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Authors	Dmitry Ryabukhin, Alexey Turdakov, Natalia Soldatova, Mikhail Kompanets, Alexander Ivanov, Irina Boyarskaya and Aleksander Vasilyev
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ORCID® iDs	Alexander Ivanov - https://orcid.org/0000-0002-4228-1248; Aleksander Vasilyev - https://orcid.org/0000-0003-3628-1492

Reactions of 2-carbonyl and 2-hydroxy(or methoxy)alkyl substituted benzimidazoles with arenes in the superacid CF_3SO_3H. NMR and DFT study of dicationic electophilic species

Dmitry S. Ryabukhin,[a] Alexey N. Turdakov,[a] Natalia S. Soldatova,[b] Mikhail O. Kompanets,[c,d] Alexander Yu. Ivanov,[e] Irina A. Boyarskaya,[f] Aleksander V. Vasilyev*[a,f]

[a]Department of Chemistry, Saint Petersburg State Forest Technical University, Institutsky per., 5, Saint Petersburg , 194021, Russian Federation

[b]National Research Tomsk Polytechnic University, Lenin Avenue 30, Tomsk, 634050, Russian Federation

[c] Litvinenko Institute of Physico-Organic and Coal Chemistry, NAS of Ukraine, Kharkivske Hgw, 50, Kyiv, 02160, Ukraine

[d] National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute", Prosp. Peremohy, 37, Kyiv, 03056, Ukraine

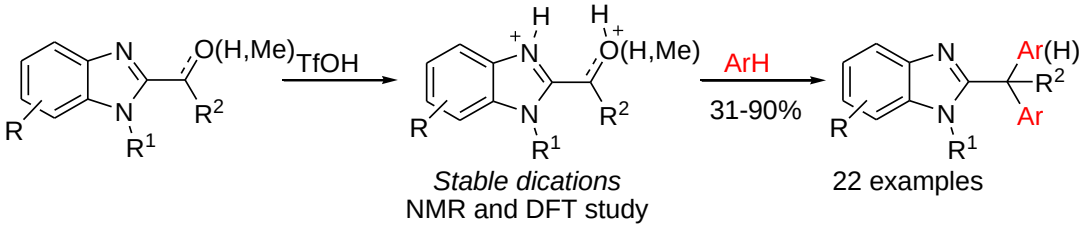
[e]Center for Magnetic Resonance, Research Park, Saint Petersburg State University, Universitetskiy pr., 26, Saint Petersburg, Petrodvoretz, 198504, Russian Federation

[f]Department of Organic Chemistry, Institute of Chemistry, Saint Petersburg State University, Universitetskaya nab., 7/9, Saint Petersburg, 199034, Russian Federation

*Corresponding author: A.V. Vasilyev; e-mails: *aleksvasil@mail.ru; a.vasilyev@spbu.ru*

Keywords: benzimidazoles; triflic acid; Friedel-Crafts reaction; cations

Graphical abstract



Abstract

Interaction of 2-carbonyl and 2-hydroxy(or methoxy)alkyl benzimidazoles with arenes in the Brønsted superacid TfOH resulted in the formation of the corresponding Friedel-Crafts reaction products, 2-diarylmethyl and 2-arylmethyl substituted benzimidazoles in yields up to 90%. The reaction intermediates, N,O-diproptonated species derived from starting benzimidazoles in TfOH, were thorougly studied by means of NMR and DFT calculations. The plausible reaction mechanisms have been discussed.

Introduction

Imidazoles and benzimidazoles are an important heterocyclic scaffolds in pharmaceuticals and agrochemicals [1-10]. They also have applications in the fields of dyes, chemo-sensing, and fluorescent materials [3]. (Benz)imidazoles are common motif present in some components of human organisms, histidine, vitamin B12, purines, histamine, bionin, and in natural compounds, lepidiline A and B [6].

Over the years of active research, benzimidazole derivatives have been involved in medicinal chemistry covering a wide range of biological activities including antiparasitic (albendazole, mebendazole), antiulcer (omeprazole), antihypertensive (candesartan, telmisartan, azilsartan, medoxomil, mebefradil), anti-cencer (bendamustine), antiemetic/antipsychotics (droperidole), antihistaminic (astemizole, emedastine) and many others (Figure 1) [1-10]. Benzimidazole fungicides (carbendazim, benomyl, thiabendazole and fuberidazole) have been widely used to fight against destructive plant pathogens (Figure 1) [7]. Interestingly, most of the above listed drugs are 2- or 1,2-disubstituted benzimidazole derivatives [2].

Thus, further development of the synthesis of benzimidazole derivatives and study of their properties are important goals for chemistry, medicine and material science.

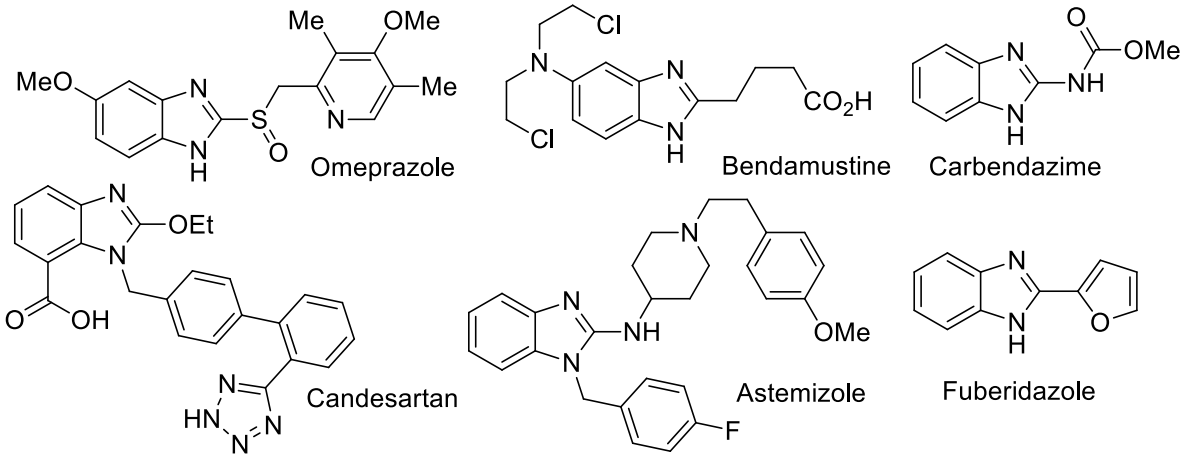


Figure 1. Examples of some commercially available pharmaceuticals and agrochemicals containing benzimidazole scaffold.

The concept of superelectrophilic activation was first proposed by George Olah [11], and since then, a study of superelectrophilic intermediates has been a very active area of research. Superelectrophilic intermediates are typically generated when a cationic electrophile is additionally protonated by a Brønsted superacid or coordinated by a Lewis superacid to produce a di-(tri- or more)cationic species [11-13]. The acid-catalyzed condensation of ketones and aldehydes with aromatic compounds is known as the hydroxyalkylation reaction [14]. Recently, several hydroxyalkylation reactions followed by alkylation of arenes have been reported involving heterocycle-based superelectrophiles: pyridines, thiazoles, quinolines, isoquinolines, pyrazines,

pyrazoles, imidazole and furanes, bearing formyl (carbonyl) group [15-23]. These carbonyl-substituted heteroarenes possess basic sites (nitrogen or oxygen atoms of heterocyclic system), which are fully protonated in acid, so that upon subsequent protonation of the carbonyl oxygen, more reactive dicationic electrophiles can be generated.

Previously, superelectrophilic activation of carbonyl group was achieved for 5-formyl and 5-acetyl imidazoles in triflic acid CF_3SO_3H (TfOH) by Klumpp [19]. It was proposed that the triflic acid initially protonated the imidazole ring and equilibrium was established with the dicationic superelectrophile. These dications reacted with benzene leading to products of the transformation of carbonyl group into diphenylmetyl one (Figure 2) [19].

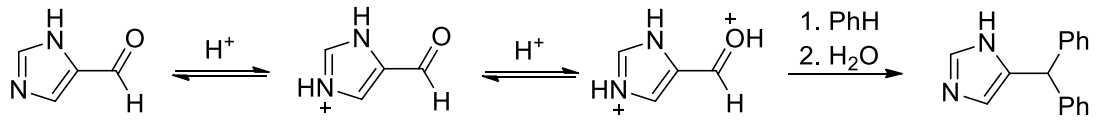


Figure 2. Formation of cationic species at the protonation of 5-formylimidazole in TfOH and their reaction with benzene (data from ref. [19]).

However, up to the moment, there are no data on generation of superelectrophilic species from carbonyl substituted benzimidazoles and their reactions. Based on our previous studies on the chemistry of heterocycles under superelectrophilic activation [22-27], we undertook this research on reactions of benzimidazole derivatives in (super)acids.

The main goal of this work was a study of reactions of substituted benzimidazoles **1-8** (Figure 3) with arenes under the action of Brønsted (super)acids CF_3SO_3H (TfOH, triflic acid), H_2SO_4 and strong Lewis acid AlX_3 (X = Cl, Br). One would expect the electrophilic activation of carbonyl or 2-hydroxyalkyl groups of these benzimidazoles in hydroxyalkylation and alkylation of arenes.

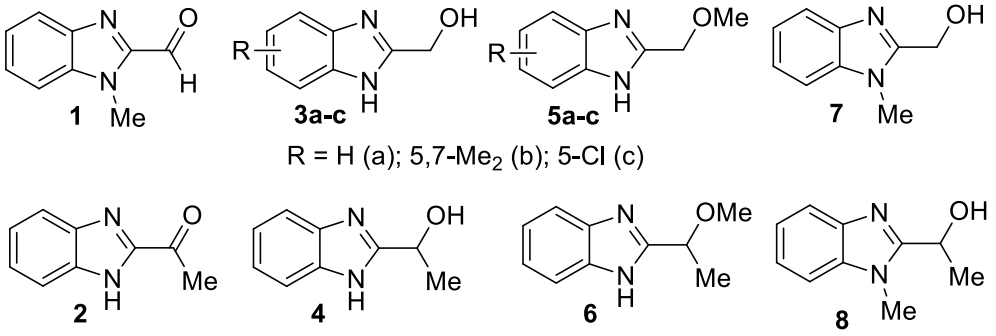


Figure 3. Benzimidazoles **1-8** used in this study.

Results and Discussion

Protonation of formyl and acetyl benzimadazoles **1** and **2** gives rise to *N*,*O*-diprotonated species **I** and **II** correspondingly (see Table 1). Protonation of hydroxyl group of benzimidazoles **3-8** in strong acids gives rise, firstly, to dicationic species **III**,**V**,**VII**,**VIII**, the dehydration of the latter results in the formation of heteroaromatic benzyl type dication **IV**,**VI**,**IX**, respectively. Electronic characteristics, energies of HOMO/LUMO, electrophilicity indices ω [28,29], charge distribution, and contribution of atomic orbital into the LUMO) of species **I-IX** were calculated by DFT method to estimate their electrophilicity and electronic properties (Table 1). Apart from that, ΔG_{298} of reactions of the formation of cations **I-IX** from parent benzimidazoles **1-8** were calculated to estimate a thermodynamic possibility of the species formation (Table 1).

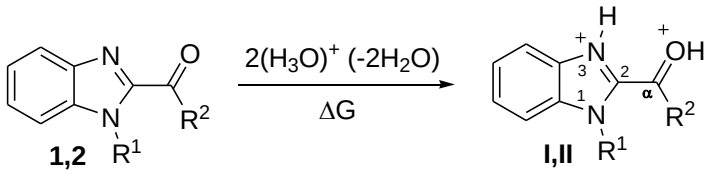
According to DFT calculations, protonation of the benzimidazole nitrogen N^3 and the oxygen of carbonyl or hydroxymethyl group in **1-8** leading to dicationic species **I-III**, **V**, **VII**, **VIII** is thermodynamically favorable due to the negative values of ΔG_{298} values of the corresponding reactions (–18.6 - –25.8 kcal/mol) (Table 1). On the other hand, the dehydration of species **III**, **V**, **VII**, **VIII** is rather unfavorable, since ΔG_{298} values for the reaction formation of dications **IV**, **VI**, **IX**) are 7.2–15.8 kcal/mol (Table 1). These data reveal that, in the case of carbonyl substituted bezimidazoles **1**, **2**, the formation of dications **I**, **II** is very likely, and these species should be reactive electrophiles. While, in the case of hydroxyalkyl benzimidazoles **3-8**, *N*,*O*-diprotonated species **III**, **V**, **VII**, **VIII**, the most probably, may be reactive intermediates.

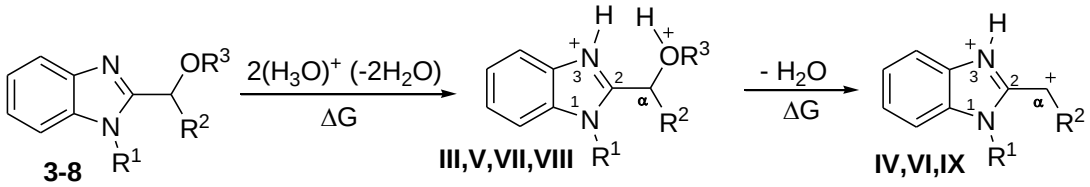
The calculation of electrophilic properties of these cations show that species **I** and **II** have higher values of electrophilicity indices ω 4.4 and 4.9 eV, correspondingly, compare to cations **III**, **V**, **VII**, **VIII** with ω 2.1–2.2 eV. Among all studied species, the heteroaromatic benzyl dication **IV**,**VI**,**IX** have the highest electrophilicity indices ω 5.6–6.1 eV (Table 1).

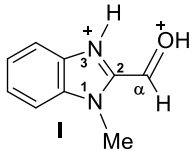
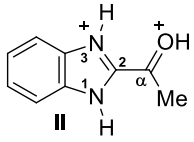
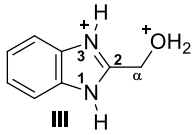
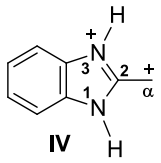
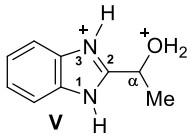
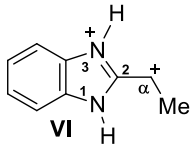
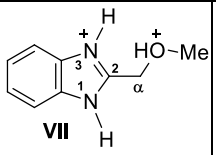
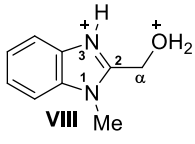
In the dications **I** and **II**, the carbon C^{α} bears a large positive charge (0.47 and 0.65 e) and gives a big contribution into the LUMO (22.1 and 35.4 %) (Table 1). It points out that this particular carbon should be an electrophilic reactive center by both charge and orbital factors. For comparison, the carbon C^2 in **I** and **II** has less positive charge (0.33 and 0.35 e) and much less contribution in LUMO (2.3 and 4.7 %).

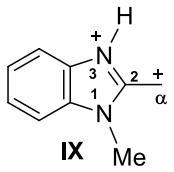
In hydroxonium type species, **III**, **V**, **VII**, **VIII**, charge on the carbon C^{α} is from -0.06 to 0.11 e (Table 1). However, this carbon provides a big contribution into LUMO, 13.9-22 %. This reveals that electrophilic properties of this carbon are mainly ruled by orbital factors. Despite the carbon C^2 in these species has large positive charge (0.46-0.48 e) and great orbital coefficient (17.3-26.3 %), reactions of nucleophiles with this atom is less probable, since it leads to a loss of aromaticity of benzimidazole system. The same should be for a reactivity of the carbon C^2 in dications **I** and **II.**

Table 1. Selected calculated (DFT) electronic characteristics of protonated forms of benzimidazoles.





Species	E_{HOMO}, eV	E_{LUMO}, eV	ω,[a] eV	q(C$^{\alpha}$),[b] e	q(C^{2}),[b] e	q(N^{1}),[b] e	q(N^{3}),[b] e	k(C$^{\alpha}$)$_{LUMO}$,[c] %	k(C^{2})$_{LUMO}$,[c] %	ΔG,[d] kcal/mol
 **I**	-9.53	-6.39	4.9	0.47	0.33	-0.29	-0.44	22.1	2.3	-18.6
 **II**	-9.38	-4.16	4.4	0.65	0.35	-0.30	-0.44	35.4	4.7	-21
 **III**	-9.11	-2.02	2.2	-0.06	0.46	-0.47	-0.48	17.3	26.3	-21.5
 **IV**	-10.07	-5.23	6.1	-0.06	0.31	-0.42	-0.42	28.2	0.6	15.8
 **V**	-9.03	-1.85	2.1	0.11	0.48	-0.34	-0.49	13.9	20.4	-25.6
 **VI**	-9.77	-4.92	5.6	0.14	0.33	-0.28	-0.43	30.5	1.4	7.6
 **VII**	-9.09	-1.90	2.1	-0.06	0.47	-0.48	-0.47	16.3	22.6	-25.8
 **VIII**	-9.04	-2.01	2.2	-0.06	0.47	-0.34	-0.48	22.1	17.3	-23.7

 **IX**	-9.96	-5.14	5.9	-0.08	0.33	-0.29	-0.43	26.5	0.6	14.4

Notes. [a]Global electrophilicity index $\omega = (E_{HOMO} + E_{LUMO})^2/8(E_{LUMO} - E_{HOMO})$. [b]Natural charges. [c]Contribution of atomic orbital into the molecular orbital. [d]Cibbs energy of the species formation reaction.

Then we studied protonation of benzimidazoles in the superacid TfOH by means of NMR. Selected ^1H, ^{13}C and ^{15}N NMR data for starting neutral benzimidazoles **1, 3a, 7** [in $CDCl_3$, $(CD_3)_2CO$, CD_3OD] and their corresponding protonated form **I**, **III**, **VIII** in TfOH are presented in Table 2.

Signal of the proton attached to the nitrogen N^3 in ^1H NMR spectra of all species **I**, **III**, **VIII** in TfOH comes out in the range of 11.37-12.12 ppm (Table 2, see spectral figures in Supporting Information). However, signal of the proton bonded to oxygen of formyl or hydroxyl groups is not observed due to the fast proton exchange for these groups in TfOH at room temperature. Signals of H^α protons for species **I**, **III**, **VIII** in TfOH are down field shifted relatively to the same signals in their neutral precursors **1**, **3a**, **7** [in $CDCl_3$, $(CD_3)_2CO$, CD_3OD], correspondingly (see $\Delta\delta$ values in Table 2). That reveals substantial solvatation of formyl or hydroxyl oxygen of benzimidazoles **1**, **3a**, **7** in TfOH.

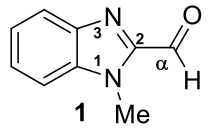
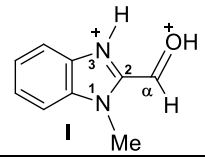
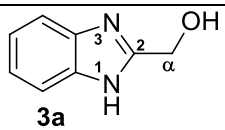
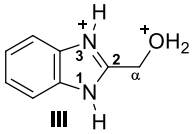
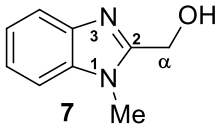
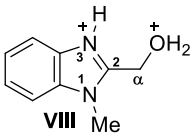
In ^{13}C NMR spectra, signal of carbon C^α in species **I**, **III**, **VIII** in TfOH is slightly up field shifted due to positive charge delocalization into benzimidazole ring. Apart from that, the chemical shift of C^α in hydroxonium type species **III** and **VIII** at 57.5 and 56.9 ppm, which are close to shifts in starting neutral precursors **3a** and **7**, proves unambiguously that no dehydration of these species leading to heteroaromatic benzyl type cations take place.

Based on HSQC and HMBC N–H correlations, we were able to measure ^{15}N chemical shifts of nitrogen atoms for cations **I**, **III**, **VIII** in TfOH (Table 2). Nitrogens N^1 and N^3 have absorbance in rather narrow range of 148.7-158.9 ppm due to charge delocalization between these two nitrogens for the corresponding resonance forms.

Thus, the obtained NMR data clearly demonstrate the formation of *N,O*-diprotonated species **I**, **III**, **VIII** from benzimidazoles **1**, **3a**, **7** in the superacid TfOH.

Table 2. ^1H, ^{13}C and ^{15}N NMR data of benzimidazoles **1,3a,7** in corresponding solvent and species **I, III, VIII** in TfOH at room temperature.

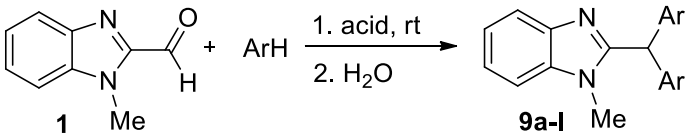
		NMR, δ, ppm

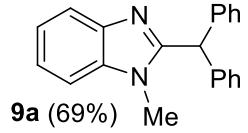
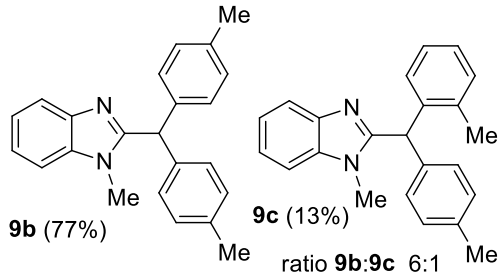
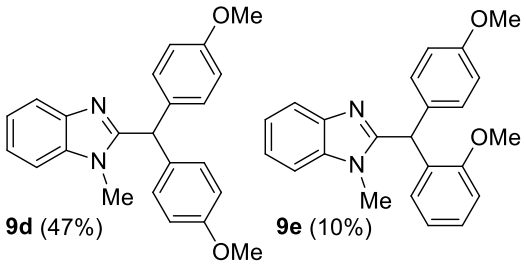
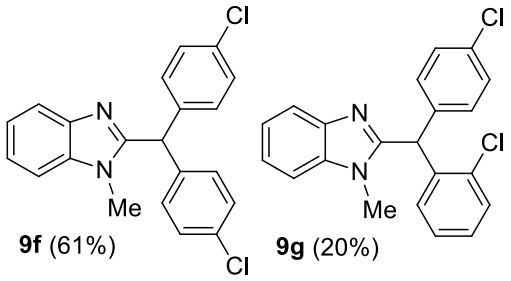
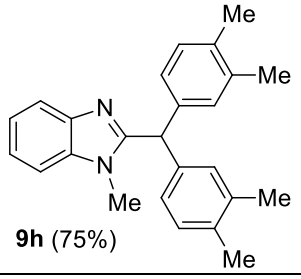
Compound or cation	Solvent	^{1}H		^{13}C		^{15}N	
		H^{α}	$^3N^+H$	C^2	C^{α}	N^1	N^3
 **1**	$CDCl_3$	10.09	-	146.1	185.0	268.4	142.2
 **I**	TfOH	10.28	12.12	137.4	176.8	158.9	151.6
$\Delta\delta$ [a]		0.19		-8.7	-8.2	109.5	9.4
 **3a**	$(CD_3)_2CO$	4.86	-	155.8	59.2	– [b]	– [b]
 **III**	TfOH	5.64	11.53	149.5	57.5	148.7	148.7
$\Delta\delta$ [a]		0.78		-1.7	-1.7	–	–
 **7**	CD_3OD	4.85	-	142.5	57.7	no data	no data
 **VIII**	TfOH	5.57	11.37	148.4	56.9	152.5	149.1
$\Delta\delta$ [a]		0.72		5.9	-0.8	– [b]	– [b]

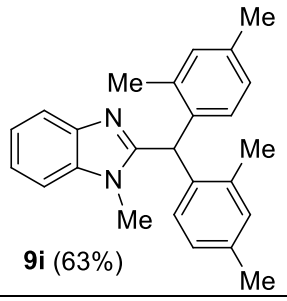
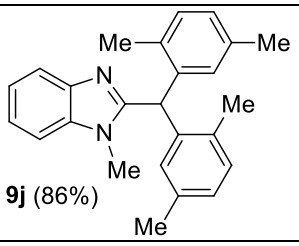
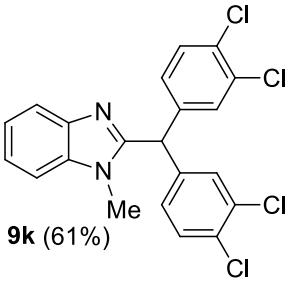
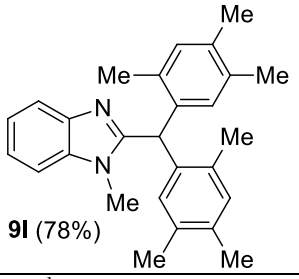
Notes. [a]$\Delta\delta = \delta_{cation} - \delta_{initial}$. [b]No correlation was observed in HSQC and HMBC N–H spectra.

Then, we carried out Friedel-Crafts reactions of benzimidazoles **1-8** with arenes under the action of Brønsted acids (H_2SO_4, TfOH) or Lewis acids (AlX_3, X = Cl, Br). Reactions of 2-formyl-1-methylbenzimidazole **1** with various arenes (benzene, and its methyl, methoxy or chloro substituted derivatives) are given in Table 3. These reactions proceed on the formyl group of **1** and give rise to the corresponding 2-diarylmethyl benzimidazoles **9a-l**. The best results were obtained in neat triflic acid TfOH, which gave high yields of reaction products (57-86%) at room temperature for 2-3 h. Other acids were not so efficient. Thus, reactions under the action of sulfuric acid H_2SO_4 or $AlCl_3$ and $AlBr_3$ took longer time 24-27 h (entries 1, 2, 4). In some cases, the use of H_2SO_4 resulted in the formation of oligomeric reaction products in the reaction of **1** with electron donating *p*-xylene (entry 10). Apart from that, acidity of H_2SO_4 was not enough to activate **1** in the reaction with poor π-nucleophilic 1,2-dichlorobenzene (entry 13).

Table 3. Reactions of 2-formyl-1-methylbenzimidazole **1** with arenes under the action of various acids at room temperature.

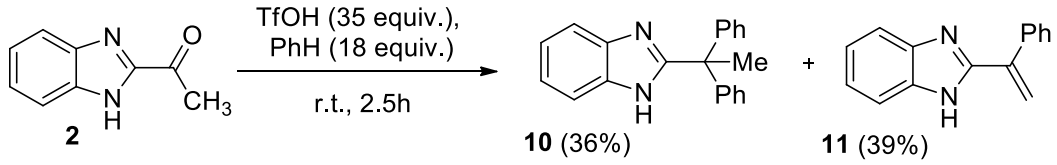


Entry	Arene (equiv.)	Reaction conditions[a]		Reaction products **9**, yield (%)
		Acid (equiv)	Time, h	
1	benzene (18 equiv.)	H_2SO_4 (120 equiv.)	24	 **9a** (69%)
2	benzene (18 equiv.)	TfOH (35 equiv.)	2	**9a** (61%)
3	benzene (100 equiv.)	$AlCl_3$ (5 equiv.)	25	**9a** (54%)[b]
4	benzene (100 equiv.)	$AlBr_3$ (5 equiv.)	27	**9a** (80%)
5	toluene (2.2 equiv.)	TfOH (35 equiv.)	2	 **9b** (77%) **9c** (13%) ratio **9b**:**9c** 6:1
6	anisole (2.2 equiv.)	TfOH (35 equiv.)	2	 **9d** (47%) **9e** (10%) ratio **9d**:**9e** 5:1
7	chlorobenzene (2.2 equiv.)	TfOH (35 equiv.)	2	 **9f** (61%) **9g** (20%) ratio **9f**:**9g** 3:1
8	*o*-xylene (2.2 equiv.)	TfOH (35 equiv.)	3	 **9h** (75%)

9	*m*-xylene (2.2 equiv.)	TfOH (35 equiv.)	3	 **9i** (63%)
10	*p*- xylene (2.2 equiv.)	H_2SO_4 (120 equiv.)	24	oligomeric materials
11	*p*- xylene (2.2 equiv.)	TfOH (35 equiv.)	3	 **9j** (86%)
12	1,2-dichlorobenzene (2.2 equiv.)	TfOH (35 equiv.)	3	 **9k** (61%)
13	1,2-dichlorobenzene (2.2 equiv.)	H_2SO_4 (120 equiv.)	24	–[c]
14	1,2,4-tremethylbenzene (2.2 equiv.)	TfOH (35 equiv.)	3	 **9l** (78%)

Notes. [a]All reactions were carried out at room temperature. [b]Starting benzimidazole **1** was recovered in yield of 26%. [c]Starting benzimidazole **1** was recovered in yield of 72%.

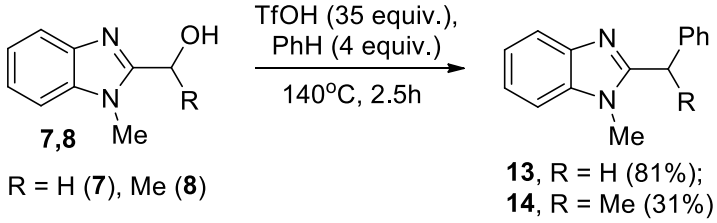
2-Acetylbenzimidazol **2** reacted with benzene in TfOH in the same way, which gave two reaction products **10** and **11** (Scheme 2). Compound **10** was obtained as a result of addition of two benzene molecule to the carbonyl group of **2**. Alkenyl substituted benzimidazole **11** was formed in an alternative way of transformation of intermediate cations (see reaction mechanism below in Scheme 4). It should be noted, that compound **11** in reaction with benzene in TfOH at room temperature for 24 h afforded benzimidazole **10**.



Scheme 2. Reaction of 2-acetylbenzimidazol **2** with TfOH and benzene.

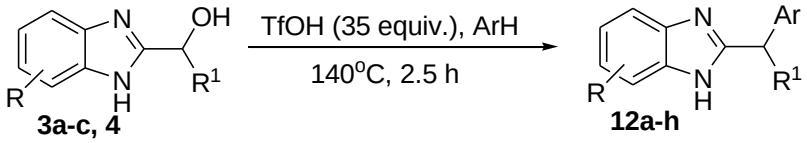
Then, we studied reactions of 2-hydroxyalkyl benzimidazoles **3a-c**, **4**, **7**, **8**. It was found that these reactions needed extremely harsh conditions, heating in neat TfOH at 140°C in glass high pressure tube (Table 4, Scheme 3). Only at this high temperature the formation of Friedel-Crafts reaction products **12a-h**, **13**, **14** was achieved. No reactions took place at lower temperature or under the action of Lewis acids AlX_3 (X = Cl, Br). For these 2-hydroxyalkyl benzimidazoles **3a-c**, **4**, **7**, **8**, we were able to get compounds **12-14** only in reactions with benzene, 1,2-dichlorobenzene and 1,3-dibromobenzene (Table 4). Transformations with methyl substituted benzenes (xylenes) at these harsh conditions gave complex mixtures of oligomeric materials.

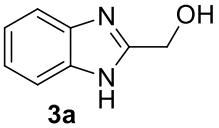
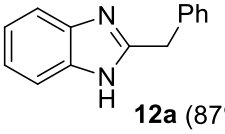
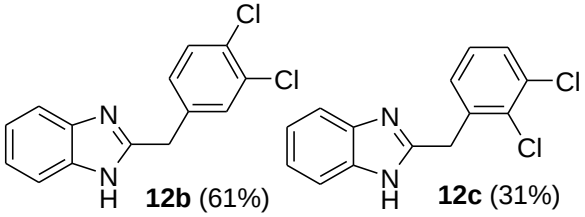
The same interactions of 2-methoxyalkyl benzimidazoles **5a-c, 6** with benzene in TfOH at 140°C resulted in the formation of compounds **12a,f-h** (Table 5).



Scheme 3. Reactions of hydroxymethyl substituted benzimidazole **7** and **8** with TfOH and benzene.

Table 4. Reactions of 2-hydroxyalkyl benzimidazoles **3a-c** and **4** with arenes in TfOH at 140°C.



Entry	Starting benzimidazole	Starting arene (equiv.)	Reaction products **12**, yield (%)
1	 **3a**	benzene (18 equiv.)	 **12a** (87%)
2	**3a**	1,2-dichlorobenzene (4 equiv.)	 **12b** (61%) **12c** (31%) ratio **12b** : **12c** 1:0.5

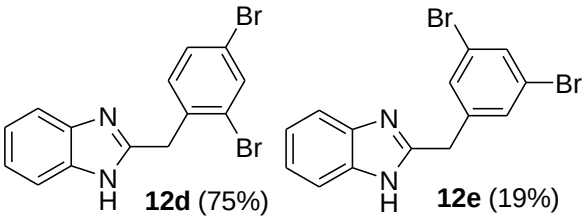
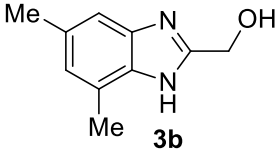
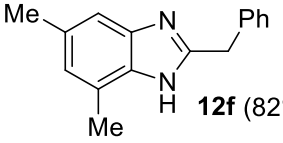
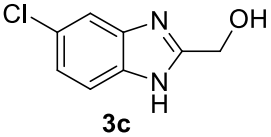
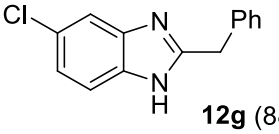
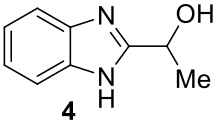
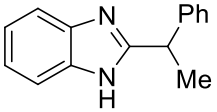
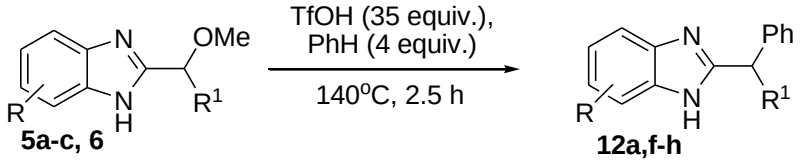
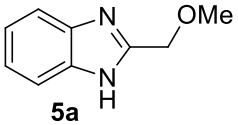
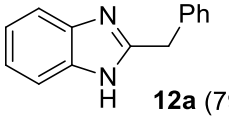
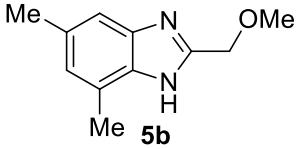
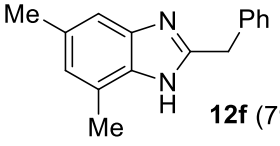
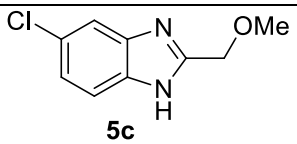
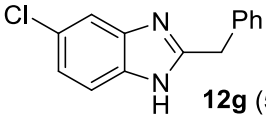
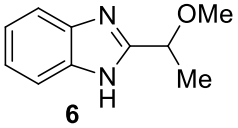
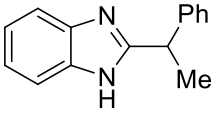
3	**3a**	1,3-dibromobenzene (4 equiv.)	 **12d** (75%) **12e** (19%) ratio **12d** : **12e** 1:0.25
4	 **3b**	benzene (18 equiv.)	 **12f** (82%)
5	 **3c**	benzene (18 equiv.)	 **12g** (88%)
6	 **4**	benzene (18 equiv.)	 **12h** (90%)

Table 5. Reactions of 2-methoxyalkyl benzimidazoles **5a-c,6** with benzene in TfOH at 140°C.

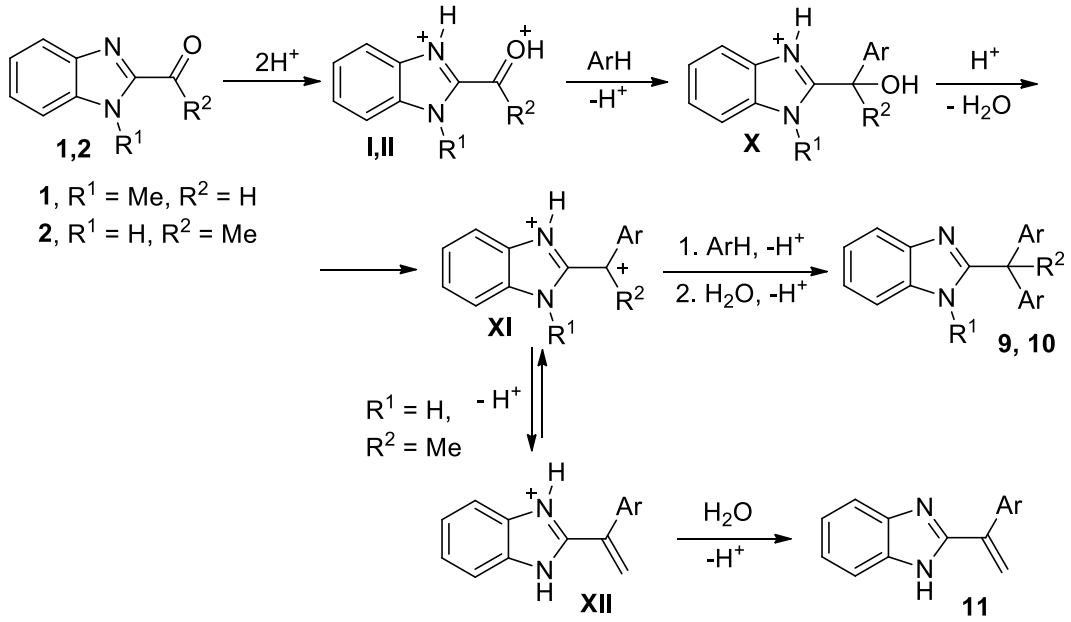


5a-c, 6 **12a,f-h**

Entry	Strarting benzimidazole	Reaction products **12**, yield (%)
1	 **5a**	 **12a** (79%)
2	 **5b**	 **12f** (79%)
3	 **5c**	 **12g** (52%)
4	 **6**	 **12h** (84%)

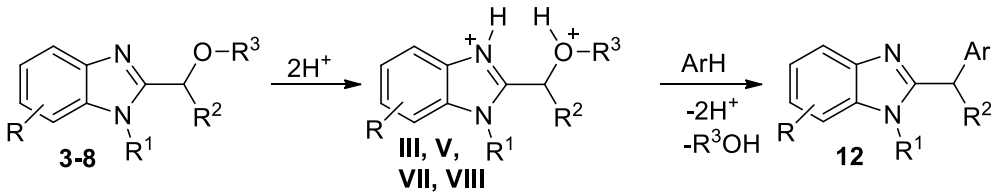
Summarizing all data obtained on DFT calculation (Table 1) and NMR study (Table 2) of intermediate cations generated from benzimidazoles **1-8** in TfOH, and their reactions with arenes (Tables 3-5, Schemes 2,3), one may propose the reaction mechanisms (Schemes 4, 5).

2-Carbonyl substituted benzimidazoles **1**, **2** give rise to *N*,*O*-diprotonated forms **I**, **II**. These species in reaction with arenes furnish hydroxyalkylation products **X**, which are further transformed into cations **XI**. These species consequently react with arenes forming the target compounds **9** and **10** after final hydrolysis of superacidic reaction mixtures. There is another reaction pathway for 2-acetyl benzimidazole **2** on the stage of the formation of cation **XI**. The latter may undergoe deprotonation from the methyl group, that results in the formation of alkenyl benzimidazole **11**, which may be also transformed into compound **10** by reaction with arenes in TfOH (see Scheme 2 and the corresponding discussion to it).



Scheme 4. Reaction mechanism of the formation of compounds **9-11**.

Hydroxy(or methoxy)alkyl substituted benzimidazoles **3-8** form dications **III, V, VII**, **VIII**, correspondingly. These species react with arenes, the most probably, in S_N2 way to give benzimidazoles **12** (Scheme 5)



Scheme 5. Reaction mechanism of the formation of compounds **12**.

It should be specially emphasized that such 2-diarylmethyl and 2-arylmethyl substituted benzimidazoles **9-12** are synthetically hardly available compounds [30, 31]. For instance, they were investigated as AMP-activated protein kinase activators [30].

Conclusion

Reactions of 2-carbonyl and 2-hydroxy(or methoxy)alkyl substituted benzimidazoles with arenes in the Brønsted superacid TfOH were studied for the first time. These reactions proceed onto carbon atom of 2-carbonyl or 2-hydroxyalkyl group leading to the corresponding 2-diarylmethyl or 2-arylmethyl substituted benzimidazoles. Reactive intermediate electrophilic species in these transformations are *N,O*-diproptonated species of starting benzimidazoles.

Supporting Information

These data contain experimental details, compounds characterization, copies of ^{1}H, ^{13}C NMR spectra, and details of DFT calculations.

Acknowledgment

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