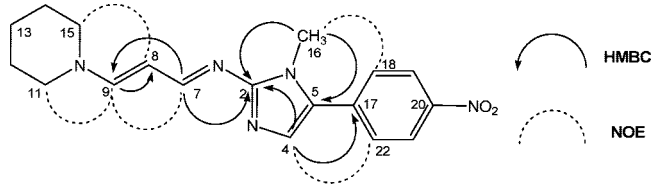
TABLE 1. Synthesis of 1,5-Substituted 2-Aminoimidazoles 5a−g and Azadienes 10a−g under Conventional Conditions



entry	compd	R_1	R_2	yield of **3**[a] (%)[b]	yield of **4**[c] (%)[b]	yield of **5**[d] (%)[b]	yield of **10**[d] (%)[b]	X
1	**a**	Me	F	88	93	86	67	CH_2
2	**b**	Me	NO_2	89	95	89	98	CH_2
3	**c**	Bn	Cl	75	83	84	89	CH_2
4	**d**	*i*-Pr	Ph	63	94	51	91	CH_2
5	**e**	cyclohexyl	CN	74	97	80	76	CH_2
6	**f**	cyclohexyl	Cl	67	81	75	84	O
7	**g**	cyclododecyl	NO_2	48	44	95	79	O

[a] Reactions were run on a 6 mmol scale of 2-alkylaminopyrimidine **1** with 1.2 equiv of α-bromo ketone **2** in 12 mL of MeCN in the presence of catalytic amounts of DMAP. [b] Isolated yields. [c] Reactions were run on a 3 mmol scale of salts **3**. [d] Reactions were run on a 1 mmol scale of salts **4**.

TABLE 2. NMR Data and NOE and HMBC Correlations of Azadiene 10b[a]



atom no.	δ_H (m, *J* in Hz)	δ_C (type)	NOESY[b]	HMBC (δ_H to δ_C)
2		156.0 (C)		
4	7.12 (s)	128.2 (CH)	18, 22	2, 17
5		129.4 (C)		
7	8.74 (d, 10.1)	164.1 (CH)	9	2, 9
8	5.50 (dd, 13.6, 10.1)	98.2 (CH)	11, 15	
9	6.90 (d, 12.8)	155.1 (CH)	11, 15	8
11, 15	3.28 (br)	25.5 (CH_2)	8, 9	13
12, 14	1.64 (br)	24.0 (CH_2)	11, 13, 15	12, 14
13	1.64 (br)	24.0 (CH_2)	11, 12, 14, 15	11, 15
16	3.68 (s, NCH_3)	30.8 (CH_3)	18, 22	2, 5
17		137.5 (C)		
18, 22	8.20 (d, 8.7)	126.7 (CH)	16, 19, 21	17
19, 21	7.52 (d, 8.7)	124.2 (CH)	18, 22	
20		145.8 (C)		

[a] $CDCl_3$, 400 MHz; δ are given in ppm. [b] NOESY correlations reported as ^1H to ^1H atom number.

Detailed analysis of the structure was performed for azabutadienes **10a−e** using 2D correlation NMR spectroscopy. The composition of the products was confirmed by HRMS. For example, ^{13}C NMR and DEPT spectra of the compound **10b** (Table 2) showed 18 carbons, indicating four quaternary carbons, eight methine, five methylene, and one methyl group. Its ^1H NMR spectrum was simple and showed signals for 21 protons, comprising signals of protons of the piperidine, azadiene, imidazole, and aryl moieties. The coupling constants in the ^1H NMR spectrum of **10b** support the all-(*E*) configuration of the azabutadiene motif. Finally, the structure **10b** was established by NOESY and HMBC correlations (Table 2).

A possible mechanism for the pyrimidine ring cleavage upon reaction of salts **4** with amines, involves the formation of azabutadienes **10** (Scheme 2). Initially, the imidazo[1,2-*a*]pyrimidin-1-ium salt **4** undergoes a nucleophilic attack by a first molecule of amine at its C-5 position. After rearrangement of the intermediate **A** and isomerization of the resulting **B**, (*E*,*E*)-azabutadiene **10** is formed. Initiated by protonation, the azabutadiene intermediate **C** in turn undergoes 1,4-addition with a

SCHEME 2. Proposed Mechanism for the Ring Opening and Cleavage Reaction of Imidazo[1,2-*a*]pyrimidin-1-ium Salts 4 with Amines

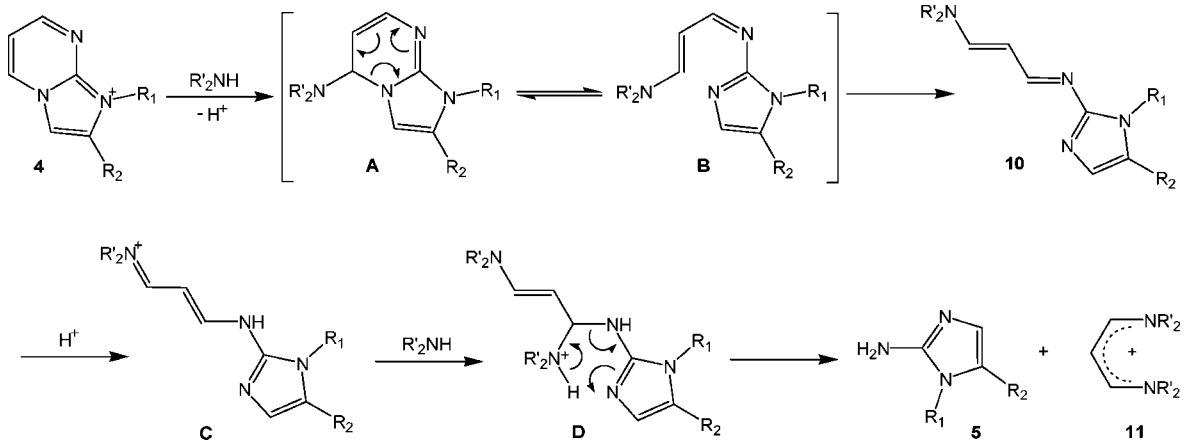
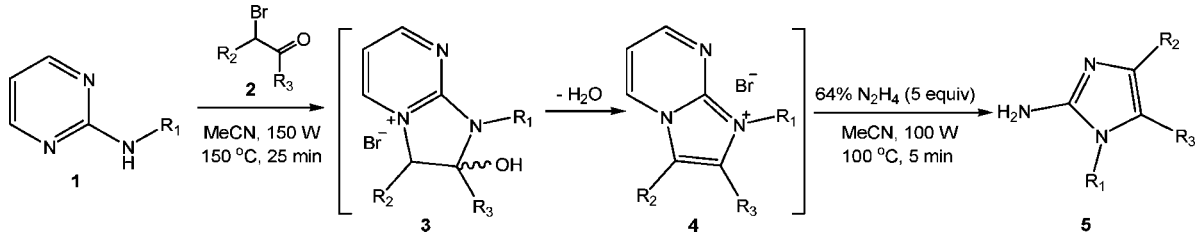


TABLE 3. One-Pot Two-Step Microwave-Assisted Synthesis of 1,4-, 1,5-, and 1,4,5-Substituted 2-Aminoimidazoles[a]



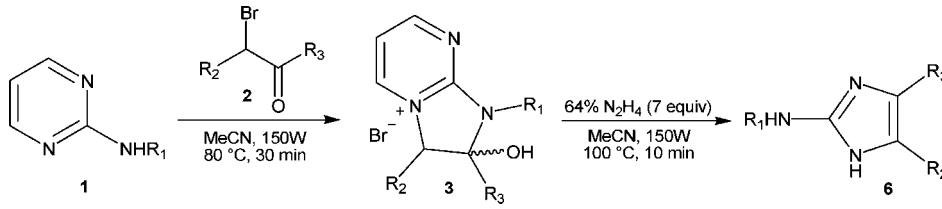
entry	imidazole	R_1	R_2	R_3	yield (%)[b]
1	**5h**	Me	H	4-ClPh	68
2	**5i**	Me	H	4-CNPh	73
3	**5j**	2′-BrBn	H	Ph	81
4	**5k**	3,4-diMeOPh$(CH_2)_2$	H	Ph	79
5	**5l**	4-MeOPh	H	4-CF_3Ph	46
6	**5m**	Me	Bn	H	88
7	**5n**	Bn	Bn	H	74
8	**5o**	Me	4-MeOPh	H	89
9	**5p**	Me	4-MeOBn	H	71
10	**5q**	4-MeOBn	4-MeOBn	H	59
11	**5r**	Pr	Me	4-FPh	71
12	**5s**	MeO$(CH_2)_2$	Me	4-BrPh	77
13	**5t**	Cyclohexyl	Ph	Ph	95
14	**5u**	*i*-Bu	4-MePh	4-ClPh	89
15	**5v**	Ph	4-MePh	4-ClPh	65

[a] All reactions were carried out on a 10 mmol scale of 2-alkylaminopyrimidine **1** with 1.35 equiv of α-bromocarbonyl compound **2** in 20 mL of MeCN. [b] Isolated yields.

second molecule of amine, finally resulting in the formation of 2-aminoimidazole **5** together with diazapentadienium salt **11**. Consistent with this mechanism, the corresponding imidazo[1,2-*a*]pyrimidin-1-ium salts **4** can directly be cleaved to 2-aminoimidazoles **5** upon stirring with a large excess of secondary amine (6 or more equiv) at room temperature, when the isolated azabutadienes **10a**−**g** appeared to be stable to 20 and more equivalents of piperidine in refluxing acetonitrile for 1 h. In contrary, azabutadienes **10a**−**g** were quantitatively cleaved to 2-aminoimidazoles **5a**−**g** in the presence of 1.5 equiv of triethylamine hydrochloride salt (Table 1).

To avoid the isolation of the intermediates and the use of strong acidic conditions in the synthesis of polysubstituted 2-aminoimidazoles **5**, we have developed a general microwave-assisted, one-pot, two-step procedure for the synthesis of 1,4-, 1,5-, and 1,4,5-substituted 2-aminoimidazoles (Table 3). Applying the optimized cyclization and dehydratation conditions,[17] we were able to expand the scope of α-bromocarbonyl compounds **2** from α-bromo acetophenones (entries 1−5) to α-bromo aldehydes (entries 6−10) and 1,2-disubstituted α-bromo ketones (entries 11−15). At the first step 2-aminopyrimidines **1** react with α-bromocarbonyl compounds **2** to give imidazo[1,2-*a*]pyrimidin-1-ium salts **4** (Table 3). At the next step, the cleavage of salts **4** was performed using excess hydrazine hydrate at 100 °C. The reaction conditions also allowed the incorporation of other functional groups, e.g., sensitive to acids 4-cyanophenyl (entry 2). The yields of 2-aminoimidazoles **5h**−**v** varied from good to excellent. Heterocyclization reactions of α-bromo aldehydes are hardly known due to their high reactivity. Nevertheless, we were even able to generate the corresponding 1,4-disubstituted 2-aminoimidazoles **5m**−**q** in high yields by applying our microwave-assisted protocol (Table 3, entries 6−10). The compounds bearing two aromatic substituents at positions 4 and 5 of the imidazole ring precipitated directly from the reaction mixture as white crystals (Table 3, entries 11−15).

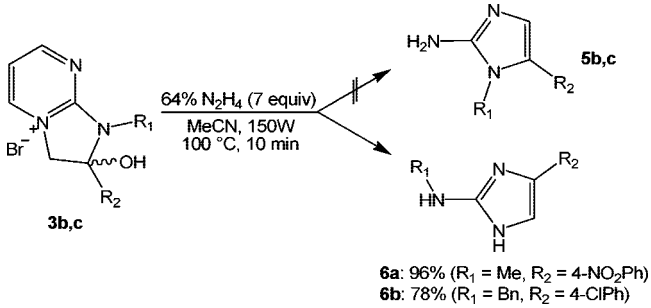
TABLE 4. Microwave-Assisted Synthesis of 2-Amino-1*H*-imidazoles 6c−n



entry	product[a] **3**	product [b] **6**	R_1	R_2	morpholin-4-ylcarbonyl	yield of **3** (%)[c]	yield of **6** (%)[c]
1	**h**	**c**	H	H	4-CNPh	76	54
2	**i**	**d**	H	H	4-NO_2Ph	67	83
3	**j**	**e**	Et	H	CONHEt	89	67
4	**k**	**f**	cyclopropyl	H	Morpholin-4-ylcarbonyl	65	98
5	**l**	**g**	cyclohexyl	H	3-NO_2Ph	90	84
6	**m**	**h**	cyclododecyl	H	3-NO_2Ph	68	75
7	**n**	**i**	4-MeOBn	H	4-NO_2Ph	53	95
8	**o**	**j**	piperonyl	H	4-FPh	89	76
9	**p**	**k**	hexyl	Me	Ph	65	98
10	**q**	**l**	$MeO(CH_2)_2$	Me	4-FPh	89	89
11	**r**	**m**	homoveratryl	Ph	4-ClPh	47	91
12	**s**	**n**	*t*-Bu	4-tolyl	4-ClPh	73	87

[a] All reactions were run on a 5 mmol scale of 2-alkylaminopyrimidine **1** with 1.2 equiv of α-bromo ketone **2** in 15 mL of MeCN in the presence of catalytic amounts of DMAP. [b] All reactions were run on a 2 mmol scale of salt **3** in 5 mL of MeCN. [c] Isolated yields.

SCHEME 3. Formation of 2-Amino-1*H*-imidazoles 6a,b



Next, we subjected the isolated intermediate 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyrimidin-4-ium salts **3b** and **3c** to microwave irradiation in the presence of 7 equiv of hydrazine hydrate at 100 °C for 10 min (Scheme 3).

To our surprise, the cleavage of these salts resulted in the formation of isomeric 2-amino-1*H*-imidazoles **6a** and **6b**. Interestingly, no interconversion was observed between the 1-substituted 2-aminoimidazoles **5** and their 1-unsubstituted isomers **6** under the reaction conditions applied. The structures of two 2-amino-1*H*-imidazoles **6a** and **6b** were established by NOESY and HMBC correlations (Figure 1).

In the ^{1}H NMR spectra of the products **6a**,**b**, the chemical shift of the *endo*-NH_a of the imidazole ring is situated between 10.5−11.0 ppm while for the *exo*-NH_b values between 4.3−6.5 ppm were detected.[5a] This observation, together with the existence of H_b−H_c couplings, are proof for the proposed 2-amino-1*H*-imidazole structure. In the ^{13}C NMR spectra of the products **6a**−**n** (Scheme 3 and Table 4), the signals of C-4 and C-5 of the imidazole ring appeared as broad peaks or were even not detected, presumably, due to the fast proton exchange in 2-amino-1*H*-imidazoles between N-1 and N-3.[5a]

Hence, we started our investigation of this new reaction by examining the heterocyclization of the parent 2-aminopyrimidines **1** with α-bromo ketones **2** at moderate temperature. The optimized two-step protocol was successfully applied to synthesize 12 substituted 2-amino-1*H*-imidazoles **6c**−**n** (Table 4). Irradiating an acetonitrile solution of 2-aminopyrimidines **1** with

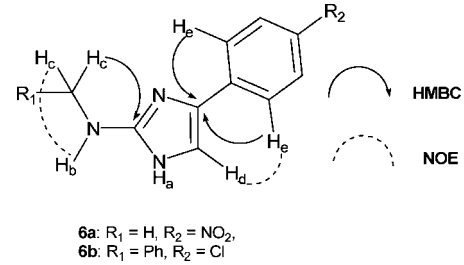


FIGURE 1. HMBC and NOE correlations for compounds **6a** and **6b**.

1.2 equiv of α-bromo ketones **2** afforded 2-hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium salts **3h**−**s** in good or excellent yields (Table 4). The cleavage step was performed under microwave irradiation at 100 °C, using 7 equiv of hydrazine hydrate. The resulting 2-amino-1*H*-imidazoles **6c**−**n** were obtained in high yields. Importantly, secondary and tertiary amide functions survived cleavage conditions, and the corresponding 2-amino-1*H*-imidazoles **6e**,**f** were obtained in 67% and 98% yields, respectively (entries 3 and 4, Table 4).

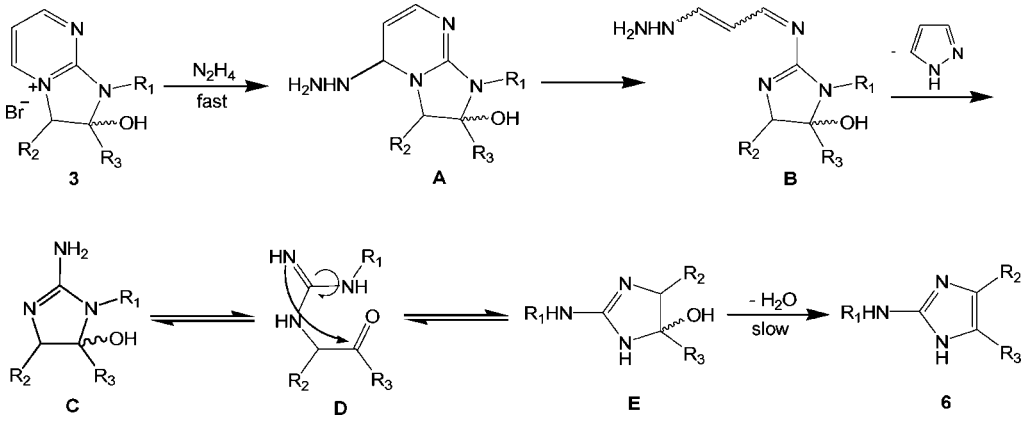
All the intermediary salts **3h**−**s** and the final 2-amino-1*H*-imidazoles **6a**−**n** were characterized by ^{1}H and ^{13}C NMR spectroscopy. The composition of 2-amino-1*H*-imidazoles **6a**−**n** was also confirmed by HRMS.

Regarding the mechanism of the transformation of 2-hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium salts **3** into 2-amino-1*H*-imidazoles **6**, we presume that the reaction proceeds via an unusual Dimroth-type rearrangement[21] (Scheme 4).

In the first step, the 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyrimidinium salt **3** undergoes cleavage of the pyrimidine ring, resulting in the generation of pyrazole and 2-amino-5-hydroxyimidazolidine **C**, which is in equilibrium with the open form **D**. This can cyclize again leading to the isomeric 2-amino-5(4)-hydroxyimidazolidines **E**. Both isomers **C** and **E** were detected

(21) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. *Adv. Heterocycl. Chem.* **1999**, *75*, 79. (a) Wahren, M. *Z. Chem.* **1969**, *9*, 241. (b) Brown, D. J. *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1968; Vol. 1, pp 209.

SCHEME 4. Proposed Mechanism for the Dimroth-Type Rearrangement of 2-Hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium Salts



by mass spectrometry. Final dehydration upon microwave irradiation results in the rearranged 2-amino-1*H*-imidazoles **6**. This dehydration step, as judged by mass spectra, was found to be the slowest step of the transformation. While some 2-amino-5(4)-hydroxyimidazolidines **E** lost water spontaneously at room temperature, others required higher temperature upon microwave irradiation. Therefore, all of the reactions were run at 100 °C, preventing the sequence from stopping after the first step (Scheme 4).

Conclusion

In summary, two novel and complimentary methods for the synthesis of functionalized 1-substituted and 1-unsubstituted and 2-aminoimidazoles **5** and **6** have been developed, applying 2-aminopyrimidines **1** as protected and substituted guanidines in a cyclocondensation reaction with α-bromo carbonyl compounds. The cleavage of the intermediate imidazo[1,2-*a*]pyrimidin-1-ium salts **4** with hydrazine hydrate gives access to 1,4,5-substituted 2-aminoimidazoles **5**, while the reaction with secondary amines at room temperature leads to novel azabutadienes **10**. The cleavage of 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyrimidinium salts **3** by hydrazine is believed to be followed by a Dimroth-type rearrangement via in situ generated 2-amino-5-hydroxyimidazolidines, resulting in the formation of 2-amino-1*H*-imidazoles **6**. Finally, this general methodology provides an efficient and practical route for the synthesis of analogues of different bioactive marine alkaloids, possessing a 2-aminoimidazole skeleton. Further research is in progress.

Experimental Section

Representative Procedure for the Synthesis of 3a−g (with 3d as an Example). To a solution of 2-isopropylaminopyrimidine (0.83 g, 6 mmol) and 1-(1,1′-biphenyl-4-yl)-2-bromoethanone (2.0 g, 7.2 mmol, 1.2 equiv) in acetonitrile (12 mL) was added 4-dimethylaminopyridine (6 mg, 0.05 mmol). After being stirred at 85 °C for 5 h, the reaction mixture was diluted with acetone (20 mL), and the precipitate was filtered, washed with acetone (2 × 20 mL) and ether (2 × 20 mL), and dried over P_2O_5 to give **3d** (1.78 g, 63% yield) as a white solid.

2-(1,1′-Biphenyl-4-yl)-2-hydroxy-1-isopropyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium bromide (3d). mp 272−274 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (m, 1H), 7.98 (s, 1H), 7.78 (m, 6H), 7.39 (m, 4H), 4.87 (dd, J = 33.8, 14.6 Hz, 2H), 3.45 (m, 1H), 1.45 (d, J = 6.4 Hz, 2H), 1.27 (d, J = 6.4 Hz, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.7, 154.8, 149.3, 141.7, 140.1, 138.7, 130.1, 129.9 (×2), 128.7, 128.6 (×2), 127.9, 127.7 (×2), 127.5 (×2), 111.7, 92.3, 63.5, 47.2, 22.4, 20.7, 20.3; DEPT-135 (75.5 MHz, DMSO-d_6) δ 167.6, 149.3, 129.9 (×2), 128.7, 128.6 (×2), 127.7 (×2), 127.5 (×2), 111.7, −63.5, 47.2, 20.7, 20.3; MS (*m*/*z*) 366 [(M − Br + CO)]$^+$, 338 [(M − Br)]$^+$, 230 [(M − Br − OH − *i*-Pr)]$^+$.

General Procedure for the Synthesis of 4a−g (with 4d as an Example). A mixture of 84% polyphosphoric acid (3 g) and **3d** (1.24 g, 3 mmol) was heated in 50 mL beaker upon intensive stirring at 150 °C for 15 min. After being cooled to room temperature, the resulting viscous mass was dissolved in 30 mL of water, and 1 mL (10 mmol) of 70% $HClO_4$ was added dropwise upon mild stirring. The white precipitate was washed with distilled water (3 × 10 mL) and ether (2 × 10 mL) until a neutral reaction showed on pH paper and then dried over P_2O_5 to give salt **4d** (1.17 g, 94% yield) as fine white crystals.

2-(1,1′-Biphenyl-4-yl)-1-isopropylimidazo[1,2-*a*]pyrimidin-1-ium perchlorate (4d). mp 193−195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (br, 1H), 8.58 (br, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.77 (m, 5H), 7.56−7.45 (m, 3H), 4.82 (t, J = 6.4 Hz, 1H), 1.70 (d, J = 6.4 Hz, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.7, 143.4, 142.8, 139.7, 139.4, 137.6, 131.6, 131.6 (×2), 130.1 (×2), 129.2, 128.5 (×2), 127.8 (×2), 125.3, 115.2, 112.3, 51.8, 21.3 (×2); MS (*m*/*z*) 271 [(M − ClO_4 − i-Pr)]$^+$.

General Procedure for the Synthesis of 5a−g (with 5d as an Example). To a solution of **4d** (1 mmol, 414 mg) in acetonitrile (10 mL) was added piperidine (168 μL, 3.5 mmol, 3.5 equiv), and the reaction mixture was refluxed at 85 °C for 45 min upon vigorous stirring. After being cooled to room temperature, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (2 × 100 mL). The combined organic extracts were then washed with 3 M NH_4Cl (1 × 100 mL), brine (2 × 100 mL), and water (2 × 100 mL). The organic phase was dried over Na_2SO_4, and then the solvent was removed at reduced pressure and the residue was subjected to the flash column chromatography (silica gel; CH_2Cl−-MeOH, 9:1 v/v) to give **5d** (141 mg, 56% yield) as colorless crystals.

5-(1,1′-Biphenyl-4-yl)-1-isopropyl-1*H*-imidazol-2-amine (5d). mp >350 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 (m, 4H), 7.48−7.22 (m, 5H), 6.45 (s, 1H), 5.29 (br, 2H), 4.27 (m, 1H), 1.39 (d, J = 5.8 Hz, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 151.1, 140.6, 139.1, 131.6, 129.9 (×2), 129.5 (×2), 128.5, 128.3, 127.7 (×2), 127.4 (×2), 124.5, 46.9, 21.5 (×2); HRMS-EI *m*/*z* [M]$^+$ calcd for $C_{18}H_{19}N_3$ 277.1579, found 277.1578.

General Procedure for the Synthesis of 10a−g (with 10d as an Example). Perchlorate salt **4d** (414 mg, 1 mmol) was dissolved in acetonitrile (5 mL), piperidine (280 μL, 3.5 mmol, 3.5 equiv) was added to the solution dropwise, and the reaction mixture was stirred for 10 min at room temperature. After 3 min,

a deeply colored solid began to precipitate, and the reaction mixture was poured in dichloromethane (100 mL), washed with water (4 × 100 mL) and brine (2 × 100 mL), and dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was subjected to the flash chromatography on silica gel, using dichloromethane as an eluent to give **10d** (363 mg, 91% yield) as bright yellow needles.

5-(1,1′-Biphenyl-4-yl)-1-isopropyl-*N*-[(1*E*,2*E*)-3-piperidin-1-ylprop-2-enylidene]-1*H*-imidazol-2-amine (10d). mp 219−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 9.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 6H), 7.42 (m, 6H), 7.32 (m, 1H), 6.83 (m, 2H), 5.50 (dd, J = 13.0, 9.8 Hz, 1H), 4.56 (m, 1H), 3.24 (br, 6H), 1.63 (br, 4H), 1.55 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.2, 153.8, 140.6, 140.0, 131.0, 130.8, 129.6 (×2), 128.8 (×2), 127.4 (×2), 127.1, 127.0 (×2), 125.2, 98.7, 47.4, 25.5, 24.1, 22.3 (×2); DEPT-135 (100 MHz, $CDCl_3$) δ 162.0, 153.8, 129.6 (×2), 128.8 (×2), 127.4, 127.1 (×2), 127.0 (×2), 125.2, 98.7, 47.4, 25.5, 24.1, 22.2 (×2); HRMS-EI m/z $[M]^+$ calcd for $C_{26}H_{30}N_4$ 398.2471, found 398.2461.

General Procedure for the Microwave-Assisted Synthesis of 5h−v (with 5h as an Example). In a 30 mL microwave vial were successively brought dry acetonitrile (20 mL), 2-methylaminopyrimidine (1.09 g, 10 mmol), and 4-chlorophenacyl bromide (3.15 g, 13.5 mmol). The reaction tube was sealed and irradiated a microwave reactor at a ceiling temperature of 150 °C at 150 W maximum power for 25 min. After the reaction mixture was cooled with an air flow for 15 min, hydrazine hydrate (2.5 mL, 50 mmol of a 64% solution) was added, and the mixture was irradiated at 100 W 100 °C for another 5 min at a ceiling temperature of 100 °C at 100 W maximum power. The reaction was worked up by diluting with dichloromethane (300 mL), washing with satd NH_4Cl solution (150 mL), brine (150 mL), and water (2 × 150 mL), and drying over anhydrous Na_2SO_4. After filtration and concentration, the resulting residue was purified by column chromatography (silica gel; CH_2Cl_2−MeOH, 9:1 v/v with 3% TEA) to afford **5h** (1.41 g, 68% yield) as colorless plates.

5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-amine (5h): mp 179−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.34 (m, 4H), 6.70 (s, 1H), 4.05 (br, 2H), 3.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.8, 131.4, 130.8, 129.5 (×2), 128.9 (×2), 127.5, 124.6, 31.4; HR-MS (EI) $C_{10}H_{10}ClN_3$ calcd 207.0563, found 207.0571.

General Procedure for the Microwave-Assisted Synthesis of 3h−s (with 3o as an Example). In a 30 mL microwave vial were successively brought acetonitrile (15 mL), *N*-(1,3-benzodioxol-5-ylmethyl)pyrimidin-2-amine (1.15 g, 5 mmol), 4-fluorophenacyl bromide (1.3 g, 6 mmol, 1.2 equiv), and a catalytic amount of 4-dimethylaminopyridine (6 mg, 0.05 mmol). The reaction tube was sealed and irradiated in a microwave reactor at a ceiling temperature of 80 °C at 150 W maximum power for 30 min. After the reaction mixture was cooled with an air flow for 15 min, the precipitate was washed with acetone (25 mL), ether (20 mL) and dried in vacuum to afford **3o** (1.98 g, 89% yield) as a white powder.

1-Benzo[1,3]dioxol-5-ylmethyl-2-(4-fluorophenyl)-2-hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-4-ium bromide (3o). mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (m, 1H), 8.96 (m, 1H), 7.97 (s, 1H), 7.73 (m, 2H), 7.39 (t, J = 5.2 Hz, 1H), 7.18 (t, J = 8.6 Hz, 2H), 6.68 (d, J = 7.7 Hz, 1H), 6.62 (s, 1H), 6.48 (d, J = 7.8 Hz, 2H), 5.92 (d, J = 3.2 Hz, 2H), 4.90 (s, 2H), 4.48 (d, J = 15.9 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.5, 164.9, 161.7, 155.7, 149.3, 147.8, 147.2, 134.8, 130.7, 130.5, 130.3, 122.2, 115.9, 115.6, 112.7, 109.1, 108.6, 101.7, 91.3, 63.5, 44.5; MS (m/z) 366 $[(M - Br)]^+$, 214 $[(M - Br - OH - piperonyl)]^+$.

General Procedure for the Microwave-Assisted Synthesis of 6a−t (with 6j as an Example). To a suspension of salt **3** (2 mmol) in acetonitrile (5 mL) was added hydrazine hydrate (0.7 mL, 14 mmol of a 64% solution, 7 equiv), and the mixture was irradiated in the sealed reaction tube for 10 min at a ceiling temperature of 100 °C at 150 W maximum power. After the mixture was cooled, hydrazine hydrate was evaporated with toluene (3 × 20 mL). The resulting residue was purified by column chromatography (silica gel; MeOH−DCM 1:4 v/v with 5% of 6 M NH_3 in MeOH) to afford 2-amino-1*H*-imidazole **6j** (473 mg, 76% yield) as an amorphous solid.

Benzo[1,3]dioxol-5-ylmethyl-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]amine (6j). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.51 (br, 1H), 7.62 (t, J = 7.0 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 11.7 Hz, 2H), 6.85 (m, 2H), 6.22 (t, J = 6.3 Hz, 1H), 5.96 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 151.8, 148.8, 147.9, 146.8, 135.4, 132.0, 129.2, 126.0, 121.5, 116.1, 114.7, 108.9 (×2), 101.6 (×2), 63.9, 45.1; HRMS-EI: m/z $[M]^+$ calcd for $C_{17}H_{14}FN_3O_2$ 311.1070, found 311.1066.

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Supporting Information Available: Experimental details for compounds **1**; spectral and analytical data for compounds **1**, **3**−**6**, and **10**; copies of ^{1}H NMR and ^{13}C NMR spectra of **1**, **3**−**6**, and **10**; copies of 2D NMR (NOESY, HMBC) spectra for **6a**,**b** and **10a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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