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Efficient One-Pot, Two-Step, Microwave-Assisted Procedure for the Synthesis of Polysubstituted 2-Aminoimidazoles

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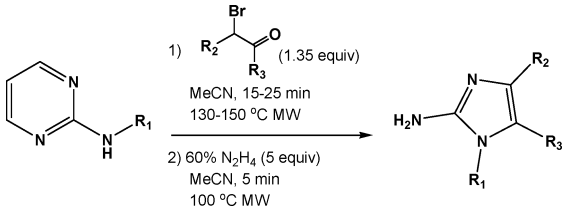
ABSTRACT



A microwave-assisted, one-pot, two-step protocol was developed for the construction of polysubstituted 2-aminoimidazoles. This process involves the sequential formation of imidazo[1,2-*a*]pyrimidinium salts from readily available 2-aminopyrimidines and α-bromocarbonyl compounds, followed by opening of the pyrimidine ring with hydrazine.

In the last decades, several marine alkaloids possessing a 2-aminoimidazole skeleton have been given particular attention, as many of them demonstrate interesting biological properties. The naamine alkaloids, for example, isolated from the marine sponge *Leucetta* sp., have been reported to possess antiviral and anticancer activity.[1,2] These compounds are usually substituted with benzyl or aryl groups at the 1, 4, and/or 5 positions. Several approaches for the synthesis of 2-aminoimidazoles have been described in the literature. Ohta and co-workers performed the synthesis of polysubstituted 2-aminoimidazoles via functionalization of the imidazole ring.[3] Other general applicable strategies involve the reaction of α-diketones with guanidine,[4] the reaction of α-halo ketones with *N*-acetylguanidine,[5] and the iminophosphorane-mediated cyclization of α-azido esters.[6] The condensation of α-aminocarbonyl compounds with cyanamide or isothioureas appears to be the most popular method for the direct construction of the 2-aminoimidazole ring.[7,8] However, this reaction is strongly pH-sensitive and can lead to the self-

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(1) (a) Carmely, S.; Ilan, M.; Kashman, Y. *Tetrahedron* **1989**, *45*, 2193. (b) Bedoya-Zurita, M.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1990**, *45*, 6713. (c) Gross, H.; Kehraus, S.; Koenig, G. M.; Woerheide, G.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1190. (d) Hassan, W.; Edrada, R.; Ebel, R.; Wray, V.; Berg, A.; Van Soest, R.; Wiryowidagdo, S.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 817.

(2) (a) Copp, B. R.; Fairchild, C. R.; Cornell, L.; Casazza, A. M.; Robinson, S.; Ireland, C. M. *J. Med. Chem.* **1998**, *41*, 3909. (b) Colson, G.; Raboult, L.; Lavelle, F.; Zeaial, A. *Biochem. Pharmacol.* **1992**, *43*, 1717. (c) Pitts, W. J.; Wityak, J.; Smallheer, J. M.; Tobin, A. E.; Jetter, J. W.; Buynitsky, J. S.; Harlow, P. P.; Solomon, K. A.; Corjay, M. H.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 27. (d) Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Forsythe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41.

(3) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939.

(4) Nishimura, T.; Kitajima, K. *J. Org. Chem.* **1979**, *44*, 818.

(5) Little, T. L.; Webber, S. E. *J. Org. Chem.* **1994**, *59*, 7299.

(6) Molina P.; Fresneda P.; Sanz, M. *J. Org. Chem.* **1999**, *64*, 2540.

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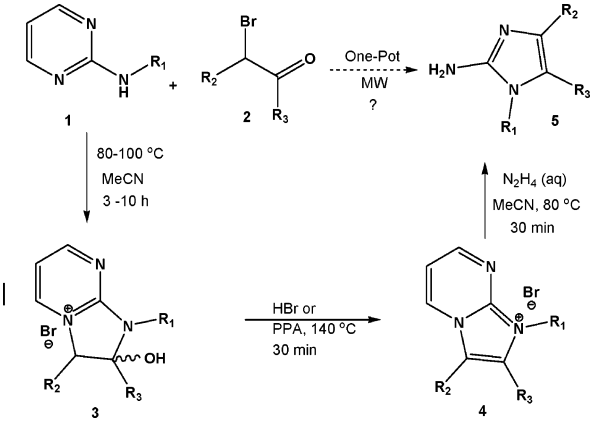
condensation of α-aminoaldehydes or ketones resulting in the formation of symmetrical pyrazines.[9]

An alternative strategy for the synthesis of 2-aminoimidazoles involves the formation of imidazo[1,2-*a*]pyrimidines, followed by cleavage of the pyrimidine ring upon treatment with strong nucleophiles as hydrazine or amines.[10−14] However, this procedure yields only *N*-1-unsubstituted 2-aminoimidazoles.

On the contrary, when the corresponding *N*-1-substituted imidazo[1,2-*a*]pyrimidinium salt should be cleaved, this would result in the formation of *N*-1-substituted 2-aminoimidazoles.[15] We previously reported a new and convenient three-step procedure for the synthesis of polysubstituted 2-aminoimidazoles **5** out of *N*-1-substituted imidazo[1,2-*a*]-pyrimidinium salts **4**, which are generated upon reaction of 2-aminopyrimidines **1** with α-bromoketones **2** (Scheme 1).[16]

Scheme 1. Two-Step Conventional Synthesis of 2-Aminoimidazoles

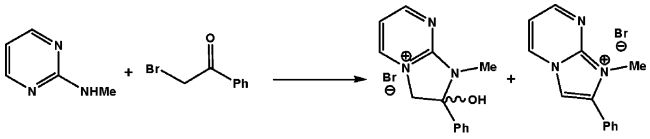


The first step was performed at 80−100 °C resulting in the formation of the hydroxy salt **3**, which underwent water elimination upon treatment with concentrated HBr or polyphosphoric acid at 140 °C, resulting in the formation of salt **4**. Final treatment with aqueous hydrazine in acetonitrile at 80 °C yielded the *N*-1-substituted 2-aminoimidazole **5**. We have demonstrated that a considerable amount of the imidazo[1,2-*a*]pyrimidinium salt **4** was directly formed when the condensation in the first step was performed at elevated temperature (>130 °C).

As a result, we now wish to present an ameliorated and convenient one-pot two-step protocol for the synthesis of *N*-1-substituted 2-aminoimidazoles, applying microwave irradiation.

We carefully investigated the dehydration of salt **3** resulting in the formation of salt **4** (Scheme 1) under conventional heating conditions as well as upon microwave irradiation. As a proof of concept, the condensation of 2-methylaminopyrimidine (**1**, R_1 = Me) and α-phenacyl bromide (**2**, R_2 = H, R_3 = Ph) was studied (Table 1). A sealed vial containing a solution of the starting compounds **1** and **2** in acetonitrile was heated at 80−100 °C for 30−60 min. However, only a trace amount of the desired 1-methyl-

Table 1. Investigation of the Condensation under Conventional Heating and Microwave Irradiation Conditions[a]



entry	conditions	time (min)	T (°C)	**3** (yield, %)[b]	**4** (yield, %)[b]
1		30	80	64	0
2		60	80	77	0
3		30	100	81	traces
4		60	100	85	traces
5		30	120	68	17
6		60	120	53	28
7		30	130	45	49
8		60	130	43	51
9	MW	30	80	88	0
10		60	80	85	0
11		30	100	48	33
12		60	100	45	35
13		30	120	12	79
14		60	120	traces	84
15		30	130	0	98
16		60	130	0	97

[a] All reactions were carried out on a 1 mmol scale of 2-methylaminopyrimidine (**1**, R_1 = Me) with 1.35 equiv of α-phenacylbromide (**2**, R_2 = H, R_3 = Ph) in 5 mL of acetonitrile. [b] Isolated yield after recrystallization from acetonitrile.

(7) (a) Lawson, A. *J. Chem. Soc.* **1956**, 307. (b) Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118. (c) Lencini, G. C.; Lazzari, E. *J. Heterocycl. Chem.* **1966**, *3*, 152.

(8) Aberle, N.; Guillaume, L.; Watson, K. *Org. Lett.* **2006**, *8*, 419.

(9) (a) Lancini, G. C.; Lazzari, E. *J. Heterocycl. Chem.* **1966**, *29*, 3118. (b) Cavalleri, B.; Ballotta, R.; Lancini, G. C. *J. Heterocycl. Chem.* **1972**, *9*, 979.

(10) Casagrande, C.; Ferrini, R.; Miragoli, G.; Ferrari, G. *Farmaco (Ed. Sci.)* **1972**, *27*, 715.

(11) Fajgelj, S.; Stanovnik, B.; Tisler, M. *Heterocycles* **1986**, *24*, 379.

(12) Commercon, A. France Patent 539229, 1993.

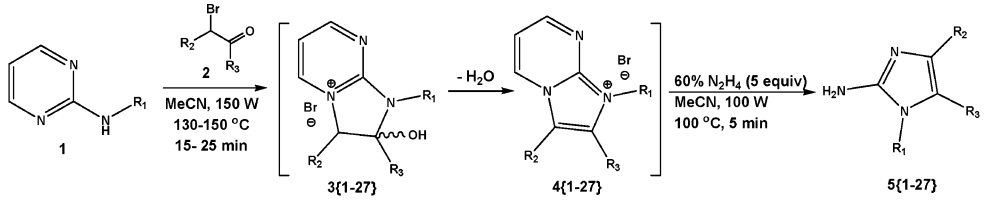
(13) Pearson, N. R.; Kleschick, W. A.; Bartley, S. L. U.S. Patent Appl. 4731446, 1988.

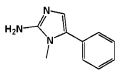
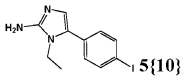
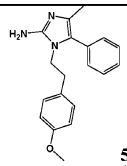
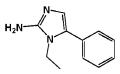
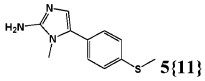
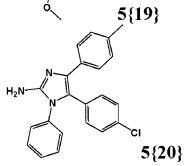
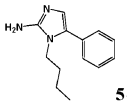
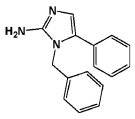
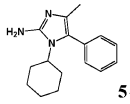
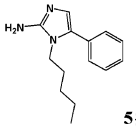
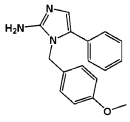
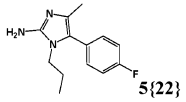
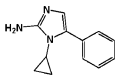
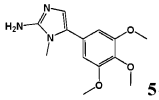
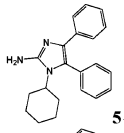
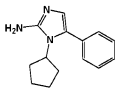
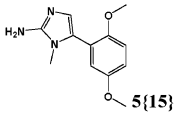
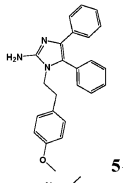
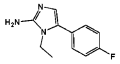
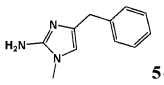
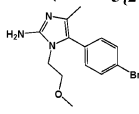
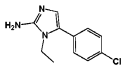
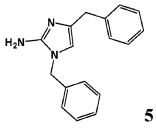
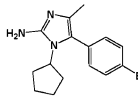
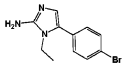
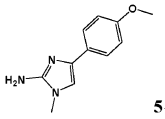
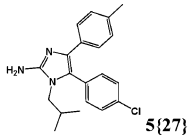
(14) Grell, W.; Haaksma, E.; Binder, K.; Zimmermann, R.; Wienen, W.; Hallermayer, G. German Patent DE 19548797, 1999.

(15) This method has previously been used in one single case, i.e. for the synthesis of 1-methyl-2-aminoimidazole starting from imidazo[1,2-*a*]-pyrimidine, by Paudler, W. W.; Helmick, L. S. *J. Heterocycl. Chem.* **1968**, *5*, 691.

(16) (a) Babaev, E. V. Abstracts of Papers. 2nd International Conference of Pure, Applied and Environmental Chemistry, 17−19 April 2000, Yarmouk University, Irbid, Jordan, IL-5. (b) Rybakov, V. B.; Babaev, E. V.; Belykh, E. N. *Acta Crystallogr., Sect. E* **2002**, *E58*, o126−128 and references therein. (c) Babaev, E. V.; Tsisevich, A. A.; Alifanov, V. L.; Ermolat'ev, D. S. Book of Abstracts. 11th Blue Danube Symposium on Heterocyclic Chemistry, Brno, Aug 28−Sep 1, 2005, OC-12. (d) Tsisevich A. A. Ph.D. Thesis, Moscow University, 2006. (e) For use of our preparation protocols and libraries in agrochemical screening, see also: Kurapov, P. B.; Smirnova, T. A.; Vetrova, E. L.; Bass, A. G.; Babaev, E. V. Abstracts of Papers. 1st Symposium of European Society of Combinatorial Chemistry (EuroCombi-1), July 1−5, 2001, Budapest, Hungary, 63. Smirnova, T. A.; Kurapov, P. B.; Vetrova, E. L.; Bass, A. G.; Nam, N. L. *Izv. Timiryazevsk. S'kh. Akad.* **2003**, *4*, 132 (in Russian).

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



entry	product	yield[b] (%)	entry	product	yield[b] (%)	entry	product	yield[b] (%)
1[c]	 5{1}	96	10[c]	 5{10}	88	19[d]	 5{19}	67
2[c]	 5{2}	75	11[c]	 5{11}	95	20[d]	 5{20}	65
3[c]	 5{3}	73	12[c]	 5{12}	48	21[d]	 5{21}	86
4[c]	 5{4}	82	13[c]	 5{13}	54	22[d]	 5{22}	71
5[c]	 5{5}	38	14[c]	 5{14}	77	23[d]	 5{23}	95
6[c]	 5{6}	71	15[c]	 5{15}	91	24[d]	 5{24}	91
7[c]	 5{7}	77	16[d]	 5{16}	88	25[d]	 5{25}	77
8[c]	 5{8}	72	17[d]	 5{17}	74	26[d]	 5{26}	88
9[c]	 5{9}	85	18[d]	 5{18}	89	27[d]	 5{27}	89

[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 acetonitrile. [b] Isolated yield. [c] The condensation was performed at 130 °C within 15 min. [d] The condensation was performed at 150 °C within 25 min.

2-phenylimidazo[1,2-*a*]pyrimidinium salt (**4**{**1**}**)** was observed next to the hydroxy salt **3**{**1**} (Table 1, entries 3 and 4). On the contrary, upon microwave irradiation at a ceiling temperature of 100 °C for 30 min, a mixture of salts **3**{**1**} and **4**{**1**} was obtained in a ratio of 48:33 (Table 1, entry 11). Further increase of the temperature up to 130 °C applying conventional heating led to a nearly equimolar mixture of salts **3**{**1**} and **4**{**1**} (Table 1, entries 7 and 8). Interestingly, using microwave irradiation at 130 °C for 30 min, we were able to drive the reaction completely to the formation of the desired imidazo[1,2-*a*]pyrimidinium salt **4**{**1**} (entry 15).

With these results in hand, we developed an elegant one-pot, two-step, microwave-assisted protocol for the synthesis

of 1,4-, 1,5-, and 1,4,5-substituted 2-aminoimidazoles starting from readily available 2-aminopyrimidines **1** and α-bromoketones **2** (Table 2). The reaction could visually be followed, as after the start, the initially formed salt **3** precipitated from the reaction mixture and then slowly dissolved at 130−150 °C, converting to the salt **4**. Then 5 equiv of hydrazine (60%) were added and the mixture was irradiated at a ceiling temperature of 100 °C for another 5 min. Upon completion, the reaction mixture was diluted with water and extracted with dichloromethane. Side products could easily be removed by washing the organic phase with water, resulting in nearly pure compounds. Following this protocol, a small library of variously substituted 2-aminoimidazoles was generated, starting from readily available α-bromocarbonyl compounds **2** and 2-aminopyrimidines **1** (Table 2).

The yields varied from good to excellent, although in some cases lowered yields were observed (Table 2, entries 5, 12, and 13) probably due to abstraction of the substituent R_1 from the imidazole ring at high temperature. Interestingly, applying conventional heating conditions, longer total reaction times (up to 10−12 h) were necessary, resulting in lower yields due to significant decomposition of the starting compounds. Moreover, since the preparation of salts **4** under conventional conditions involves the exposure of the intermediates **3** and **4** to strong acids at elevated temperature (Scheme 1), sensitive R_1 substituents as cycloalkyl and *p*-methoxybenzyl are not tolerated. Heterocyclization reactions of α-bromoaldehydes are hardly known due to their high reactivity. Nevertheless, we were able to generate the corresponding 1,4-disubstituted 2-aminoimidazoles in high yields by applying our microwave-assisted protocol (Table 2, entries 16−18). As the cyclization of α-bromoaldehydes and 1,2-disubstituted α-bromoketones with 2-aminopyrimidines was found to be slow, the temperature of the first step was raised to 150 °C and a longer irradiation time of 25 min was applied (Table 2, entries 16−27). The desired 1,4- and 1,4,5-substituted 2-aminoimidazoles were isolated in good yields (65−95%). 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 2, entries 20, 23−24, and 27).

In conclusion, we have developed an efficient microwave-assisted, one-pot, two-step protocol for the synthesis of 1,4-, 1,5-, and 1,4,5-substituted 2-aminoimidazoles from 2-aminopyrimidines and α-bromoketones or α-bromoaldehydes, applying the 2-aminopyrimidine ring as a protected guanidine fragment. This procedure opens the way for the synthesis of analogues of different bioactive marine alkaloids possessing a 2-aminoimidazole skeleton.

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Supporting Information Available: Spectroscopic data for all new compounds prepared, as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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