Tetrahedron Letters 50 (2009) 5218–5220

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted synthesis of substituted 2-amino-1*H*-imidazoles from imidazo[1,2-*a*]pyrimidines

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ARTICLE INFO

Article history:
Received 21 April 2009
Revised 24 June 2009
Accepted 29 June 2009
Available online 3 July 2009

Keywords:
Imidazo[1,2-*a*]pyrimidines
Substituted 2-amino-1*H*-imidazoles
Microwave-assisted reaction
Hydrazinolysis
Ring cleavage

ABSTRACT

An efficient method for the synthesis of mono- and disubstituted 2-amino-1*H*-imidazoles via microwave-assisted hydrazinolysis of substituted imidazo[1,2-*a*]pyrimidines is reported. This protocol avoids strong acidic conditions and is superior to the classical cyclocondensation of α-haloketones with *N*-acetylguanidine.

The 2-amino-1*H*-imidazole motif, which is common in all members of the oroidin family of marine sponge alkaloids,[1] constitutes an important class of potent antagonists of serotonergic and histaminergic receptors.[2] Very recently, it was demonstrated that naturally occurring 2-amino-1*H*-imidazoles and their synthetic analogues inhibit and disperse bacterial biofilms through a non-bactericidal mechanism.[3] Because of these interesting biological properties, numerous synthetic routes to 2-amino-1*H*-imidazoles have been reported.[4]

Modern synthetic methods for accessing 1-unsubstituted 2-amino-1*H*-imidazoles can be classified as heterocyclization of substituted or protected guanidines with 1,2-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 non-regioselectivity of the reaction 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 aluminium oxide, which provides 2-aminoimidazoles with identical substituents on positions 4 and 5 of the ring structure.[10]

An interesting microwave-assisted protocol was developed by Lam and co-workers for the construction of 2-amino-1*H*-imidazoles **1** from readily available *N*-acetylguanidine (**2**) and α-haloketones **3** (Scheme 1, route A).[4] Unfortunately, strong acidic conditions required for the deacetylation of the final products and limited availability of the starting 1,2-diaryl-α-haloketones significantly narrow the scope of the method.

Recently, we described the microwave-assisted procedure for the synthesis of polysubstituted 2-aminoimidazoles **1**.[11] This protocol is based on the cyclocondensation of 2-aminopyrimidines and α-bromocarbonyl compounds **3** at elevated temperature, followed by the cleavage of the intermediary imidazo[1,2-*a*]pyrimidin-1-ium salts **4** with excess of hydrazine (Scheme 1, route B). In this approach to 1-substituted 2-aminoimidazoles we used readily available substituted 2-aminopyrimidines as the masked guanidine function for the construction of the imidazole ring.[12]

Herein we describe an alternative strategy for the synthesis of polysubstituted 2-amino-1*H*-imidazoles **1**. Due to the fact that the bicyclic system of the imidazo[1,2-*a*]pyrimidines **6** possesses an electron-poor (π-deficient) pyrimidine ring and an electron-rich (π-excessive) imidazole ring, we started our investigations by choosing imidazo[1,2-*a*]pyrimidines **6** as templates for the modular synthesis of 4,5-disubstituted 2-amino-1*H*-imidazoles (Scheme 2). In our preliminary report[13] we developed a new microwave-assisted Pd-catalyzed synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyrimidines **5** via a Heck-type arylation of 2-substituted imidazo[1,2-*a*]pyrimidines **6**. In this Letter, we report a facile and practical microwave-assisted synthesis of 4(5)-mono- and 4,5-disubstituted 2-amino-1*H*-imidazoles from the corresponding substituted imidazo[1,2-*a*]pyrimidines **5** and **6**.

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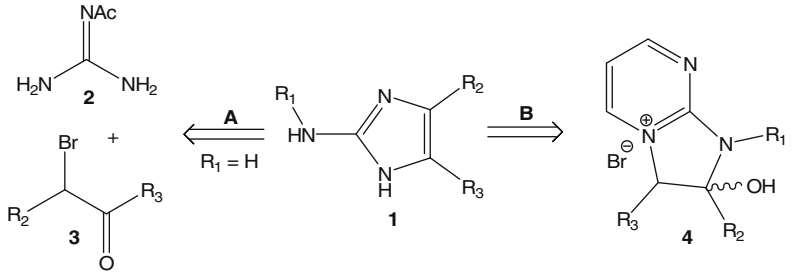
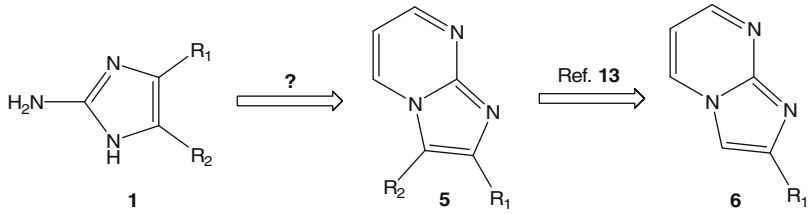
doi:10.1016/j.tetlet.2009.06.128



Scheme 1. Synthesis of substituted 2-amino-1*H*-imidazoles.

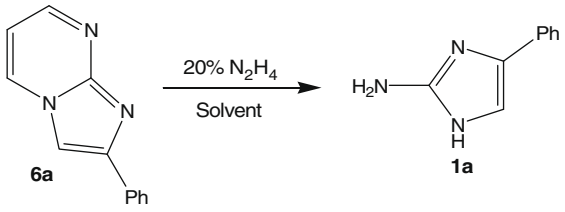


Scheme 2. Retrosynthetic analysis of the synthesis of 4,5-disubstituted 2-amino-1*H*-imidazoles.

To optimize the procedure we first studied nucleophilic cleavage of 2-phenylimidazo[1,2-*a*]pyrimidine (**6a**) under a variety of conditions and compared microwave and conventional heating conditions. Hydrazine was found to be the most reactive bis-nucleophile among the cleaving agents, such as hydroxylamine and alkylamines, giving pyrazole as the only by-product of pyrimidine ring cleavage.[14] A possible mechanism of the cleavage was given in our previous work.[11b] In a typical procedure, a mixture of 2-phenylimidazo[1,2-*a*]pyrimidine (**6a**) and 20% hydrazine hydrate in a suitable solvent was irradiated in a sealed vial at 150 W maximum power or heated in an oil bath (Table 1).

First, we tried the cleavage in MeCN under conventional heating. However, the reaction was found to be sluggish and after 12 h of heating at 80 °C only 38% of 2-amino-1*H*-4(5)-phenylimidazole (**1a**) was isolated next to a considerable amount of unreacted starting material (Table 1, entry 1). Increasing the temperature to 140 °C afforded product **1a** in 72% yield within 5 h (Table 1, entry 4). Interestingly, the cleavage was found to proceed faster in ethanol, thus providing the desired product in 83% yield within only 2 h (Table 1, entry 5). At this point, after the conventional heating attempts, we decided to carry out the cleavage of 2-phenylimidazo[1,2-*a*]pyrimidine (**6a**) under focused microwave irradiation. Unfortunately, irradiating the reaction mixture for 1 h at 80 °C provided the product in a disappointingly low yield of 13% isolated yield (Table 1, entry 6). However, contrary to the reaction under conventional heating conditions, we found that at 100 °C ceiling temperature the reaction was much faster as monitored by TLC (Table 1, entry 7). A further experiment performed at 120 °C improved substantially the yield of 2-amino-1*H*-4(5)-phenylimidazole (**1a**) and the reaction was completed within 30 min

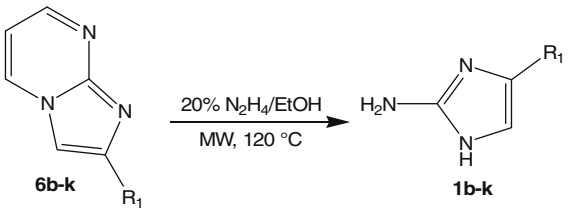
Table 1
Optimization of the conditions for the cleavage of **6a** with hydrazine[a]



Entry	Conditions	Solvent	Temperature (°C)	Time (h)	Yield (%)[c]
1	Δ	MeCN	80	12	38
2		MeCN	100	12	45
3		MeCN	120	5	69
4		MeCN	140	5	72
5		EtOH	140	2	83
6	MW[b]	MeCN	80	1	13
7		MeCN	100	1	55
8		MeCN	120	0.5	85
9		EtOH	120	0.5	91
10		Dioxane	120	0.5	47

[a] All reactions were performed on a 0.5-mmol scale in 3 mL of solvent.
[b] All the microwave experiments were performed at 150 W maximum power.
[c] All yields are isolated yields.

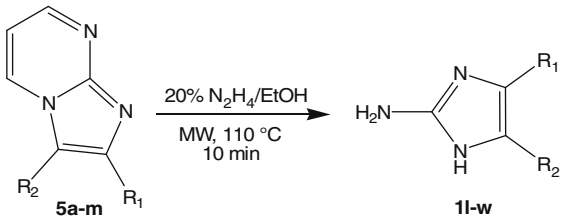
Table 2
Microwave-assisted synthesis of 4(5)-substituted 2-amino-1*H*-imidazoles **1a–k**[a]



Entry	Product	R_1	Time (min)	Yield (%)[b]
1	**1a**	Ph	10	89
2	**1b**	*p*-MeOPh	25	79
3	**1c**	*p*-FPh	10	93
4	**1d**	*p*-ClPh	10	88
5	**1e**	*p*-BrPh	10	87
6	**1f**	*p*-MePh	20	80
7	**1g**	*p*-$MeSO_2$Ph	15	88
8	**1h**	*p*-NO_2Ph	15	64
9	**1i**	Biphenyl-4-yl	20	89
10	**1j**	CONHBn	5	87
11	**1k**	CONHPh	5	93

[a] All reactions were performed on a 5-mmol scale in 12 mL of solvent. All the microwave experiments were performed at a ceiling temperature of 120 °C and 150 W maximum power.
[b] All yields are isolated yields.

Table 3
Microwave-assisted synthesis of 4,5-disubstituted 2-amino-1*H*-imidazoles **1l–w**



Entry	Product	R_1	R_2	Yield[a,b] (%)
1	**1l**	Ph	*p*-ClPh	68
2	**1m**	*p*-ClPh	*p*-FPh	83
3	**1n**	*p*-ClPh	*p*-CF_3Ph	95
4	**1o**	*p*-MePh	*p*-ClPh	94
5	**1p**	Ph	*p*-MeOPh	83
6	**1q**	*p*-FPh	*p*-FPh	89
7	**1r**	Ph	*p*-CF_3Ph	88
8	**1s**	Ph	*o*-FPh	94
9	**1t**	*p*-MeOPh	*p*-$MeSO_2$Ph	88
10	**1u**	*p*-$MeSO_2$Ph	*p*-CF_3Ph	89
11	**1v**	CONHPh	*p*-FPh	61
12	**1w**	CONHBn	Ph	84

[a] All reactions were performed on a 0.5-mmol scale in 3–4 mL of solvent. All the microwave experiments were performed at a ceiling temperature of and 150 W maximum power.
[b] All yields are isolated yields.

(Table 1, entry 8). Switching to ethanol the solvent resulted in an excellent yield of 91%. Curiously, the cleavage reaction proceeded comparatively slower in an apolar solvent as 1,4-dioxane giving the product **1a** in only 47% yield (Table 1, entry 10).

Thus, after optimizing the cleavage of 2-phenylimidazo[1,2-*a*]pyrimidine (**6a**) under microwave irradiation, we extended our strategy towards a series of 2-substituted imidazo[1,2-*a*]pyrimidines (**6a–k**). All reactions were carried out on a 5-mmol scale in 20% hydrazine monohydrate solution in ethanol at a ceiling temperature of 120 °C, applying microwave irradiation at 150 W maximum power (Table 2). The reactions proceeded smoothly with a very low amount of the starting material left and the products **1a–k** were purified by column chromatography using 15–20% MeOH in CH_2Cl_2 as the eluent. The reaction times varied from 5 to 25 min depending on the nature of substituent R_1 (Table 2). It was found that imidazo[1,2-*a*]pyrimidines bearing electron-donating substituents, for example, *p*-methoxyphenyl and *p*-tolyl (Table 2, entries 2 and 6), require up to 25 min to drive the cleavage to completion. On the contrary, the cleavage of the imidazo[1,2-*a*]pyrimidines bearing electron-withdrawing substituents was completed within 5 min (Table 2, entries 10 and 11). Importantly, the carboxamide function remained intact upon hydrazinolysis of the imidazo[1,2-*a*]pyrimidines and we have not observed any trace of transamination by-products.

The microwave-assisted cleavage of 2-(*p*-nitrophenyl)imidazo[1,2-*a*]pyrimidine (**6h**) afforded the corresponding 2-amino-1*H*-imidazole **1h** in only 64% yield, probably due to the poor solubility of the starting material (Table 2, entry 8).

Finally, we have applied the optimized protocol for the cleavage of 2,3-disubstituted imidazo[1,2-*a*]pyrimidines (Table 3). We subjected 12 compounds 5**a**–**m** to the microwave-assisted hydrazinolysis to afford the corresponding 4,5-disubstituted 2-amino-1*H*-imidazoles **1l–w**. Interestingly, all the reactions were completed within 10 min providing the products in high yields (Table 3). In a typical procedure, a mixture of 2,3-disubstituted imidazo[1,2-*a*]pyrimidines **5** and hydrazine hydrate in ethanol was irradiated in a sealed reaction vial at 150 W maximum power for 10 min at a ceiling temperature of 120 °C. The products were purified by column chromatography using 5–10% MeOH in CH_2Cl_2 as the eluent.

In conclusion, we have developed a simple and practical procedure for the preparation of 4(5)-monosubstituted and 4,5-disubstituted 2-amino-1*H*-imidazoles. We have investigated the cleavage of 2-arylimidazo[1,2-*a*]pyrimidines by hydrazine hydrate and found microwave irradiation to be very effective in this regard. A small library of 4(5)-mono- and 4,5-disubstituted 2-amino-1*H*-imidazoles was synthesized for screening for potential antiviral activity.

Acknowledgements

Support was provided by the Research Fund of the University of Leuven and by the F.W.O. (Fund for Scientific Research—Flanders (Belgium)). D.E. is grateful to the University of Leuven for obtaining a postdoctoral fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.128.

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