Chemistry of Heterocyclic Compounds, Vol. 48, No. 12, March, 2013 (Russian Original Vol. 48, No. 12, December, 2012)

SYNTHESIS OF 2-UNSUBSTITUTED 1-ARYLIMIDAZOLES

V. S. Mityanov[1]*, V. P. Perevalov[1], and I. I. Tkach[1]

A method has been developed for the synthesis of 1-arylimidazoles lacking a substituent at position 2, featuring the preparation of 1-arylimidazole N-oxides stabilized as boron trifluoride derivatives, with subsequent reduction to the desired imidazoles. This method permits broad variation of the substituents in the aryl part of these molecules.

Keywords: 1-arylimidazoles, boron trifluoride, imidazole *N*-oxides, heterocyclization, *N*-oxide reduction.

1-Arylimidazole derivatives display a broad spectrum of biological activity, such as antitumor and immunodepressant activity [1]. These compounds hold interest in the treatment of many neurological conditions such as obesity, motion disorders, and schizophrenia [1]. Thus, such imidazole derivatives undoubtedly hold pharmacological potential [2-5]. Particular attention is given to 1-arylimdiazoles lacking a substituent at position 2. However, the difficulty in preparing many such compounds has hindered the study of their properties. Thus, considerable interest is found in the development of an effective method for the synthesis of 1-arylimidazoles unsubstituted at position 2.

Two fundamentally different approaches are known for the synthesis of 1-arylimidazoles. The first method involves the direct introduction of the aryl fragment by means of aromatic nucleophilic substitution reactions [6] or cross coupling [7]. However, these methods place serious restrictions on the nature and position of the substituents in the aryl fragment. Furthermore, in the case of different substituents at positions 4 and 5 in the imidazole, a mixture of products is formed with predominance of the less sterically hindered compound. The second approach entails the preparation of 1-arylimidazoles from acyclic precursors using various cyclocondensation reactions. However, the methods described in the literature [8-11], though providing imidazoles with the desired set of substituents, involve many steps, proceed with low overall yield, and are suitable for only a limited number of compounds.

This work has been focussed on a scheme that combines the preparation of 1-arylimidazole *N*-oxides with free position 2 and subsequent reduction of the *N*-oxide function.

The first attempts to synthesize 2-unsubstituted 1-arylimidazole *N*-oxides [12-14] involved the acid-catalyzed condensation of α-diketone monooximes either with aromatic amines and formaldehyde or with previously obtained *N*-arylmethylenamines. In the former case, 1-arylimidazole *N*-oxides could not be isolated,

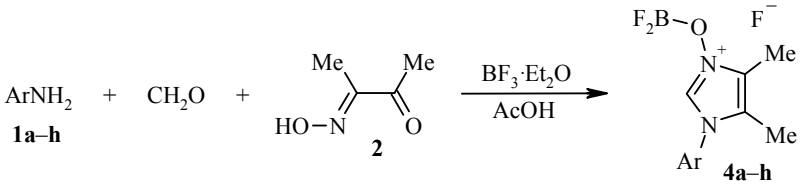
*To whom correspondence should be addressed, e-mail: mityanovvs@yandex.ru.

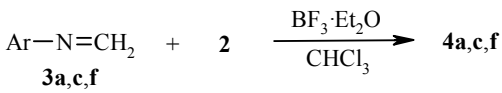
[1]D. Mendeleev University of Chemical Technology of Russia, 9 Miusskaya Sq., Moscow 125047, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1916-1923, December, 2012. Original article submitted May 22, 2012.

apparently, due to very rapid isomerization of these compounds to 2-imidazolones [14]. In the latter case, a few compounds were synthesized in low yields by minimizing the amount of water generated during the condensation. In recent years, attempts were undertaken to develop alternative methods for the synthesis of these compounds entailing the condensation of α-amino oximes with ethyl orthoformate [15] or the condensation of α-diimines with aldoximes [16], but the yields of 1-arylimidazoles were also low in these cases, while the starting α-diimines and α-amino oximes often proved not readily available.

We assumed that 2-unsubstituted imidazole *N*-oxides could be stabilized by binding them in some complex. Indeed, the condensation of aromatic amines **1a**-**h** with formaldehyde and the butane-2,3-dione monooxime (**2**), similar to the condensation of *N*-arylmethylenamines **3a**,**c**,**f** with oxime **2** in the presence of boron trifluoride etherate in acetic acid or chloroform led to the 1-aryl-3-[(difluoroboryl)oxy]-4,5-dimethyl-1*H*-imidazolium fluorides **4a**-**h** in high yield.





a Ar = Ph, **b** Ar = 2,4,6-$Me_3C_6H_2$, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 3-FC_6H_4,
e Ar = 2,4,6-$(MeO)_3C_6H_2$, **f** Ar = 3-ClC_6H_4, **g** Ar = 4-$O_2NC_6H_4$, **h** Ar = 3-Py

The use of boron trifluoride etherate is very convenient. This complex not only stabilizes imidazole *N*-oxides but also acts as an acid catalyst facilitating the reaction, such that it may proceed under mild conditions. Even such weakly basic amines as 4-nitroaniline (**1g**) and 3-aminopyridine (**1h**) readily take part in this reaction. It is interesting that 4-nitroaniline (**1g**) undergoes the reaction even when using aqueous formaldehyde in water-immiscible solvent (chloroform). We selected chloroform and acetic acid as the standard solvents in our study of this condensation, but the reaction can also be carried out in other solvents such as alcohols and dichloroethane.

In the case of mesidine **1b** and 2,4,6-trimethoxyaniline **1e**, we showed that even very sterically hindered arylamines readily undergo this reaction. We should note that imidazole derivatives with sterically hindered 2,6-diaryl fragments at the position N-1 have not been described in the literature.

Table 1 shows that the yields in the condensation of α-diketone monooxime with formaldehyde and an arylamine are independent of both the nature of the substituents in the aryl fragment and the steric hindrance, but rather are a function of the ease of the pure product isolation. Carrying out this condensation using previously obtained *N*-arylmethylenamines **3a**,**c**,**f** is preparatively more convenient and permits the use of mild conditions. The product isolation in this case does not pose difficulties, and the yields range from 54 to 85%.

Imidazolium salt **4h** was obtained as a complex with two equivalents of BF_3 as indicated by the elemental analysis. The second equivalent of BF_3 apparently forms a donor-acceptor bond with the pyridine nitrogen atom.

The starting *N*-arylmethylenamines **3a**,**c**,**f** were obtained by the reaction of arylamines with formaldehyde in ethanol [17]. According to the spectral data, azomethines **3a**,**c**,**f** exist in equilibrium with the cyclic form, namely, 1,3,5-trisubstituted hexahydro-1,3,5-triazines. The cyclic form predominates in the case of aromatic amines [13].

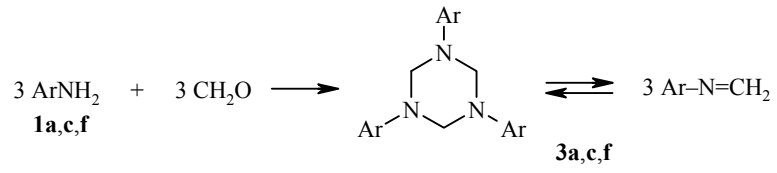
TABLE 1. Physicochemical Characteristics of Compounds **4a-h, 6a-f**,**h** and **7**

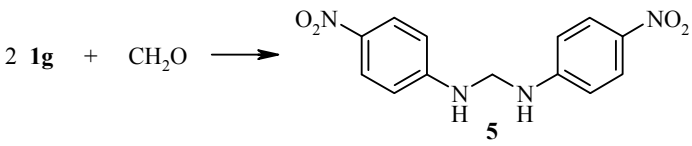
Compound	Empirical formula	Found, % / Calculated, %			Mp*, °C	Yield*[2], % (Method)
		C	H	N		
4a	$C_{11}H_{12}BF_3N_2O$	51.30 / 51.60	4.52 / 4.72	10.79 / 10.94	80-82	73 (A) 54 (B)
4b	$C_{14}H_{18}BF_3N_2O$	56.35 / 56.41	5.97 / 6.09	9.37 / 9.40	174-176	44 (A)
4c	$C_{12}H_{14}BF_3N_2O_2$	50.35 / 50.39	4.90 / 4.93	9.73 / 9.79	165-166	44 (A) 67 (B)
4d	$C_{11}H_{11}BF_4N_2O$	48.15 / 48.22	3.98 / 4.05	10.18 / 10.22	108-110	45 (A)
4e	$C_{14}H_{18}BF_3N_2O_4$	48.50 / 48.58	5.20 / 5.24	8.01 / 8.09	156-158	81 (A)
4f	$C_{11}H_{11}BClF_3N_2O$	45.38 / 45.48	3.79 / 3.82	9.60 / 9.64	189-190	55 (A) 85 (B)
4g	$C_{11}H_{11}BF_3N_3O_3$	43.84 / 43.89	3.60 / 3.68	13.92 / 13.96	203-205	58 (A) 61 (B)
4h	$C_{10}H_{11}B_2F_6N_3O$	36.87 / 36.98	3.47 / 3.41	12.86 / 12.94	165-167	65 (A)
6a	$C_{11}H_{12}N_2$	76.65 / 76.71	6.95 / 7.02	16.19 / 16.26	Oil	80
6b	$C_{14}H_{18}N_2$	78.39 / 78.46	8.67 / 8.47	12.91 / 13.07	110-112	93
6c	$C_{12}H_{14}N_2O$	71.30 / 71.26	7.16 / 6.98	13.59 / 13.85	48-50	71
6d	$C_{11}H_{11}FN_2$	69.40 / 69.46	5.80 / 5.83	14.69 / 14.73	Oil	71
6e	$C_{14}H_{18}N_2O_3$	64.04 / 64.11	6.87 / 6.92	10.61 / 10.68	138-140	84
6f	$C_{11}H_{11}ClN_2$	63.89 / 63.93	5.31 / 5.36	13.49 / 13.55	Oil	90
6h	$C_{10}H_{11}N_3$	69.28 / 69.34	6.23 / 6.40	24.21 / 24.26	>165 (decomp.)	65
7	$C_{11}H_{13}N_3$	70.50 / 70.56	6.89 / 7.00	22.39 / 22.44	128-130	40

*Recrystallization solvents: 2-propanol (compounds **4a**,**b**,**d**,**e**), ethyl acetate (compounds **4c**,**f**), acetone (compounds **4g**,**h**), heptane (compounds **6b**,**c**,**e**,**h**), and toluene–heptane (compound **7**).

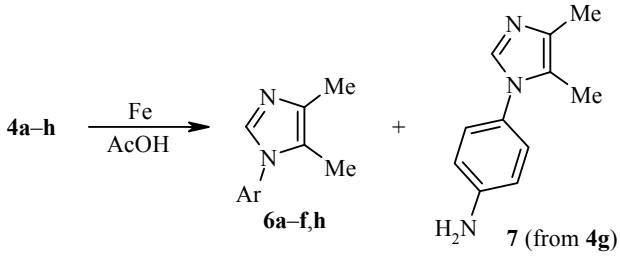
*[2]The yields of the reduction reactions are given for compounds **6a-f**,**h** and **7**.

Sprung [17] reported that heating 4-nitroaniline (**1g**) with formaldehyde in ethanol at reflux under neutral conditions proceeds somewhat unusually to give *N,N'*-bis(4-nitrophenyl)methanediamine (**5**). It is interesting that diamine **5**, similar to arylamines **1a-h** and *N*-arylmethylenamines **3a**,**c**,**f**, undergoes condensation with butane-2,3-dione monooxime (**2**) to give the corresponding derivative **4g**.





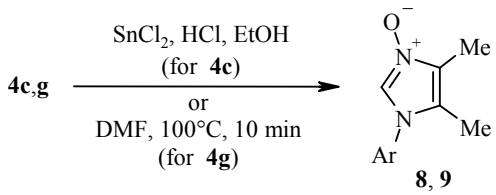
The desired 1-aryl-4,5-dimethylimidazoles **6a-f**,**h** were obtained by the reduction of 1-aryl-3-[(difluoroboryl)oxy]-4,5-dimethyl-1*H*-imidazolium fluorides **4a-f**, **h** by using iron in acetic acid. In the case of nitro derivative **4g**, reduction of the nitro group also occurs under these conditions to give the amino derivative **7**.



a Ar = Ph, **b** Ar = 2,4,6-$Me_3C_6H_2$, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 3-FC_6H_4,
e Ar = 2,4,6-$(MeO)_3C_6H_2$, **f** Ar = 3-ClC_6H_4, **h** Ar = 3-Py

The thermal stability of derivatives **4c**,**f**,**g** was studied. Upon heating in a polar solvent (DMF) on a steam bath for 0.5 h, salts **4c**,**f** did not undergo any change. After prolonged heating at reflux in DMF, the fluoride **4c** decomposed completely. Heating the 4-nitrophenyl derivative **4g** in DMF on a steam bath for 10 min gave quantitative conversion to the corresponding *N*-oxide **8**.

Heating 1-arylimidazole *N*-oxides in the weakly polar solvent bromobenzene led to a rearrangement giving 2-imidazolones [13]. However, the fluorides **4c**,**g** were not altered under these conditions.



8 Ar = 4-$O_2NC_6H_4$, **9** Ar = 4-$MeOC_6H_4$

Imidazole *N*-oxides are also known to undergo facile reduction to give imidazoles by the action of triphenylphosphine in acetic acid [18]. However, only the starting compounds were detected after prolonged heating of 3-[(difluoroboryl)oxy]-1-phenyl-1*H*-imidazolium fluoride **4a** with excess triphenylphosphine at reflux both in acetic acid and propionic acid. The presence of the difluoroboryl group at the *N*-oxide oxygen atom apparently hindered the coordination of the bulky triphenylphosphine molecule at this atom and the subsequent deoxygenation reaction.

Cleavage of the oxygen–boron bond with retention of the *N*-oxide function was found upon the reduction of fluoride **4c** using $SnCl_2$ in ethanol in the presence of hydrochloric acid both at room temperature and at reflux. The corresponding *N*-oxide **9** was obtained in 92% yield.

Table 2 shows that the ^{1}H NMR spectra of 1-aryl-3-[(difluoroboryl)oxy]-1*H*-imidazolium fluorides **4a**-**h** displayed a narrow signal at 9.16-9.58 ppm for the proton at the imidazole ring C-2 atom. This signal was shifted downfield by approximately 1 ppm in comparison with the corresponding *N*-oxides (compare compounds **4g** with **8** and **4c** with **9**).

TABLE 2. ^{1}H NMR Spectra of Compounds **4a-h**, **6a-f**,**h** and **7**

Compound	Chemical shifts*, δ, ppm (*J*, Hz)			
	H-2 (1H, s)	4,5-CH_3 (3H, s) and (3H, s)	Aromatic protons	Other signals
4a	9.42	2.25; 2.12	7.70-7.50 (5H, m)	—
4b	9.29	2.33; 2.28	7.15 (2H, s)	1.95 (6H, s, 2',6'-CH_3); 1.90 (3H, s, 4'-CH_3)
4c	9.37	2.24; 2.09	7.51 (2H, d, *J* = 9.2); 7.14 (2H, d, *J* = 9.2)	3.84 (3H, s, OCH_3)
4d	9.48	2.25; 2.15	7.70-7.47 (4H, m)	—
4e	9.13	2.22; 1.90	6.46 (2H, s)	3.87 (3H, s, 4'-OC$\underline{H}_3$); 3.79 (6H, s, 2',6'-OCH_3)
4f	9.47	2.25; 2.14	7.82 (1H, s); 7.78-7.55 (3H, m)	—
4g	9.58	2.27; 2.18	8.45 (2H, d, *J* = 9.0); 7.93 (2H, d, *J* = 9.0)	—
4h	9.50	2.26; 2.16	8.93-8.85 (2H, m); 8.31-8.25 (1H, m); 7.83-7.77 (1H, m)	—
6a	7.49-7.40*[2]	2.23; 2.09	7.49-7.40 (4H, m, H-2, H Ar); 7.26-7.23 (2H, m)	—
6b	7.23	2.32; 2.23	6.95 (2H, s)	1.91 (6H, s, 2',6'-CH_3); 1.83 (3H, s, 4'-CH_3)
6c	7.41	2.19; 2.02	7.16 (2H, d, *J* = 8.8); 6.95 (2H, d, *J* = 8.8)	3.82 (3H, s, OC$\underline{H}_3$)
6d	7.51	2.23; 2.12	7.50-7.42 (2H, m); 7.16-6.98 (2H, m)	—
6e	7.23	2.20; 1.85	6.18 (2H, s)	3.84 (3H, s, 4'-OC$\underline{H}_3$); 3.71 (6H, s, 2',6'-OCH_3)
6f	7.45	2.19; 2.08	7.40-7.12 (4H, m)	—
6h	*[3]	2.90; 2.73	9.88 (1H, s); 9.75-9.60 (1H, m); 9.43-9.30 (1H, m); 8.95-8.80 (1H, m)	—
7	7.39	2.19; 2.01	6.98 (2H, d, *J* = 8.8); 6.68 (2H, d, *J* = 8,8)	3.97 (2H, s, N$\underline{H}_2$)

*The spectra of fluorides **4a-h** were recorded in DMSO-d_6, while the spectra of imidazoles **6a-f** and **7** were recorded in $CDCl_3$, and the spectrum of **6h** was recorded in trifluoroacetic acid.

*[2]Superposition onto the multiplet of the phenyl ring proton signals.

*[3]Found within the multiplet of the pyridine ring protons.

The ^{13}C NMR spectra of fluorides **4a-h** did not provide much useful information. The signals of all the aromatic ring carbon atoms are located in an extremely narrow range. Additional study is required for the assignment of these signals.

The mass spectra of fluorides **4a-h** given in Table 3 show signals corresponding to the 1-aryl-3-[(difluoroboryl)oxy]-1*H*-imidazolium molecular cation and signals for the $[M\text{-}BR_2]^{+\cdot}$ radical cation, as well as a rather strong signal for the fragment with *m/z* 49, corresponding to the BF_2^+ cation. This suggests that compounds **4a-h** were indeed 1-aryl-3-[(difluoroboryl)oxy]-1*H*-imidazolium fluorides with a covalent bond between oxygen and boron, and not BF_3 complexes of 1-arylimidazole *N*-oxides.

Thus, the proposed synthetic method provides a pathway to the preparation of 1-arylimidazoles, which are difficult to obtain by other methods. The products obtained, which we have identified as 1-aryl-3-[(difluoroboryl)oxy]-1*H*-imidazolium fluorides, have not yet been described in the literature and may hold interest in themselves.

TABLE 3. Mass Spectra of Compounds **4a-h**, **6a-f**,**h** and **7**

Compound	*M*, g/mol	*m/z* (I_{rel}, %)*			
		$[M]^+$	$[M-BF_2]^{+\bullet}$	$[M-BF_2-O]^+$	$[M-BF_2-OH]^+$
4a	256	237 (20)	188 (100)	172 (27)	171 (49)
4b	298	279 (4)	230 (52)	214 (100)	213 (25)
4c	286	267 (16)	218 (100)	202 (19)	201 (43)
4d	274	255 (30)	206 (100)	190 (25)	189 (65)
4e	346	327 (3)	278 (61)	262 (100)	261 (33)
4f*[2]	290	271 (14)	222 (100)	206 (21)	205 (63)
4g	301	282 (13)	233 (93)	217 (100)	216 (87)
4h	324	238 (22)	189 (100)	173 (31)	172 (57)
6a	172	172 (43)	—	—	—
6b	214	214 (100)	—	—	—
6c	202	202 (100)	—	—	—
6d	190	190 (100)	—	—	—
6e	262	262 (100)	—	—	—
6f*[2]	206	206 (100)	—	—	—
6h	173	173 (96)	—	—	—
7	187	187 (80)	—	—	—

*For fluorides **4a-h**, [M] is the 1-aryl-3-[(difluoroboryl)oxy]-1*H*-imidazolium cation.
*[2]For isotope ^{35}Cl.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) with TMS as internal standard. The mass spectra were recorded on an LKB-2000 mass spectrometer equipped with a system for direct sample inlet. The ionizing electron energy was 70 eV. The elemental analysis was carried out on a Carlo Erba Model 1106 CHN analyzer manufactured in Italy. The melting points were determined on a Kofler hot stage apparatus. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates.

Anilines **1a-d**,**f-h** and oxime **2** are commercially available. The 2,4,6-trimethoxyaniline (**1e**) was obtained according to the procedure of Fukui *et al.* [19]. *N*-Phenylmethylenamine (**3a**), *N*-(4-methoxyphenyl)methylenamine (**3c**), and *N,N'*-bis(4-nitrophenyl)methanediamine (**5**) were obtained using standard procedures [17].

***N*-(3-Chlorophenyl)methylenamine (3f).** 30% Formalin (22.0 ml, 24.0 g, 24 mmol) was added to a solution of 3-chloroaniline (25.5 ml, 30.6 g, 24 mmol) in ethanol (100 ml). The reaction mixture was stirred at reflux for 2.5 h and then cooled. The precipitate formed was filtered off and washed with ethanol (20 ml) to give methylenamine **3f**. Yield 19.3 g (58%). White powder; mp 172-174°C.

1-Aryl-3-[(difluoroboryl)oxy]-4,5-dimethyl-1*H*-imidazolium Fluorides 4a-h (General Method). A. $BF_3 \cdot Et_2O$ (1.4 ml, 1.6 g, 11 mmol) (in the case of 3-aminopyridine (**1h**), 3.1 ml, 3.6 g, 25 mmol), 40% formalin (0.7 ml, 0.8 g, 10 mmol), and then amine **1a-h** (10 mmol) were added to a solution of butane-2,3-dione monooxime (**2**) (1.0 g, 10 mmol) in glacial acetic acid (10 ml). The mixture was stirred at 50-55°C for 4 h. Acetic acid was evaporated under reduced pressure, and the product was obtained from the residue by chromatography on a silica gel column using 100:1 chloroform–methanol as the eluent.

B. $BF_3 \cdot Et_2O$ (1.4 ml, 1.6 g, 11 mmol) and then *N*-arylmethylenamine **3a**,**c**,**f** (10 mmol) were added to a solution of butane-2,3-dione monooxime (**2**) (1.0 g, 10 mmol) in chloroform (10 ml). The mixture was stirred at room temperature for 4 h. Chloroform was evaporated at reduced pressure. The product was isolated by chromatography on a silica gel column using 100:1 chloroform–methanol as the eluent.

Fluoride 4a. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 133.4; 130.8; 130.2; 129.9; 126.3; 125.7; 123.8; 8.7 (CH_3); 6.9 (CH_3).

Fluoride 4c. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 160.2; 130.8; 127.7; 126.1; 125.3; 124.0; 114.8; 55.6 (OCH_3); 8.54 (CH_3); 6.92 (CH_3).

1-Aryl-4,5-dimethylimidazoles 6a-f,h, 7 (General Method). Iron powder (8.4 g, 150 mmol) was added to a solution of fluoride **4a-h** (10 mmol) in glacial acetic acid (35 ml). The reaction mixture was stirred at reflux for 2 h, cooled, and poured into water (70 ml). The iron sludge was filtered off. The filtrate was extracted with chloroform (50 ml). The extract was washed with 5% aqueous potassium carbonate until the wash water was slightly basic. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and then filtered. Chloroform was distilled off at reduced pressure. The residue was subjected to chromatography on a silica gel column using 100:1 chloroform–methanol as the eluent.

4,5-Dimethyl-1-(4-nitrophenyl)imidazole *N*-Oxide (8). A solution of fluoride **4g** (1.0 g, 3.3 mmol) in DMF (5 ml) was heated at 100°C for 25 min and then cooled. The precipitated product was filtered off, washed with water, and dried to give the *N*-oxide **8**. Yield 0.5 g (61%). Light-yellow powder; mp 172-174°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: (*J*, Hz): 8.65 (1H, s, H-2); 8.37 (2H, d, *J* = 8.8, H Ar); 7.78 (2H, d, *J* = 8.8, H Ar); 2.19 (3H, s, CH_3); 2.08 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 233 $[M]^{+\cdot}$ (93), 217 $[M\text{-}O]^{+\cdot}$, (100), 216 $[M\text{-}OH]^+$ (89). Found, %: C 56.59; H 4.71; N 17.55. $C_{11}H_{11}N_3O_3$. Calculated, %: C 56.65; H 4.75; N 18.02.

4,5-Dimethyl-1-(4-methoxyphenyl)imidazole *N*-Oxide (9). A solution of fluoride **4c** (1.0 g, 3.5 mmol) in ethanol (25 ml) was added to a solution of $SnCl_2 \cdot 2H_2O$ (4.7 g, 21 mmol) in concentrated hydrochloric acid (25 ml). The reaction mixture was stirred at reflux for 7 h, cooled, and brought to pH 9-10 by adding concentrated aqueous potassium hydroxide. The precipitate formed was filtered off, and the product in the filtrate was extracted with chloroform (100 ml). The extract was evaporated and traces of water and ethanol were removed by azeotropic distillation with benzene (10 ml) to give *N*-oxide **9**. Yield 0.7 g (92%). White powder; mp 90-94°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 8.35 (1H, s, H-2); 7.38 (2H, d, *J* = 8.8, H Ar); 7.14 (2H, d, *J* = 8.8, H Ar); 3.81 (3H, s, OCH_3); 2.05 (3H, s, CH_3); 2.04 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M]^{+\cdot}$ (100), 202 $[M\text{-}O]^{+\cdot}$ (18), 201 $[M\text{-}OH]^+$ (26). Found, %: C 66.00; H 6.40; N 12.79. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.84.

REFERENCES

1. I. M. Pastor and M. Yus, *Curr. Chem. Biol.*, **1**, 65 (2009).
2. M. Yamada, T. Yura, M. Morimoto, T. Harada, K. Yamada, Y. Honma, M. Kinoshita, and M. Sugiura, *J. Med. Chem.*, **39**, 596 (1996).
3. L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinski-Mozng, D. Frost, S. H. Rosenberg, and H. L. Sham, *J. Med. Chem.*, **45**, 1697 (2002).
4. J. L. Romine, S. W. Martin, V. K. Gribkoff, C.G. Boissard, S. I. Dworetzky, J. Natale, Y. Li, Q. Gao, N. A. Meanwell, and J. E. Starrett, *J. Med. Chem.*, **45**, 2942 (2002).
5. C. Almansa, J. Alfón, A. F. De Arriba, F. L. Cavalcanti, I. Escamilla, L. A. Gómez, A. Miralles, R. Soliva, J. Bartoli, E. Carceller, M. Merlos, and J. Garcia-Rafanell, *J. Med. Chem.*, **46**, 3463 (2003).
6. A. Kiyomori, J.-F. Marcoux, and S. I. Buchwald, *Tetrahedron Lett.*, **40**, 2657 (1999).
7. J. P. Collman, M. Zhong, I. Zeng, and S. Costanzo, *J. Org. Chem.*, **66**, 1528 (2001).
8. J. M. Khurana, G. C. Maikap, and S. Mehta, *Synthesis*, 731 (1990).
9. K.-I. Nunami, M. Yamada, T. Fukui, and K. Matsumoto, *J. Org. Chem.*, **59**, 7635 (1994).
10. A. R. Katritzky, D. Cheng, and R. P. Musgrave, *Heterocycles*, **44**, 67 (1997).

11. V. G. Pawar, W. M. De Borggraeve, K. Robeyns, L. Van Meervelt, F. Compernolle, and G. Hoornaert, *Tetrahedron Lett.*, **47**, 5451 (2006).
12. I. J. Ferguson and K. Schofield, *J. Chem. Soc*., *Perkin Trans. 1*, 275 (1975).
13. R. Bartnic, W. E. Hahn, and G. Mloston, *Rocz. Chem.*, **51**, 49 (1977).
14. H. Lettau, *Z. Chem.*, **10**, 462 (1970).
15. H. Cerecetto, A. Gerpe, and M. González, *Synthesis*, 2678 (2004).
16. J. Alcázar, M. Begtrup, and A. de la Hoz, *J. Chem. Soc.*, *Perkin Trans. 1*, 2467 (1995).
17. M. A. Sprung, *Chem. Rev.*, **26**, 297 (1940).
18. G. V. Nikitina and M. S. Pevzner, *Khim. Geterotsikl. Soedin.*, 147 (1993). [*Chem. Heterocycl. Compd.*, **29**, 127 (1993)].
19. Y. Fukui, Y. Kuwahara, K. Saheki, and M. Mori, *Yakugaku Zasshi*, **80**, 1472 (1960).