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PII: S0040-4020(14)01747-5

DOI: 10.1016/j.tet.2014.12.043

Reference: TET 26264

To appear in: *Tetrahedron*

Received Date: 3 November 2014

Revised Date: 11 December 2014

Accepted Date: 12 December 2014

Please cite this article as: Lee Y-S, Cho Y-H, Lee S, Bin J-K, Yang J, Chae G, Cheon C-H, Significant facilitation of metal-free aerobic oxidative cyclization of imines with water in synthesis of benzimidazoles, *Tetrahedron* (2015), doi: 10.1016/j.tet.2014.12.043.

Graphical Abstract

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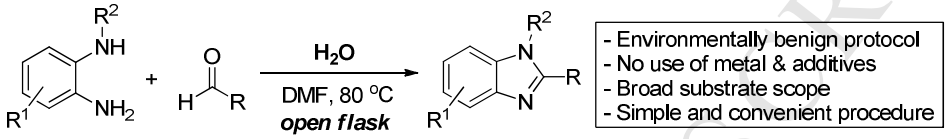

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Benzimidazole
Aerobic oxidation
Metal-free
Nucleophilic catalyst
Water
Baldwin's rules

ABSTRACT

A simple, convenient, and environmentally benign protocol for the synthesis of benzimidazoles from *ortho*-phenylenediamines and aldehydes via aerobic oxidation was developed in wet organic solvents. Notably, water significantly accelerated this transformation, which allowed us to achieve this important transformation without the assistance of any metal catalysts and other co-oxidants. Mechanistic studies suggested that water acts as the nucleophilic catalyst for this transformation by the conversion of disfavored 5-*endo-trig* cyclization of imines to favored 5-*exo-tet* cyclization via tetrahedral intermediates and the subsequent aerobic oxidation of the resulting benzimidazolines affords benzimidazoles.

Introduction

Benzimidazoles are important building blocks found in biologically and therapeutically active compounds, natural products, and functional materials.[1] Therefore, tremendous effort has been made to develop efficient methods for the synthesis of these compounds.[2,3] One conventional method for the synthesis of benzimidazoles involves the oxidative cyclization of imines derived from *ortho*-phenylenediamines with aldehydes in the presence of oxidants.[4] However, many of these protocols produce toxic and/or environmentally problematic by-products, which often requires tedious workup and purification procedures.

Because molecular oxygen is an abundant, inexpensive and environmentally benign oxidant, aerobic oxidations using molecular oxygen as the terminal oxidant have attracted much attention from the synthetic community as green protocols.[5] In this regard, a number of protocols for the synthesis of benzimidazoles under aerobic oxidation conditions have been developed.[6] In contrast to the aerobic oxidation protocols for the synthesis of other benzofused 1,3-azoles, such as benzoxazoles and benzothiazoles, generally requiring transition metal catalysts,[7,8] there have been a few examples of the synthesis of benzimidazoles via the metal-free aerobic oxidation protocols.[9,10] However, none of these previous reports for the synthesis of benzimidazoles under the metal-free aerobic oxidation conditions have specified the reaction parameters required to control this transformation. Herein, we report the synthesis of benzimidazoles from *ortho*-phenylenediamines and aldehydes via metal-free aerobic oxidation in wet organic solvents. Notably, we for the first time elucidated the key controlling parameter in the synthesis of benzimidazoles via metal-free aerobic oxidation; water plays a crucial role in the synthesis of benzimidazoles under aerobic oxidation conditions by converting the disfavored 5-*endo-trig* cyclization of imines to the favored 5-*exo-tet* cyclization through tetrahedral intermediates. This finding enables us to synthesize benzimidazoles without using any metal catalysts and/or co-oxidants.

Results/Discussion

Our group has been interested in the development of new protocols for the synthesis of biologically important heteroaromatic compounds via metal-free aerobic oxidation reactions in the presence of a nucleophile which could facilitate this transformation by converting the less favored *endo*-cyclization of imines to the more favored *exo*-cyclization through tetrahedral intermediates generated by the addition of the nucleophile to the imines.[11-14] For example, we recently developed a highly efficient method for the synthesis of benzoxazoles **1** from 2-aminophenol and aldehydes via metal-free aerobic oxidation using cyanide as the nucleophilic catalyst.

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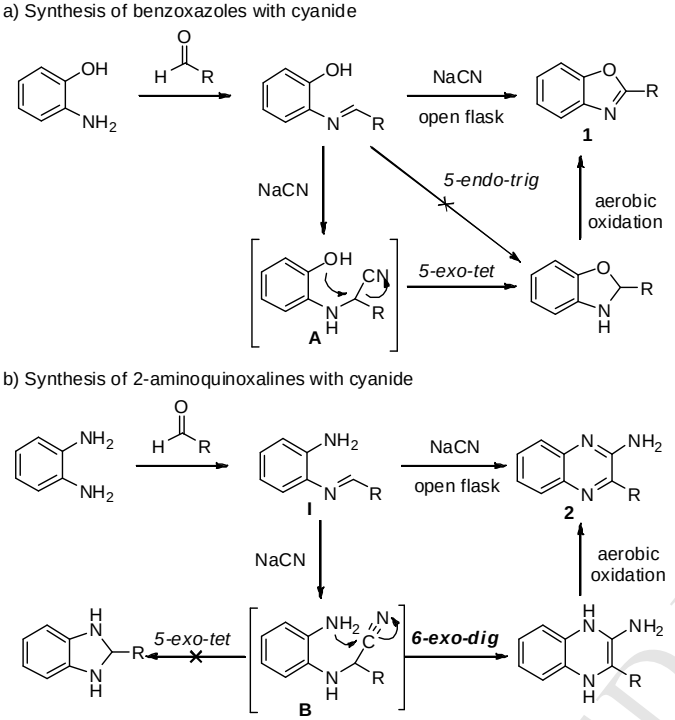
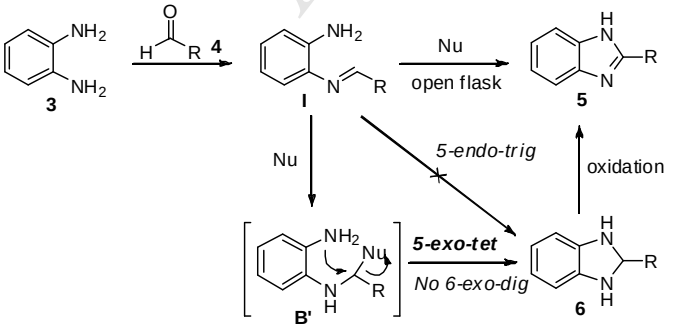
It was found that cyanide significant accelerated this transformation by promoting the cyclization of an imine by converting disfavored 5-*endo-trig*-cyclization of the imine into favored 5-*exo-tet*-cyclization through tetrahedral intermediate **A** (Scheme 1a).[11]

When this protocol was attempted to be extended to the synthesis of benzimidazoles with *ortho*-phenylenediamine and aldehydes, the expected benzimidazoles were not obtained; instead, 2-aminoquinoxalines **2** were obtained in good yields via the 6-*exo-dig* cyclization at the carbon of the nitrile group in tetrahedral intermediates **B** (Scheme 1b).[13]



Scheme 1. Synthesis of heteroaromatic compounds via metal-free aerobic oxidation in the presence of cyanide.

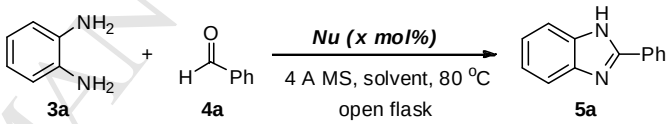
Although the aerobic oxidation of *ortho*-phenylenediamines and aldehydes in the presence of cyanide only afforded 2-aminoquinoxalines, in which tetrahedral intermediates **B** underwent 6-*exo-dig* cyclization rather than 5-*exo-tet* cyclization, we envisioned that the benzimidazoles could be intrinsically synthesized with a different nucleophile (instead of cyanide) under aerobic oxidation conditions, where tetrahedral intermediates **B'**, generated by the addition of the nucleophile to imines **I**, undergo only 5-*exo-tet* cyclization, not 6-*exo-dig* cyclization (Scheme 2).



Scheme 2. Working hypothesis for the synthesis of benzimidazoles **5** via metal-free aerobic oxidation with a different nucleophile.

To test this hypothesis, several nucleophiles were investigated as catalysts for the synthesis of benzimidazoles under the similar reaction conditions[11] used for the benzoxazole synthesis (Table 1). Delightfully, iodide was found to significantly accelerate this transformation; benzimidazole **5a** was obtained from *ortho*-phenylenediamine **3a** and benzaldehyde **4a** in an excellent yield in the presence of a stoichiometric amount of iodide at 80 °C (entry 2). However, **5a** was not obtained in the absence of iodide, presumably because imine **I** could not undergo cyclization through the disfavored 5-*exo-trig* cyclization (entry 1). When this reaction was carried out under argon atmosphere, only a trace amount of **5a** was obtained, indicating that the molecular oxygen present in air acts as the terminal oxidant in this transformation (entry 3). Next, other nucleophiles were investigated as the catalysts in this transformation. However, other nucleophiles did not promote this transformation at all (entries 4 and 5). The nucleophilicity of the halide turned out to slightly affect this transformation; KCl and KBr also afforded the desired product in high yields, but longer reaction times were needed with these less nucleophilic halides than iodide (entries 6 and 7).

Table 1. Optimization of Reaction Conditions



[a] Isolated yield of **5a**.

Entry	Nu (x mol%)	Solvent	Time (h)	Yield[a] (%)
1	-	DMF	48	N.R.[b]
2	KI (100)	DMF	24	93
3[c]	KI (100)	DMF	48	Trace
4	NaOAc (100)	DMF	48	N.R.[b]
5	DMAP (100)	DMF	48	N.R.[b]
6	KCl (100)	DMF	36	89
7	KBr (100)	DMF	36	90
8	KI (100)	DMSO	24	91
9	KI (100)	CH_3CN	24	N.R.[b]
10	KI (100)	1,4-Dioxane	24	N.R.[b]
11	KI (100)	Toluene	24	N.R.[b]
12	KI (10)	DMF	48	91
13	KI (5)	DMF	96	84
14	KI (1)	DMF	120	50

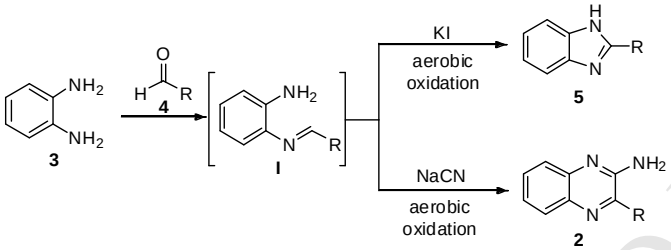
[b] N.R. means no reaction.
[c] Under argon atmosphere.

Because previous studies on the metal-free aerobic oxidation protocols for the synthesis of benzimidazoles demonstrated that these transformations could be performed in diverse solvents,[9]

the effect of reaction media was further investigated (entries 2 and 8-11). Rather unexpectedly, the choice of the solvent significantly affected the efficiency of this transformation; the desired product **5a** was obtained in high yields in DMF and DMSO (entries 2 and 8), whereas no reaction was observed in any other solvent (entries 9-11). Because the reaction in DMF afforded the desired product **5a** in a slightly better yield than that in DMSO, DMF was selected for further study.

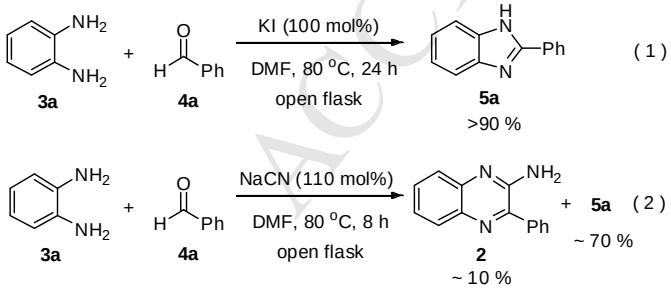
On the basis of the working hypothesis in conjugation with our previous studies on the synthesis of benzoxazoles via aerobic oxidation in the presence of a nucleophile, this transformation was intrinsically possible with a catalytic amount of KI. Thus, we investigated this transformation with a catalytic amount of KI (entries 2, 12-14). To our delight, a catalytic amount of KI was sufficient enough to promote this transformation; even with 5 mol % of KI, the desired product was obtained in high yield, albeit a long reaction time was needed.

With these results in hand, we attempted to demonstrate the advantages of the methods developed by our group in the selective synthesis of either benzimidazoles **5** or 2-aminoquinoxalines **2** from the same substrate depending on the choice of a nucleophilic reagent (Scheme 3). For example, benzimidazole **5** was expected to be produced with KI as the nucleophilic catalyst as shown in Scheme 3, while NaCN would yield 2-aminoquinoxaline **2** under the similar reaction conditions.



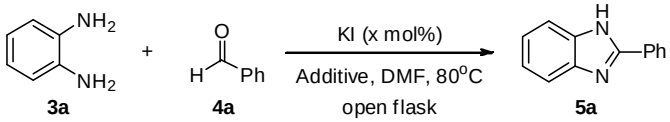
Scheme 3. Diverse synthesis of 2-aminoquinoxalines **2** or benzimidazoles **5** from the same substrates depending on the choic of the nucleophile.

When KI was used as a nucleophilic catalyst, as expected, the corresponding benzimidazole **5a** was obtained in an excellent yield (Eq. 1). However, the reaction with NaCN furnished 2-aminoquinxoline **2** in low yield; rather unexpectedly, benzimidazole **5a** was obtained as the major product (Eq. 2).



Because the formation of benzimidazole **5a** has never been achieved during our previous attempts in the synthesis of benzimidazoles with NaCN,[13] we carefully compared the reaction conditions in Eq. 2 with those used previously for the synthesis of 2-aminoquinoxaline,[13] and found that molecular sieves were not accidently added to the reaction mixture in Eq. 2. This result strongly suggested that water play a crucial role in this transformation.[15]

Table 2. Effect of Additives on the Synthesis of Benzimidazoles via Aerobic Oxidation



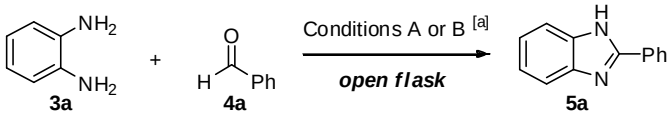
Entry	KI (x mol%)	Additive	Time (h)	Yield[a] (%)
1	100	4A MS	24	93
2	100	-	12	91
3	-	-	12	54
4	-	water[b]	2	94

[a] Isolated yield of **5a**.
[b] 10 vol % of water was used.

On the basis of this interesting finding, the role of molecular sieves, i.e., the role of water, was explored on this transformation (Table 2). It was found that molecular sieves were not actually needed in this transformation; the formation of **5a** took place in the absence of molecular sieves without any loss of efficiency even in a short reaction time (entries 1 and 2). Surprisingly, this reaction proceeded in the absence of KI and molecular sieves; the desired product **5a** was obtained in 54 % yield (entry 3). Furthermore, water was found to significantly accelerate the formation of **5a**; when water was intentionally added to the reaction mixture, this aerobic oxidation proceeded much faster to yield **5a** in an excellent yield and a much shorter reaction time (entry 4).

With these unexpected results, we conducted a literature survey on the synthesis of benzimidazoles via aerobic oxidation and found that there have been a few reports of metal/additive-free aerobic oxidation protocols for the synthesis of benzimidazoles.[9] However, none of them clearly specified whether their optimized reaction medium was completely anhydrous. Since our result strongly suggested that water significantly facilitate the formation of benzimidazoles under metal-free aerobic oxidation conditions,[13] the effect of water on this transformation in various aprotic organic solvents was investigated (Table 3). As expected, water significantly accelerated this transformation in various organic solvents; **5a** was obtained in good-to-excellent yields in any wet aprotic solvent, while only a trace amount of **5a** was obtained in a dry solvent (entries 1-5).

Table 3. Effect of water on the synthesis of benzimidazoles



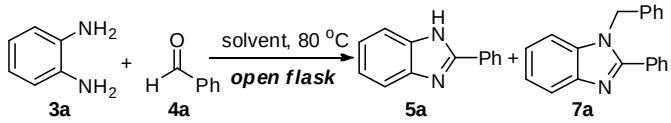
			Yield[b] (%)	
Entry	solvent	Time (h)	Method A	Method B
1	DMF	3	Trace[c]	98 (91)[d]
2	DMSO	8	Trace[c]	85
3	MeCN	24	Trace[c]	78

4	1,4-Dioxane	24	Trace[c]	67
5	Toluene	24	Trace[c]	69

[a] Conditions A: 4 Å MS, 80 °C, open flask with a $CaCl_2$ tube. Conditions B: H_2O (10 % (v)), 80 °C, open flask without a $CaCl_2$ tube.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] Less than 5 % of yield of **5a**.
[d] The value in parentheses indicates the isolated yield of **5a**.

Based on the result shown in Table 3, we expected that an alcoholic solvent might play a similar role as water in this transformation; i.e., an alcoholic solvent would accelerate the transformation (Table 4).[16] As expected, the aerobic oxidation reaction took place in any alcoholic solvent in the absence of any metal catalyst. However, a significant amount of 1,2-disubstituted benzimidazole **7a** was obtained in an alcoholic solvents including water and the amount of **7a** decreases as the alkyl group in the alcohol became bulkier (entries 1-4).

Table 4. Effect of Alcoholic Solvents on the Synthesis of Benzimidazoles

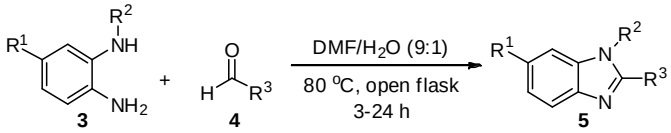


Entry	Solvent	Time (h)	Yield[a] (%) (**5a** : **7a**)
1	H_2O	6	30 : 32
2	MeOH	6	36 : 30
3	EtOH	6	57 : 20
4	i-PrOH	6	67 : 13

[a] Isolated yield of **5a** and **7a**, respectively.

Next, the substrate scope of this transformation was investigated in wet DMF (Table 5). Various aromatic aldehydes were applicable to this protocol (entries 1-10). The electronic natures of aromatic aldehydes had little influence on the formation of benzimidazoles; the desired products were obtained in high-to-excellent yields regardless of electronic natures of aromatic aldehydes (entries 1-6). In addition, sterically congested aldehydes bearing a substituent at the *ortho*-position were amenable to this protocol, affording the desired benzimidazoles without any loss of efficiency (entries 7-10) This protocol could be extended to fused aromatic aldehydes, heteroaromatic aldehydes, and α,β-unsaturated aldehydes (entries 11-16). Furthermore, aliphatic aldehydes were also applicable to this protocol. However, aliphatic aldehydes furnished the desired benzimidazoles in slightly lower yields than aromatic ones (entries 17-19). In addition, formaldehyde was applicable to this protocol affording the parent benzimidazole in 83 % yield (entry 20). The substituents on the *ortho*-phenylenediamine moiety were also investigated. The substituents slightly affected this transformation and the desired products were obtained in excellent yields regardless of the electronic nature of *ortho*-phenylenediamine moiety (entries 1 and 21-23). Moreover, *N*-substituted *ortho*-phenylenediamines were applicable to this protocol, affording 1,2-disubstituted benzimidazoles without any loss of efficiency (entries 24-26).

Table 5. Substrate Scope



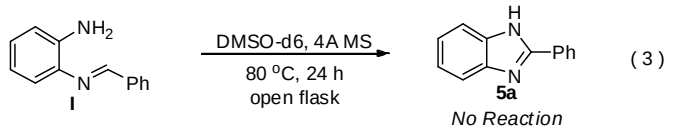
Entry	**5**	R^1	R^2	R^3	Yield[a] (%)
1	**5a**	H	H	C_6H_5	91
2	**5b**	H	H	4-$MeOC_6H_4$	87
3	**5c**	H	H	4-MeC_6H_4	91
4	**5d**	H	H	4-ClC_6H_4	93
5	**5e**	H	H	4-$MeO_2CC_6H_4$	92
6	**5f**	H	H	4-$NO_2C_6H_4$	92
7	**5g**	H	H	2-$MeOC_6H_4$	82
8	**5h**	H	H	2-MeC_6H_4	95
9	**5i**	H	H	2-ClC_6H_4	96
10	**5j**	H	H	2-HOC_6H_4	90
11	**5k**	H	H	1-naphthyl	96
12	**5l**	H	H	2-naphthyl	94
13	**5m**	H	H	2-furyl	90
14	**5n**	H	H	2-thienyl	93
15	**5o**	H	H	2-pyridyl	93
16	**5p**	H	H	cinnamyl	69
17	**5q**	H	H	*n*-hexyl	69
18	**5r**	H	H	*c*-hexyl	70
19	**5s**	H	H	*t*-butyl	70
20	**5t**	H	H	H	83
21	**5u**	Me	H	C_6H_5	86
22	**5v**	Cl	H	C_6H_5	80
23	**5w**	CO_2H	H	C_6H_5	82
24	**5x**	H	Me	C_6H_5	90
25	**7a**	H	Bn	C_6H_5	90
26	**5y**	H	Ph	C_6H_5	96

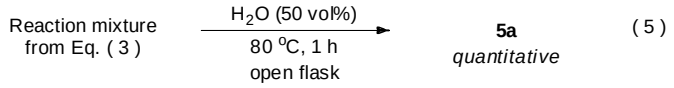
[a] Isolated yield.

With these results, we attempted to elucidate the reaction mechanism, particularly the role of water (or KI) in this aerobic oxidation protocol for the synthesis of benzimidazoles. As shown in Scheme 2, the oxidative cyclization of *ortho*-phenylenediamine **3** with aldehyde **4** is generally believed to proceeds as follows: (1) the formation of imine **I**, (2) the cyclization of the imine to form benzimidazoline **6**, and (3) the oxidation of **6** to afford **5**. Similar to our previous studies on the synthesis of benzoxazoles via aerobic oxidation using cyanide as the catalyst, we believed that the cyclization step would be the

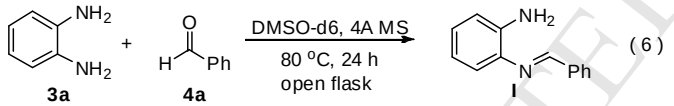
rate-determining step for this transformation under aerobic oxidation conditions, because the 5-*endo-trig* cyclization of **I** is a disfavored transformation according to the Baldwin's rules.[14]

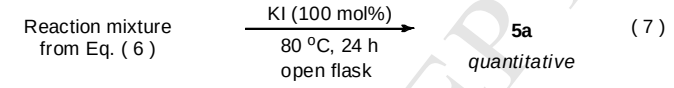
To test this idea, when imine **I**[17] was subjected to the aerobic oxidation conditions in the absence of any nucleophilic catalyst, **I** remained intact and no formation of benzimidazole **5a** was observed even after a long reaction time (Eq. 3). However, when KI was added to the above reaction mixture from Eq. 3, the aerobic oxidative cyclization smoothly proceeded to afford **5a** in an excellent yield (Eq. 4).[18] Moreover, when water (50 vol % of DMF) was added to the above reaction mixture from Eq. 3, **5a** was also obtained without any loss of efficiency (Eq. 5).[18]

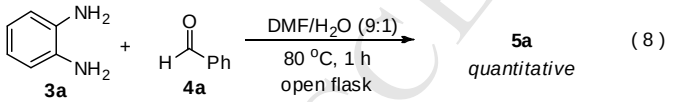




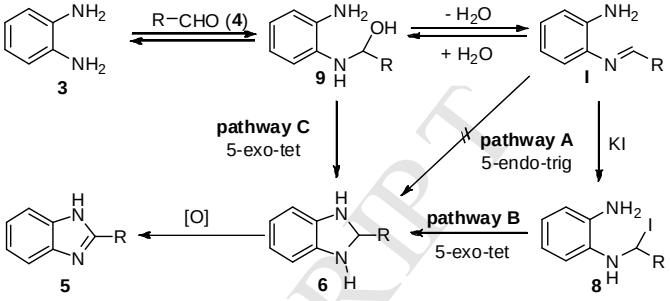
Furthermore, when **3a** and **4a** were directly subjected to dry reaction conditions with molecular sieves, the desired benzimidazole **5a** was not formed and imine **I** was obtained in moderate yield (Eq. 6). However, when KI was added to the above reaction mixture from Eq. 6, this aerobic oxidation proceeded to completion affording the desired product **5a** in quantitative yield (Eq. 7). Furthermore, when **3a** and **4a** were directly subjected to the reaction conditions in wet DMF, **3a** and **4a** were completely converted to the corresponding benzimidazole **5a** even in a short reaction time (Eq. 8).





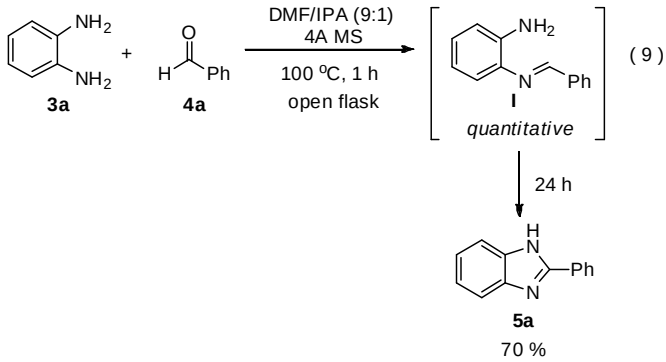


Based on these experimental results along with our recent report on the benzoxazole synthesis under the aerobic oxidation conditions, a possible reaction mechanism was proposed (Scheme 4). The cyclization of imine **I** might be the rate-determining step and not take place without any assistance of a nucleophile because the 5-*endo-trig* cyclization of **I** is a disallowed transformation according to the Baldwin's rules. Thus, the desired benzimidazole **5** could not be formed in the absence of a nucleophilic catalyst (pathway A). However, in the presence of KI, tetrahedral intermediate **8**, generated by adding iodide to **I**, could undergo the favored 5-*exo-tet* cyclization to furnish benzimidazoline **6**. The subsequent aerobic oxidation of **6** affords the desired benzimidazole **5** (pathway B). For the significant acceleration by water, we believed that water would play a similar role as KI under anhydrous conditions. In the absence of water, **I** remained intact even after a long reaction time due to the disfavored 5-*endo-trig* cyclization of **I**. However, when water was added to the imine solution, the equilibrium could be shifted from imine **I** to the starting diamine **3** and aldehyde **4** through tetrahedral intermediate **9**. During this equilibrium, intermediate **9** could undergo the favored 5-*exo-tet* cyclization to generate benzimidazoline **6**. Final oxidation of **6** yields compound **5** (pathway C).[19]



Scheme 4. Proposed Reaction Mechanism

To further verify the validity of the proposed reaction mechanism, the same reaction was carried out using an alcohol as the nucleophilic catalyst. When **3a** and **4a** were subjected to the reaction conditions in a mixture of DMF and 2-propanol (9:1), initially all the starting materials were completely converted into imine **I** and no formation of the desired product **5a** was observed. However, in the presence of alcohol, the initially formed imine was gradually converted into the desired product leading to the formation of the desired product **5a** in 70 % yield after 24 h (Eq. 9). This result also implied that an alcohol could act as the nucleophilic catalyst, which could facilitate the cyclization of imine through a tetrahedral intermediate, even though an alcohol was not as efficient as water.



This proposed reaction mechanism also explained why the reaction from imine **I** required a much larger amount of water (50 vol % of DMF) than the direct reaction of **3a** and **4a** (10 vol % of DMF). Because **I** might be more stable than starting materials **3a** and **4a**, a significantly large amount of water was needed to shift the equilibrium from imine to the starting materials through tetrahedral intermediate **9**, which could be susceptible for the 5-*exo-tet* cyclization to form intermediate **6**.

Conclusion

We developed a highly efficient and environmentally benign protocol for the synthesis of benzimidazoles via metal-free aerobic oxidation in wet organic solvents. Although a few reports on the synthesis of benzimidazoles via metal/additive-free aerobic oxidation have been reported, we, for the first time,

elucidated the key controlling parameter in the synthesis of benzimidazoles through metal/additive-free aerobic oxidation; water plays a crucial role in this aerobic oxidation reaction. Furthermore, we further clarified the role of water (or KI) as the nucleophilic catalyst, which could promote the cyclization of imines through the conversion of disfavored 5-*endo-trig* cyclization to favored 5-*exo-tet* cyclization via a tetrahedral intermediate generated by the addition of the nucleophile to the imine. Further explorations on the applications of this aerobic oxidation protocol for benzimidazole synthesis are currently underway in our laboratory.

Experimental Section

General. All reactions were carried out in oven-dried glassware in an open flask unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. Liquid aldehydes were freshly distilled under an atmosphere of dry argon, and solid aldehydes were purified by flash chromatography on silica gel. All the *ortho*-phenylenediamine derivatives were purchased from commercial sources and used directly without further purification. *N*-Methyl- and *N*-benzyl-1,2-phenylenediamines were prepared by the literature procedures.[18,19] NMR spectra were recorded at 25 ^{o}C unless stated otherwise: ^{1}H NMR spectra were recorded at 400/300 MHz. Tetramethylsilane was used as internal standards for ^{1}H NMR (δ: 0.0 ppm). The proton spectra were reported as follows δ (position of proton, multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad).

Synthesis of benzimidazoles via metal-free aerobic oxidation in wet DMF (Table 5): To a solution of an *ortho*-phenylenediamine derivative **3** (1.0 mmol; 1.0 equiv) and an aldehyde **4** (1.1 mmol; 1.1 equiv) were dissolved in wet DMF (DMF 9.0 mL, H_2O 1.0 mL). The resulting reaction mixture was stirred at 80 ^{o}C in an open flask, and the reaction progress was monitored by TLC. On the complete consumption of **3**, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel to afford the corresponding benzimidazole **5**.

*2-Phenyl-1H-benzimidazole (**5a**).*[20] A white solid. Yield: 176 mg (91 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.17 – 8.19 (m, 2H), 7.46 – 7.59 (m, 5H), 7.19 (dd, *J* = 5.9, 3.2 Hz, 2H). Mp 297-299 ^{o}C (lit. 293-296 ^{o}C).

*2-(4-Methoxyphenyl)-1H-benzimidazole (**5b**).*[20] A pale yellow solid. Yield: 196 mg (87 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:1:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.10 (d, *J* = 8.8 Hz, 2H), 7.54 (br, 2H), 7.15 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H). Mp 233-234 ^{o}C (lit. 226 ^{o}C).

*2-(4-Methylphenyl)-1H-benzimidazole (**5c**).*[20] A yellow solid. Yield: 190 mg (91 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.06 (d, *J* = 8.0 Hz, 2H), 7.57 (br, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.18 (dd, *J* = 5.8, 3.0 Hz, 2H), 2.38 (s, 3H). Mp 270-271 ^{o}C (lit. 276 ^{o}C).

*2-(4-Chlorophenyl)-1H-benzimidazole (**5d**).*[20] A yellow solid. Yield: 213 mg (93 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.19 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.21 (dd, *J* = 6.0, 3.0 Hz, 2H). Mp 299-301 ^{o}C (lit. 302 ^{o}C).

*2-(4-Methoxycarbonylphenyl)-1H-benzimidazole (**5e**).*[21] A yellow solid. Yield: 232 mg (92 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:2:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.32 (d, *J* = 8.5 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.63 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.24 (dd, *J* = 6.0, 3.0 Hz, 2H), 3.90 (s, 3H). Mp 232-234 ^{o}C (lit. 220 ^{o}C).

*2-(4-Nitrophenyl)-1H-benzimidazole (**5f**).*[21] A light gray solid. Yield: 220 mg (92 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:2:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.41 (s, 4H), 7.65 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.25 (dd, *J* = 6.0, 3.0 Hz, 2H). Mp over 300 ^{o}C (lit. 315 ^{o}C).

*2-(2-Methoxyphenyl)-1H-benzimidazole (**5g**).*[20] A light brown solid. Yield: 184 mg (82 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.31 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.63 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.2, 1H), 7.16 – 7.20 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 4.03 (s, 3H). Mp 186-188 ^{o}C (lit. 150-180 ^{o}C).

*2-(2-Methylphenyl)-1H-benzimidazole (**5h**).*[20] A yellow solid. Yield: 199 mg (95 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.73 (d, *J* = 6.6 Hz, 1H), 7.60 (br, 2H), 7.34 – 7.41 (m, 3H), 7.21 (dd, *J* = 5.8, 3.0 Hz, 2H), 2.61 (s, 3H). Mp 227-228 ^{o}C (lit. 200-220 ^{o}C).

*2-(2-Chlorophenyl)-1H-benzimidazole (**5i**).*[22] A light brown solid. Yield: 219 mg (96 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.89 – 7.92 (m, 1H), 7.60 – 7.67 (m, 3H), 7.49 – 7.57 (m, 2H), 7.24 (dd, *J* = 5.9, 3.2 Hz, 2H). Mp 237-238 ^{o}C (lit. 235 ^{o}C).

*2-(2-Hydroxylphenyl)-1H-benzimidazole (**5j**).*[22] A white solid. Yield: 189 mg (90 %). R_f = 0.5 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.06 (d, *J* = 8.0 Hz, 1H), 7.67 (br, 2H), 7.35 – 7.42 (m, 1H), 7.29 (dd, *J* = 6.0, 3.0 Hz, 2H), 6.99 – 7.09 (m, 2H). Mp 244-246 ^{o}C (lit. 242 ^{o}C).

*2-(1-Naphthyl)-1H-benzimidazole (**5k**).*[23] A yellow solid. Yield: 235 mg (96 %). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 9.11 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.00 – 8.06 (m, 2H), 7.60 – 7.72 (m, 5H), 7.26 (dd, *J* = 5.9, 3.2 Hz, 2H). Mp 267-269 ^{o}C (lit. 270 ^{o}C).

*2-(2-Naphthyl)-1H-benzimidazole (**5l**).*[20] A yellow solid. Yield: 230 mg (94 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.73 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.97 – 8.04 (m, 2H), 7.58 – 7.62 (m, 4H), 7.21 (dd, *J* = 5.9, 3.2 Hz, 2H). Mp 220-222 ^{o}C (lit. 217 ^{o}C).

*2-(Furan-2-yl)-1H-benzimidazole (**5m**).*[20] A brown solid. Yield: 166 mg (90 %). R_f = 0.4 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.94 (s, 1H), 7.55 (br, 2H), 7.16 – 7.23 (m, 3H), 6.73 (dd, *J* = 3.4, 1.8 Hz, 1H). Mp was not available due to decomposition of **5m** at 290 ^{o}C (lit. 290 ^{o}C).

*2-(Thien-2-yl)-1H-benzimidazole (**5n**).*[20] A light yellow solid. 186 mg (93 %). R_f = 0.5 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.83 (d, *J* = 3.6 Hz, 1H), 7.73(d, *J* = 4.9 Hz, 1H), 7.50 – 7.59 (m, 2H), 7.15 – 7.26 (m, 3H). Mp over 300 ^{o}C (lit. 330 ^{o}C).

*2-(Pyrid-2-yl)-1H-benzimidazole (**5o**).*[23] A yellow solid. Yield: 182 mg (93 %). R_f = 0.5 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 10.55 (br, 1H), 8.65 (d, J = 4.7 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.83 – 7.92 (m, 2H), 7.48 – 7.56 (m, 1H), 7.30 – 7.42 (m, 3H). Mp 226-228 ^{o}C (lit. 218 ^{o}C).

*2-trans-Cinnamyl-1H-benzimidazole (**5p**).*[23] A yellow oil. Yield: 152 mg (69 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.54 - 7.73 (m, 4H), 7.39 - 7.50 (m, 3H), 7.36 (d, J = 6.9 Hz, 1H), 7.11 - 7.27 (m, 3H). Mp 200-202 ^{o}C (lit. 190-200 ^{o}C).

*2-Hexyl-1H-benzimidazole (**5q**).*[24] A white solid. Yield: 140 mg (69 %). R_f = 0.4 (EtOAc:hexanes = 1:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.14 (br, 1H), 7.34 - 7.60 (m, 2H), 7.09 (d, J = 3.0 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 1.74 (br, 2H), 1.29 (br, 6H), 0.85 (br, 3H). Mp 135-136 ^{o}C (lit. 135 ^{o}C).

*2-Cyclohexyl-1H-benzimidazole (**5r**).*[25] A white solid. Yield: 140 mg (70 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.09 (br, 1H), 7.31 - 7.60 (m, 2H), 6.97 - 7.22 (m, 2H), 2.83 (tt, J = 11.40, 3.57 Hz, 1H), 2.00 (d, J = 12.64 Hz, 2H), 1.75 - 1.86 (m, 2H), 1.74 - 1.18 (m, 6H). Mp 268-270 ^{o}C (lit. 270-285 ^{o}C).

*2-(t-Butyl)-1H-benzimidazole (**5s**).*[3b] A brown solid. Yield: 122 mg (70 %). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.06 (s, 1H), 7.51 (d, J = 6.9 Hz, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.06 – 7.13 (m, 2H), 1.38 (s, 9H). Mp over 300 ^{o}C (lit. 330 ^{o}C).

*Benzimidazole (**5t**).*[26]A white solid. Yield: 97.7 mg (83 %). R_f = 0.5 (Acetone:MeOH = 30:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.44 (br, 1H), 8.20 (s, 1H), 7.46-7.70 (m, 2H), 7.18 (br, 1H).). Mp 178-180 ^{o}C (lit. 171-173 ^{o}C).

*5-Methyl-2-phenyl-1H-benzoimidazole (**5u**).*[20] A yellow solid. Yield: 179 mg (86 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.15 (d, J = 7.1 Hz, 2H), 7.44 - 7.57 (m, 4H), 7.32 (br, 1H), 7.02 (d, J = 7.1 Hz, 1H), 2.43 (s, 3 H).). Mp 245-249 ^{o}C (lit. 243 ^{o}C).

*5-Chloro-2-phenyl-1H-benzoimidazole (**5v**).*[20] A pink solid. Yield: 183 mg (80 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.13 - 8.19 (m, 2H), 7.51 - 7.66 (m, 3H), 7.23 (dd, J = 8.7, 2.1 Hz, 1H).). Mp 232-233 ^{o}C (lit. 215^{o}C).

*2-Phenyl-3H-benzoimidazole-5-carboxylic acid (**5w**).*[27] A yellow solid. Yield: 208 mg (82 %). R_f = 0.4 (EtOAc:hexanes:MeOH = 6:5:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.20 (d, J = 6.9 Hz, 3H), 7.84 (d, J = 8.5 Hz, 1H), 7.51 - 7.67 (m, 4H).). Mp over 300 ^{o}C (lit. 325 ^{o}C).

*1-Methyl-2-phenyl-1H-benzoimidazole (**5x**).*[25] A yellow solid. Yield: 188 mg (90 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.84 – 7.87(m, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.57 – 7.63 (m, 4H), 7.22 – 7.33 (m, 2H), 3.88 (s, 3H).). Mp 96-98 ^{o}C (lit. 95 ^{o}C).

*1-Benzyl-2-phenyl-1H-benzoimidazole (**7a**).*[28] A yellow solid. Yield: 256 mg (90 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.71 – 7.74 (m, 3H), 7.52 – 7.54 (m, 3H), 7.45 – 7.48 (m, 1H), 7.21 – 7.31 (m, 5H), 6.98 (d, J = 7.0 Hz, 2H), 5.59 (s, 2H).). Mp 138-139 ^{o}C (lit. 133 ^{o}C).

*1,2-diphenyl-1H-benzoimidazole (**5y**).*[29] A white solid. Yield: mg (90 %). R_f = 0.35 (CH_2Cl_2:hexanes:MeOH = 8:1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.71 – 7.74 (m, 3H), 7.52 – 7.54 (m, 3H), 7.45 – 7.48 (m, 1H), 7.21 – 7.31 (m, 5H), 6.98 (d, J = 7.0 Hz, 2H), 5.59 (s, 2H). Mp 109-110 ^{o}C (lit. 110 ^{o}C).

Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (NRF-2013R1A1A1008434 and NRF-20100020209). C.-H.C. also thanks for a financial support from an NRF grant funded by the Korean Government (NRF-2014-011165, Center for New Directions in Organic Synthesis).

References

1. For reviews on benzimidazoles, see: (a) Singla, P.; Luxami, V.; Paul, K. *RSC Adv.* **2014**, *4*, 12422; (b) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208.

2. Another conventional method for the synthesis of benzimidazoles involves the amide formation between *ortho*-phenylenediamines and carboxylic acids and their derivatives, followed by the dehydration of the amides in the presence of acid or microwave irradiation. For recent examples, see: (a) Rambabu, D.; Murthi, P. R. K.; Dulla, B.; Rao, M. V. B.; Pal, M. *Synth. Commun.* **2013**, *43*, 3083; (b) Wen, X.; Bakali, J. E.; Deprez-Poulain, R.; Deprez, B.; *Tetrahedron Lett.* **2012**, *53*, 2440; (c) Maras, N.; Kocevar, M. *Helv. Chim. Acta*, **2011**, *94*, 1860; (d) Niknam, K.; Fatehi-Raviz, A. *J. Iran. Chem. Soc.* **2007**, *4*, 438; (e) Wang, R.; Lu, X.-X.; Yu, X.-Q.; Shi, L.; Sun, Y. *J. Mol. Catal. A: Chem.* **2007**, *266*, 198; (f) Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823; (g) Charton, J.; Girault-Mizzi, S.; Sergheraert, C. *Chem. Pharm. Bull.* **2005**, *53*, 492.

3. For the examples of transition-metal catalyzed synthesis of benzimidazoles, see: (a) Kumar, R. K.; Punniyamurthy, T. *RSC Adv.* **2012**, *2*, 4616; (b) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577; (c) Biju, A. T.; Hirano, K.; Glorius, F. *J. Org. Chem.* **2009**, *74*, 9570.

4. For recent examples, see: (a) with IBD: Du, L.-H.; Wang, Y.-G.; *Synthesis* **2007**, *5*, 675; (b) with $In(OTf)_3$: Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2006**, *245*, 8; (c) with I_2: Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2006**, *47*, 79; (d) with $Yb(OTf)_3$: Curini, M.; Epifano, F.; Montanari, F.; Rosati, O.; Taccone, S. *Synlett* **2004**, 1832; (e) with DDQ: Eynde, J. J. V.; Delfosse, F.; Lor, P.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 5813.

5. For reviews on aerobic oxidation in organic synthesis, see: (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234; (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381; (c) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L. Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

6. Selected examples of the synthesis of benzimidazoles under aerobic oxidation conditions in the presence of metal catalysts and/or additives, see: (a) Qiu, D.; Wei, H.; Zhou, L.; Zeng, Q. *Appl. Organometal. Chem.* **2014**, *28*, 109; (b) Yu, J.; Xu, J.; Lu, M. *Appl. Organometal. Chem.* **2013**, *27*, 606; (c) Lei, M.; Ma, L.; Hu, L. *Synth. Commun.* **2012**, *42*, 2981; (d) Riadi, Y.; Mamouni, R.; Azzalou, R.; Haddad, M. E.; Routier, S.; Gullaumet, G.; Lazar, S. *Tetrahedron Lett.* **2011**, *52*, 3492; (e) Mao, Z.; Wang, Z.; Li, J.; Song, X.; Luo,

Y. *Synth. Commun.* **2010**, *40*, 1963; (f) Mukhopadhyay, C.; Tapaswi, P. K.; Butchere, R. J. *Aust. J. Chem.* **2009**, *62*, 140; (g) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330; (h) Mukhopadhyay, C.; Tapaswi, P. K. *Tetrahedron Lett.* **2008**, *49*, 6237.

7. For examples of the synthesis of benzoxazoles via aerobic oxidation, see: (a) Yoo, W.-J.; Yuan, H.; Miyamura, H.; Kobayashi, S. *Adv. Synth. Catal.* **2011**, *353*, 3085; (b) Chen, W.-H.; Pang, Y. *Tetrahedron Lett.* **2009**, *50*, 6680; (c) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713; (d) Speier, G. *J. Mol. Catal.* **1987**, *41*, 253; (e) See ref 6(f).

8. For examples of the synthesis of benzothiazoles via aerobic oxidation, see: (a) Parikh, N.; Kumar, D.; Roy, S. R.; Chakraborti, A. K. *Chem. Commun*. **2011**, 1797; (b) see also refs 6(f) and 7(b).

9. (a) Chen, G.-F.; Shen, H.-D.; Jia, H.-M.; Zhang, L.-Y.; Kang, H.-Y.; Qi, Q.-Q.; Chen, B.-H.; Cao, J.-L.; Li, J.-T. *Aust. J. Chem.* **2013**, *66*, 262; (b) Zhang, C.; Zhang, L.; Jiao, N. *Green Chem.* **2012**, *14*, 3273; (c) Bachhav, H. M.; Bhagat, S. B.; Telvekar, V. N. *Tetrahedron Lett.* **2011**, *52*, 5697; (d) Panda, S. S.; Jain, S. C. *Synth. Commun.* **2011**, *41*, 729; (e) Lin, S.; Yang, L. *Tetrahedron Lett.* **2005**, *46*, 4315.

10. For the synthesis of benzimidazoles via metal-free aerobic oxidation under visible light irradiation, see: (a) Park, S.; Jung, J.; Cho, E. J. *Eur. J. Chem.* **2014**, 4148. (b) Samanta, S.; Das, S.; Biswas, P. *J. Org. Chem.* **2013**, *78*, 11184.

11. For benzoxazoles, see: Cho, Y.-H.; Lee, C.-Y.; Ha, D.-C.; Cheon, C.-H. *Adv. Synth. Catal*. **2012**, *354*, 2992.

12. For benzothiazoles, see: Cho, Y.-H.; Lee, C.-Y.; Cheon, C.-H. *Tetrahedron* **2013**, 69, 6565.

13. For 2-aminoquinoxalines, see: Cho, Y.-H.; Kim, K.-H.; Cheon, C.-H. *J. Org. Chem.* **2014**, *79*, 901.

14. Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

15. For the similar reactivity enhancement with water in metal-free aerobic oxidation in the synthesis of quinazolinones, see: Kim, N. Y.; Cheon, C.-H. *Tetrahedron Lett.* **2014**, *55*, 2340.

16. For the metal/additive-free synthesis of benzimidazoles via aerobic oxidation in alcoholic solvents. See ref 9a).

17. Imine **I** was prepared in ethanol under argon atmosphere at 80 ^{o}C. When the same reaction was performed under air atmosphere, **5a** and **7a** were obtained.

18. Ebenezer, W. J.; Hutchings, M. G.; Jones, K.; Lambert, D. A.; Watt, I. *Tetrahedron Lett.* **2007**, *48*, 1641.

19. Chattopadhyay, P.; Rai, R.; Pandey, P. S. *Synth. Commun.* **2006**, *36*, 1857.

20. Chen, C.; Chen, C.; Li, B.; Tao, J.; Peng, J. *Molecules* **2012**, *17*, 12506.

21. Kazerouni, M. R.; Bamoniri, A.; Mirjalili, B. F. *Chem. Heterocyclic Compd*. **2014**, *50*, 35.

22. Tushar, M.; Dhimant, K.; Kapse, G. K.; Hugar, M. H. *J. Appl. Chem.* **2013**, *2*, 50.

23. Li, G.; Wang, J.; Yuan, B.; Zhang, D.; Lin, Z.; Li, P.; Huang, H. *Tetrahedron Lett.* **2013**, *54*, 6934.

24. Weires, N. A.; Boster, J.; Magolan, J. *Eur. J. Org. Chem.* **2012**, 6508.

25. Xue, D.; Long, Y.-Q. *J. Org. Chem.* **2014**, *79*, 4727.

26. Graham, T. H.; Lin, W.; Shen, D.-M. *Org. Lett.* **2011**, *13*, 6232.

27. Shargi, H.; Aberi, M.; Doroodmand, M. M. *J. Iran Chem. Soc.* **2012**, *9*, 189.

28. Shelkar, R.; Sarode, S.; Nagarkar, J. *Tetrahedron Lett.* **2013**, *54*, 6986.

29. Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, Y.; Chen, W. *J. Org. Chem.* **2011**, *76*, 716.

Significant facilitation of metal-free aerobic oxidative cyclization of imines with water in synthesis of benzimidazoles

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1. General methods

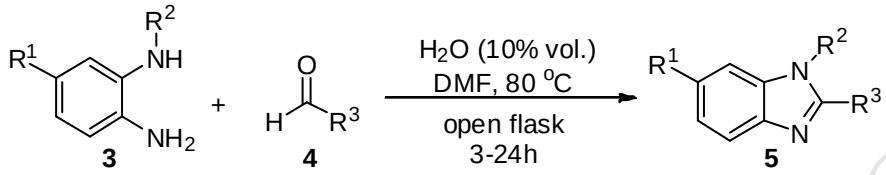
All reactions were carried out in oven-dried glassware under air atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted.

Commercial grade reagents and solvents were used without further purification. Liquid aldehydes were freshly distilled under an atmosphere of dry argon, and solid aldehydes were purified by flash chromatography on silica gel. All the *ortho*-phenylenediamine derivatives were purchased from commercial sources and used directly without further purification. *N*-Methyl- and *N*-benzyl-1,2-phenylenediamines were prepared by the literature procedures, respectively.[1,2]

^{1}H spectra were recorded on Varian Gemini 300 (300 MHz) NMR and Varian Gemini 400 (400 MHz), respectively. Tetramethylsilane (TMS) (δ: 0.00 ppm) and DMSO-d_6 (δ: 2.50 ppm) were used as internal standards for ^{1}H NMR, respectively. The proton spectra were reported as follows *δ* (position of proton, multiplicity, coupling constant *J*, number of protons) and the carbon spectra were reported only *δ* (position of carbon). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptet), m (multiplet) and br (broad).

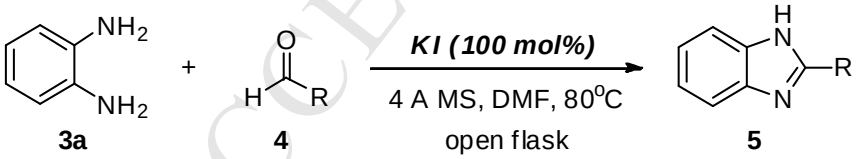
2. Synthesis of benzimidazoles 5 via metal-free aerobic oxidation in the presence of a nucleophile

Conditions A: Synthesis of benzimidazoles via metal-free aerobic oxidation in wet DMF:



To a solution of a *ortho*-Phenylenediamine derivative **3** (1.0 mmol; 1.0 equiv) and an aldehyde **4** (1.1 mmol; 1.1 equiv) were dissolved in wet DMF (DMF 9.0 mL, H_2O 1.0 mL). The resulting reaction mixture was stirred at 80 ^oC in an open flask, and the reaction progress was monitored by TLC. On the complete consumption of **3**, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel to afford the corresponding benzimidazole **5**.

Conditions B: Synthesis of benzimidazoles via metal-free aerobic oxidation in the presence of KI:

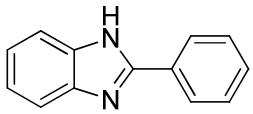


To a solution of a *ortho*-phenylenediamine derivative **3** (1.0 mmol, 1.0 equiv) and an aldehyde **4** (1.1 mmol, 1.1 equiv) in DMF were added 4Å molecular sieve and KI (1.0 mmol, 1.0 equiv). The resulting reaction mixture was stirred at 80 ^oC in an open flask, and the reaction progress was monitored by TLC. On the complete consumption of **3**, the reaction

mixture was cooled to room temperature and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel to afford the corresponding benzimidazole **5**.

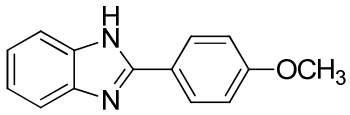
2-1. Substrate scope for benzimidazoles 5 in wet DMF (Table 5)

*2-Phenyl-1H-benzimidazole (**5a**)*[3]



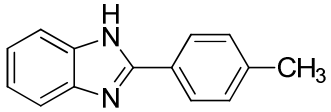
The spectroscopic data were in good agreement with the literature. A white solid. Yield: 176 mg (91 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.17 – 8.19 (m, 2H), 7.46 – 7.59 (m, 5H), 7.19 (dd, J = 5.9, 3.2 Hz, 2H).

*2-(4-Methoxyphenyl)-1H-benzimidazole (**5b**)*[3]



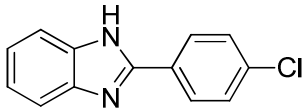
The spectroscopic data were in good agreement with the literature. A pale yellow solid. Yield: 196 mg (87 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:1:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.10 (d, J = 8.8 Hz, 2H), 7.54 (br, 2H), 7.15 (dd, J = 5.2, 3.2 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H).

*2-(4-Methylphenyl)-1H-benzimidazole (**5c**)*[3]



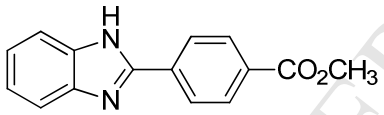
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 190 mg (91 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.06 (d, J = 8.0 Hz, 2H), 7.57 (br, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 5.8, 3.0 Hz, 2H), 2.38 (s, 3H).

*2-(4-Chlorophenyl)-1H-benzimidazole (**5d**)*[3]



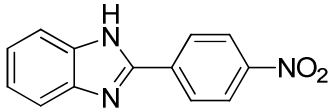
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 213 mg (93 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.19 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.21 (dd, J = 6.0, 3.0 Hz, 2H)

*2-(4-Methoxycarbonylphenyl)-1H-benzimidazole (**5e**)*[4]



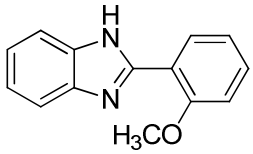
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 232 mg (92 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:2:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.32 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 7.63 (dd, J = 5.8, 3.3 Hz, 2H), 7.24 (dd, J = 6.0, 3.0 Hz, 2H), 3.90 (s, 3H).

*2-(4-Nitrophenyl)-1H-benzimidazole (**5f**)*[4]



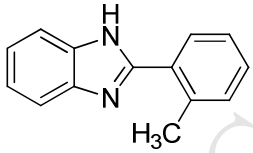
The spectroscopic data were in good agreement with the literature. A light gray solid. Yield: 220 mg (92 %). R_f = 0.3 (EtOAc:hexanes:CH_2Cl_2 = 1:2:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.41 (s, 4H), 7.65 (dd, J = 5.9, 3.2 Hz, 2H), 7.25 (dd, J = 6.0, 3.0 Hz, 2H).

*2-(2-Methoxyphenyl)-1H-benzimidazole (**5g**)*[3]



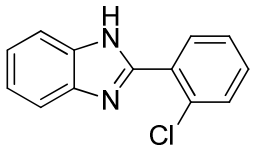
The spectroscopic data were in good agreement with the literature. A light brown solid. Yield: 184 mg (82 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.31 (d, J = 7.7 Hz, 1H), 7.58 – 7.63 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 8.2, 1H), 7.16 – 7.20 (m, 2H), 7.11 (t, J = 7.7 Hz, 1H), 4.03 (s, 3H).

*2-(2-Methylphenyl)-1H-benzimidazole (**5h**)*[3]



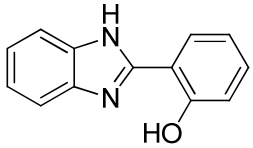
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 199 mg (95 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.73 (d, J = 6.6 Hz, 1H), 7.60 (br, 2H), 7.34 – 7.41 (m, 3H), 7.21 (dd, J = 5.8, 3.0 Hz, 2H), 2.61 (s, 3H).

*2-(2-Chlorophenyl)-1H-benzimidazole (**5i**)*[5]



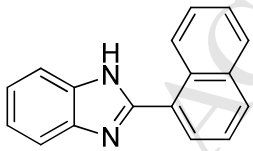
The spectroscopic data were in good agreement with the literature. A light brown solid. Yield: 219 mg (96 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.89 – 7.92 (m, 1H), 7.60 – 7.67 (m, 3H), 7.49 – 7.57 (m, 2H), 7.24 (dd, J = 5.9, 3.2 Hz, 2H).

*2-(2-Hydroxylphenyl)-1H-benzimidazole (**5j**)*[5]



The spectroscopic data were in good agreement with the literature. A white solid. Yield: 189 mg (90 %). R_f = 0.5 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.06 (d, J = 8.0 Hz, 1H), 7.67 (br, 2H), 7.35 – 7.42 (m, 1H), 7.29 (dd, J = 6.0, 3.0 Hz, 2H), 6.99 – 7.09 (m, 2H).

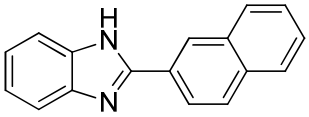
*2-(1-Naphthyl)-1H-benzimidazole (**5k**)*[6]



The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 235 mg (96 %). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 9.11 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.00 – 8.06 (m, 2H), 7.60 – 7.72 (m, 5H), 7.26 (dd,

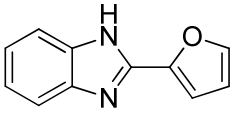
J = 5.9, 3.2 Hz, 2H).

*2-(2-Naphthyl)-1H-benzimidazole (**5l**)*[3]



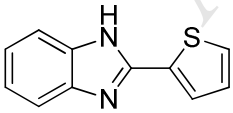
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 230 mg (94 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.73 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.97 – 8.04 (m, 2H), 7.58 – 7.62 (m, 4H), 7.21 (dd, *J* = 5.9, 3.2 Hz, 2H).

*2-(Furan-2-yl)-1H-benzimidazole (**5m**)*[3]



The spectroscopic data were in good agreement with the literature. A brown solid. Yield: 166 mg (90 %). R_f = 0.4 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.94 (s, 1H), 7.55 (br, 2H), 7.16 – 7.23 (m, 3H), 6.73 (dd, *J* = 3.4, 1.8 Hz, 1H).

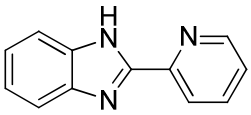
*2-(Thien-2-yl)-1H-benzimidazole (**5n**)*[3]



The spectroscopic data were in good agreement with the literature. A light yellow solid. 186

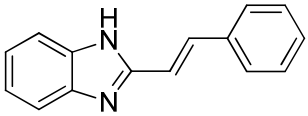
mg (93 %). R_f = 0.5 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.83 (d, J = 3.6 Hz, 1H), 7.73(d, J = 4.9 Hz, 1H), 7.50 – 7.59 (m, 2H), 7.15 – 7.26 (m, 3H).

*2-(Pyrid-2-yl)-1H-benzimidazole (**5o**)*[6]



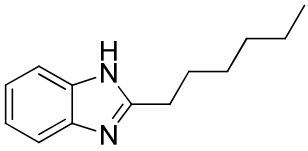
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 182 mg (93 %). R_f = 0.5 (MeOH:CH_2Cl_2 = 1:20). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 10.55 (br, 1H), 8.65 (d, J = 4.7 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.83 – 7.92 (m, 2H), 7.48 – 7.56 (m, 1H), 7.30 – 7.42 (m, 3H).

*2-trans-Cinnamyl-1H-benzimidazole (**5p**)*[6]



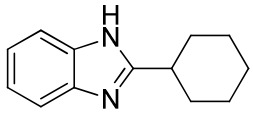
The spectroscopic data were in good agreement with the literature. A yellow oil. Yield: 152 mg (69 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.54 - 7.73 (m, 4H), 7.39 - 7.50 (m, 3H), 7.36 (d, J = 6.9 Hz, 1H), 7.11 - 7.27 (m, 3H).

*2-Hexyl-1H-benzimidazole (**5q**)*[7]



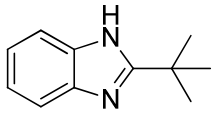
The spectroscopic data were in good agreement with the literature. A white solid. Yield: 140 mg (69 %). R_f = 0.4 (EtOAc:hexanes = 1:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.14 (br, 1H), 7.34 - 7.60 (m, 2H), 7.09 (d, J = 3.0 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 1.74 (br, 2H), 1.29 (br, 6H), 0.85 (br, 3H).

*2-Cyclohexyl-1H-benzimidazole (**5r**)*[8]



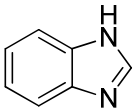
The spectroscopic data were in good agreement with the literature. A white solid. Yield: 140 mg (70 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.09 (br, 1H), 7.31 - 7.60 (m, 2H), 6.97 - 7.22 (m, 2H), 2.83 (tt, J = 11.40, 3.57 Hz, 1H), 2.00 (d, J = 12.64 Hz, 2H), 1.75 - 1.86 (m, 2H), 1.74 - 1.18 (m, 6H).

*2-(t-Butyl)-1H-benzimidazole (**5s**)*[9]



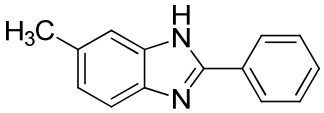
The spectroscopic data were in good agreement with the literature. A brown solid. Yield: 122 mg (70 %). R_f = 0.3 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.06 (s, 1H), 7.51 (d, J = 6.9 Hz, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.06 – 7.13 (m, 2H), 1.38 (s, 9H).

*Benzimidazole (**5t**)*[10]



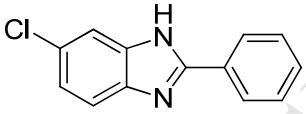
The spectroscopic data were in good agreement with the literature. A white solid. Yield: 97.7 mg (83 %). R_f = 0.5 (Acetone:MeOH = 30:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 12.44 (br, 1H), 8.20 (s, 1H), 7.46-7.70 (m, 2H), 7.18 (br, 1H).

*5-Methyl-2-phenyl-1H-benzoimidazole (**5u**)*[3]



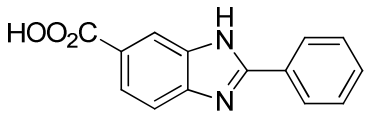
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 179 mg (86 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.15 (d, J = 7.1 Hz, 2H), 7.44 - 7.57 (m, 4H), 7.32 (br, 1H), 7.02 (d, J = 7.1 Hz, 1H), 2.43 (s, 3 H).

*5-Chloro-2-phenyl-1H-benzoimidazole (**5v**)*[3]



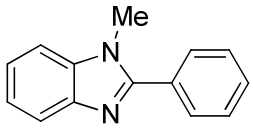
The spectroscopic data were in good agreement with the literature. A pink solid. Yield: 183 mg (80 %). R_f = 0.4 (EtOAc:hexanes = 1:3). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.13 - 8.19 (m, 2H), 7.51 - 7.66 (m, 3H), 7.23 (dd, J = 8.7, 2.1 Hz, 1H).

*2-Phenyl-3H-benzoimidazole-5-carboxylic acid (**5w**)*[11]



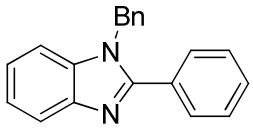
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 208 mg (82 %). R_f = 0.4 (EtOAc:hexanes:MeOH = 6:5:1). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 8.20 (d, J = 6.9 Hz, 3H), 7.84 (d, J = 8.5 Hz, 1H), 7.51 - 7.67 (m, 4H).

*1-Methyl-2-phenyl-1H-benzoimidazole (**5x**)*[8]



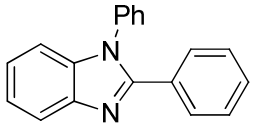
The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 188 mg (90 %). R_f = 0.3 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.84 – 7.87(m, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.57 – 7.63 (m, 4H), 7.22 – 7.33 (m, 2H), 3.88 (s, 3H).

*1-Benzyl-2-phenyl-1H-benzoimidazole (**7a**)*[12]



The spectroscopic data were in good agreement with the literature. A yellow solid. Yield: 256 mg (90 %). R_f = 0.4 (EtOAc:hexanes = 1:2). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.71 – 7.74 (m, 3H), 7.52 – 7.54 (m, 3H), 7.45 – 7.48 (m, 1H), 7.21 – 7.31 (m, 5H), 6.98 (d, J = 7.0 Hz, 2H), 5.59 (s, 2H).

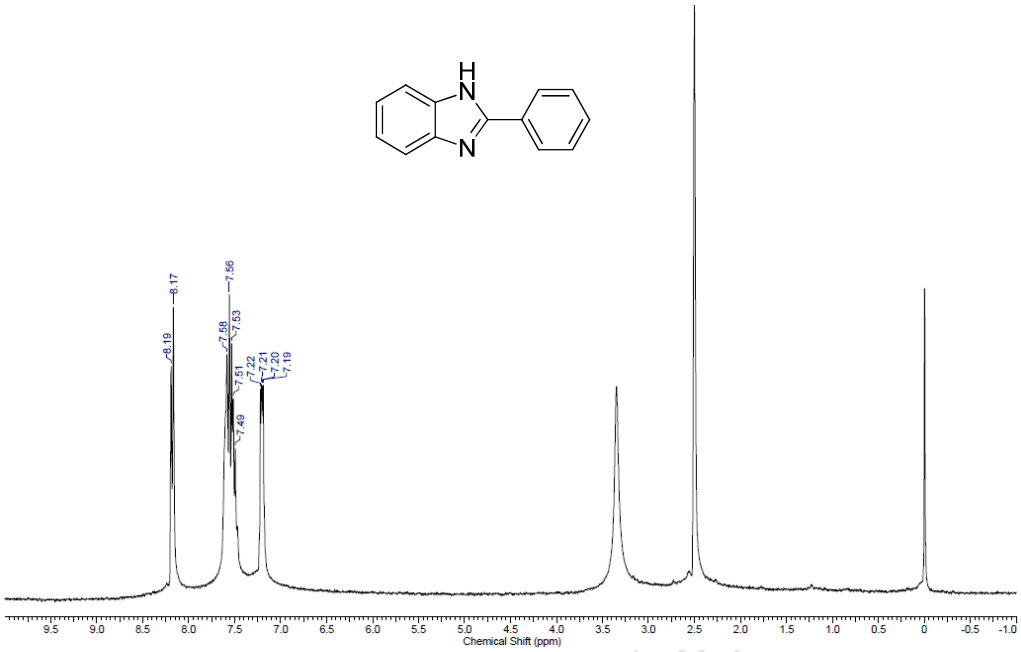
1,2-diphenyl-1H-benzoimidazole (5y)[13]



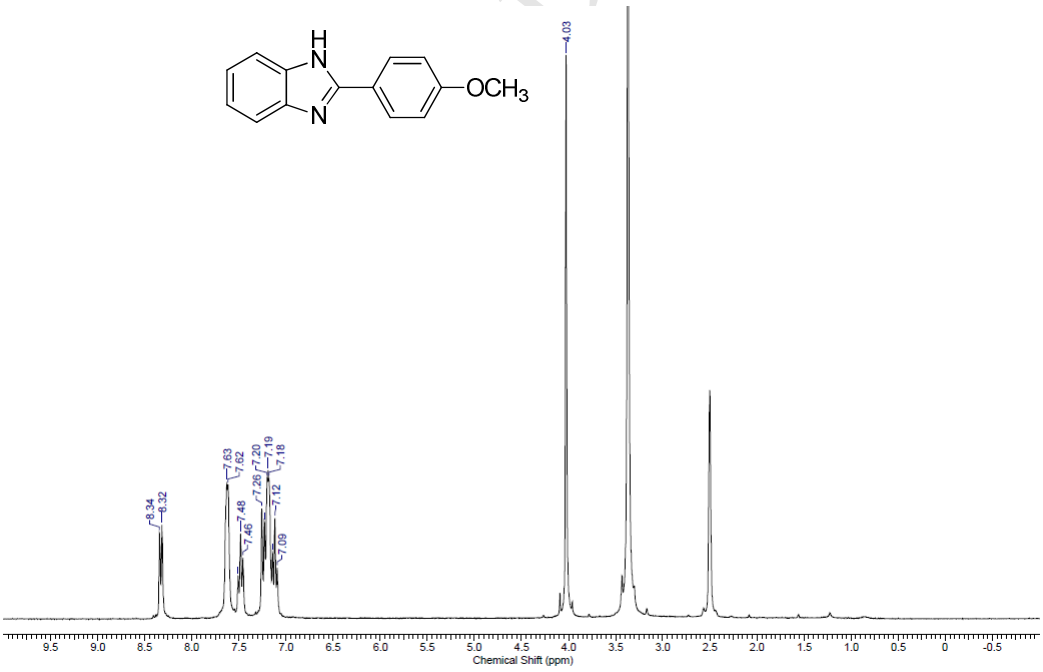
The spectroscopic data were in good agreement with the literature. A white solid. Yield: mg (90 %). R_f = (EtOAc:hexanes =). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.71 – 7.74 (m, 3H), 7.52 – 7.54 (m, 3H), 7.45 – 7.48 (m, 1H), 7.21 – 7.31 (m, 5H), 6.98 (d, J = 7.0 Hz, 2H), 5.59 (s, 2H).

3. ^{1}H NMR spectra of benzimidazoles 5

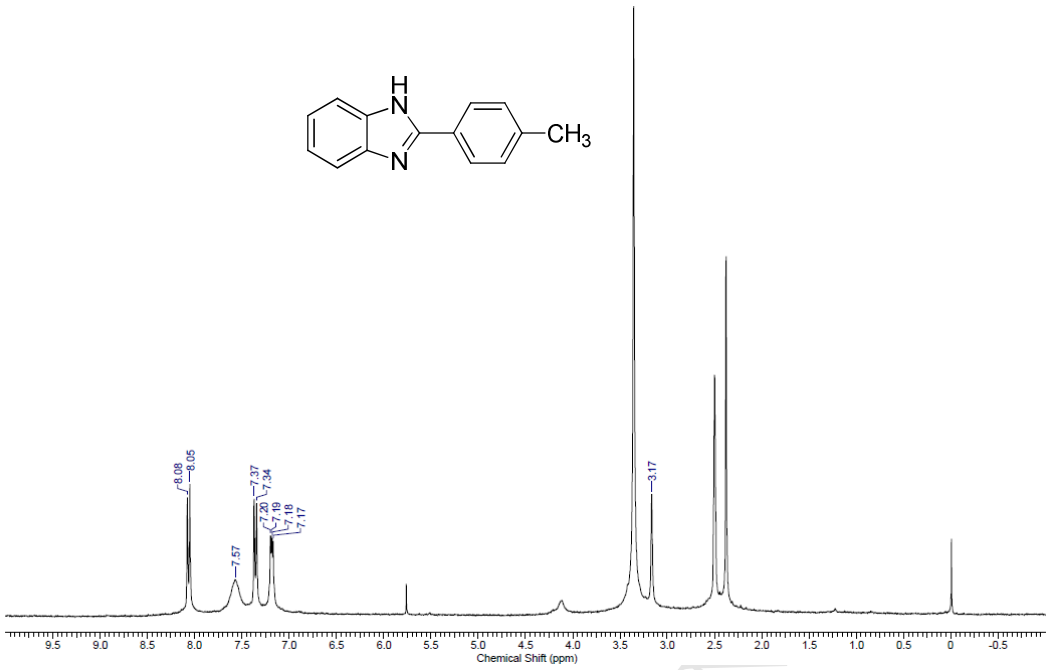
a) ^{1}H NMR spectrum of **5a**



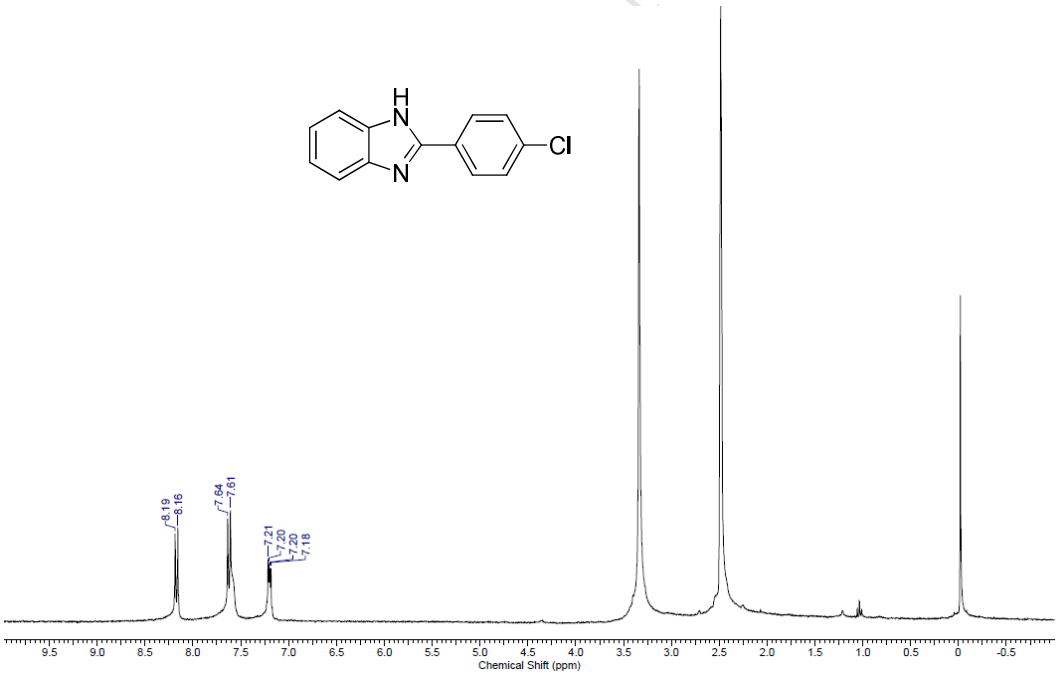
b) ^{1}H NMR spectrum of **5b**



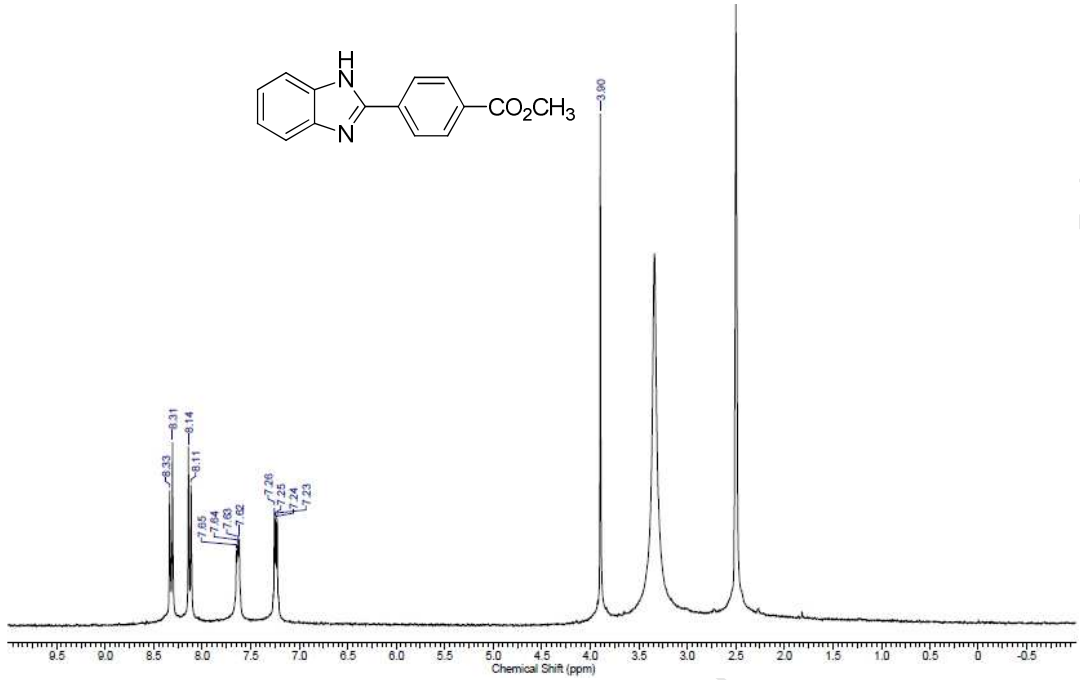
c) ^{1}H NMR spectrum of **5c**



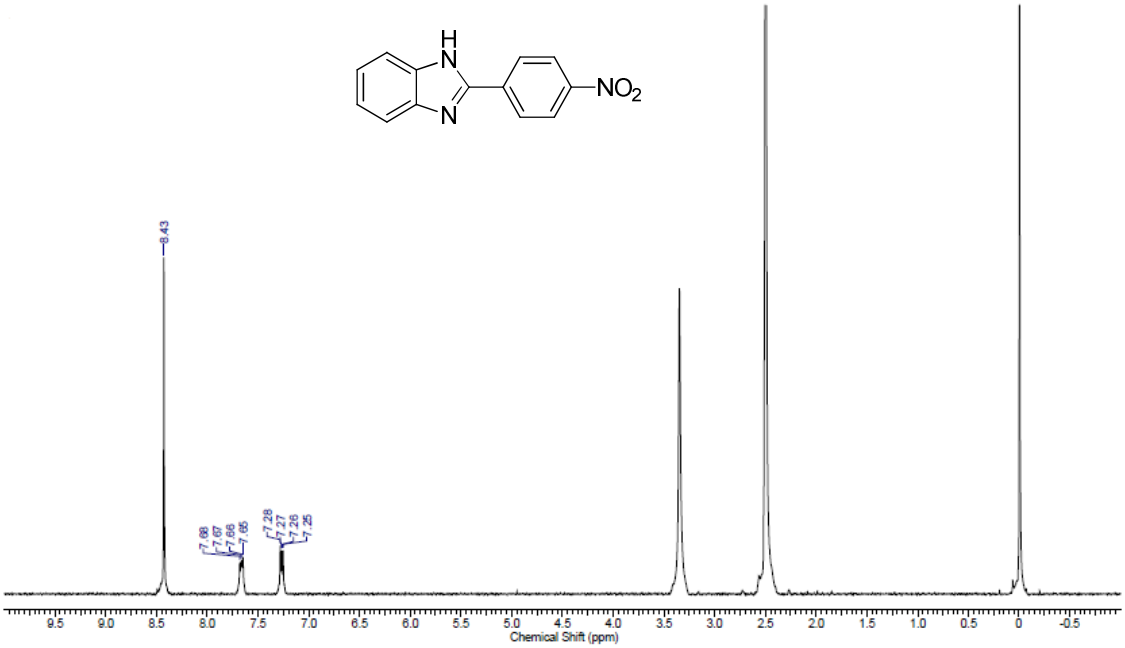
d) ^{1}H NMR spectrum of **5d**



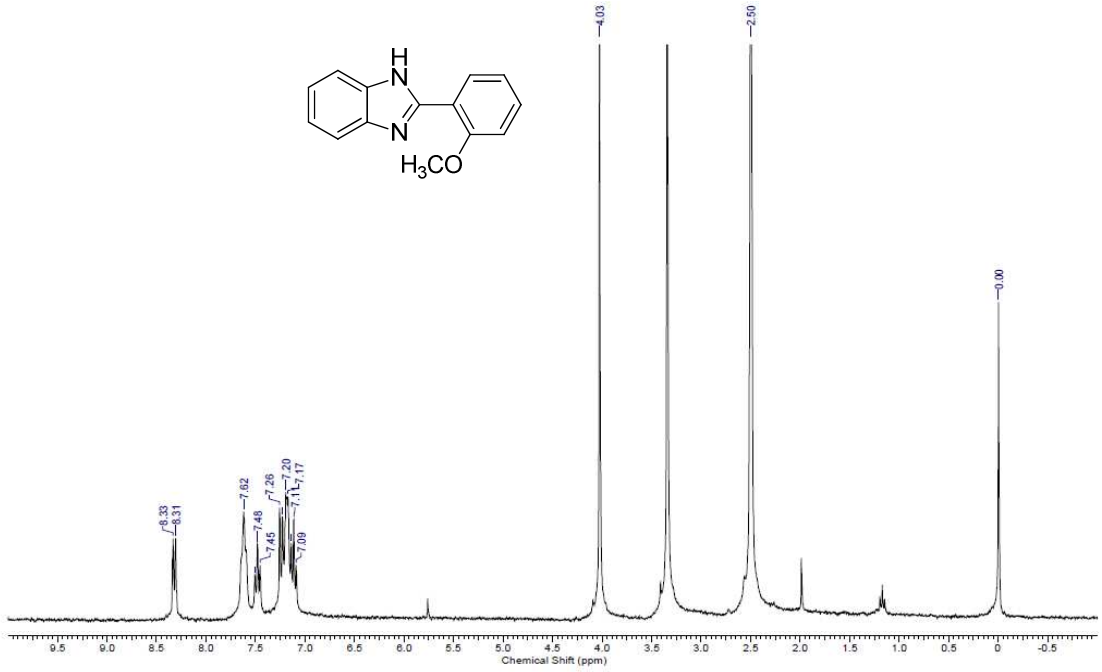
e) ^{1}H NMR spectrum of **5e**



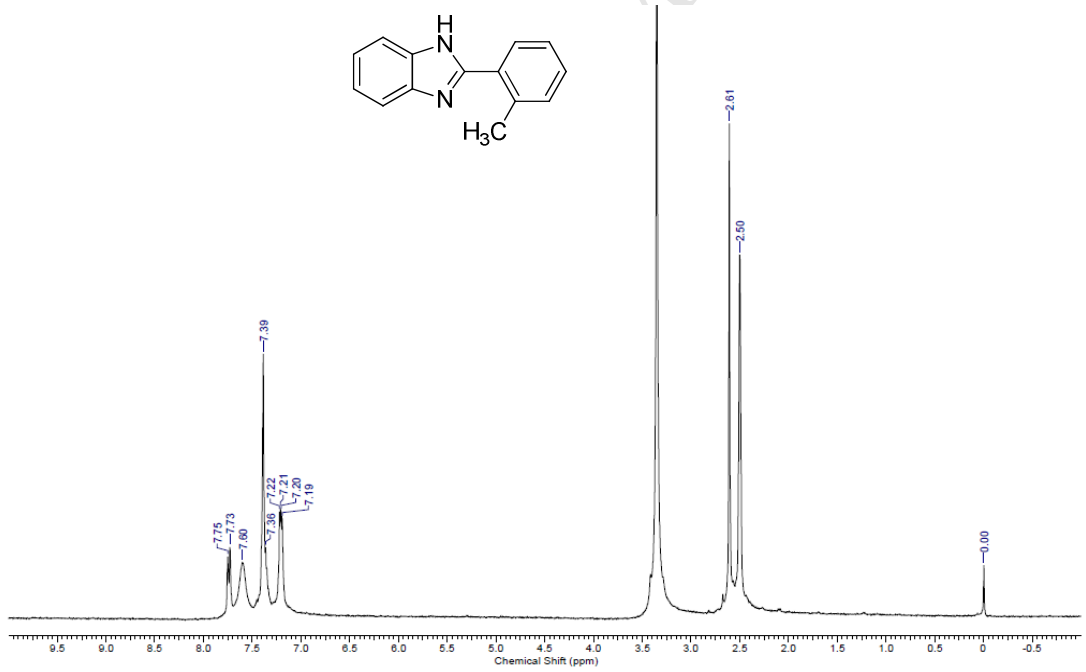
f) ^{1}H NMR spectrum of **5f**



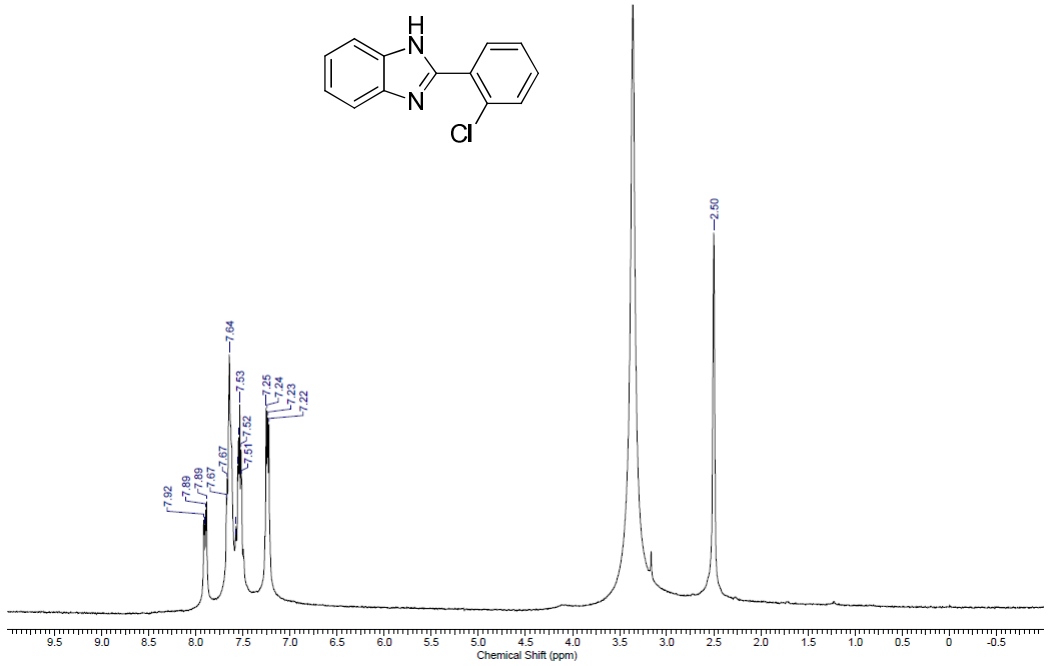
g) ^{1}H NMR spectrum of **5g**



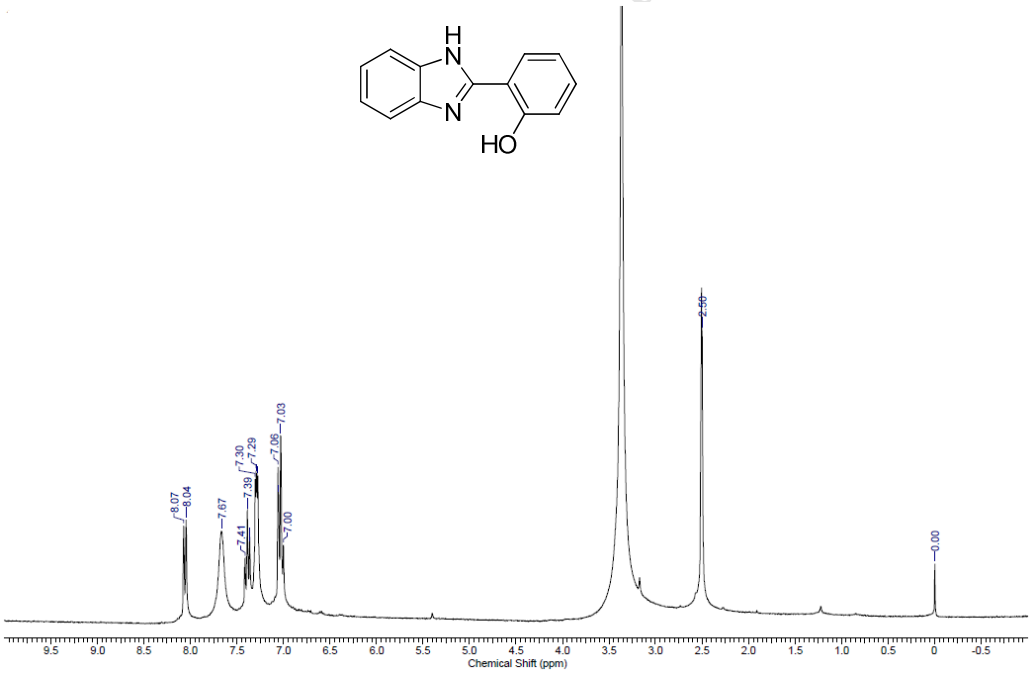
h) ^{1}H NMR spectrum of **5h**



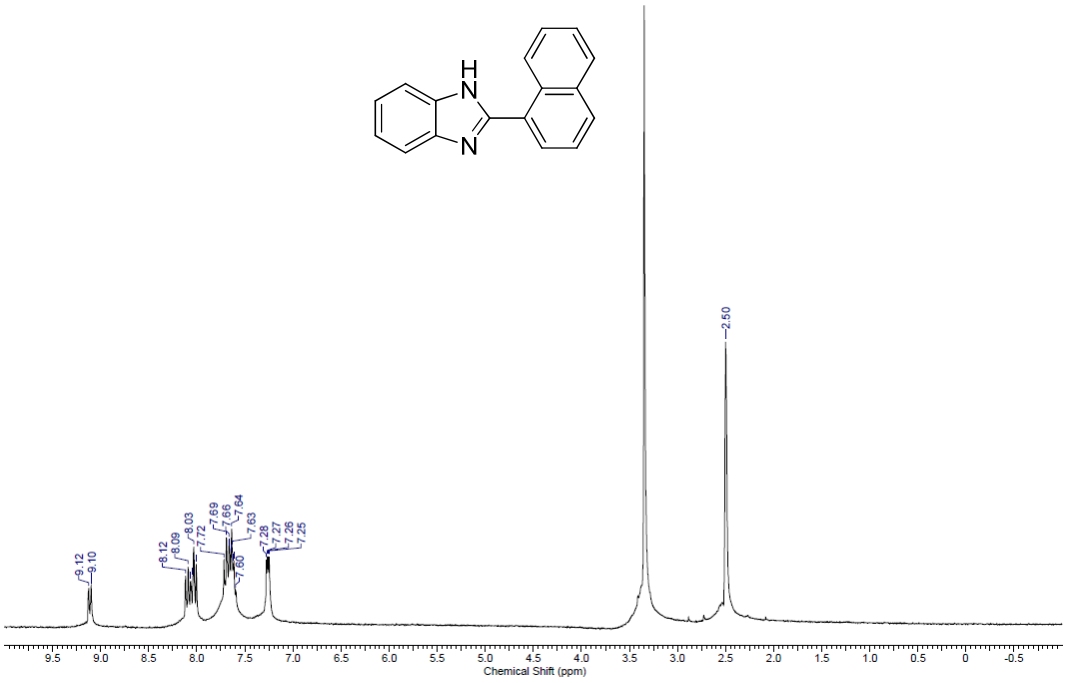
i) ^{1}H NMR spectrum of **5i**



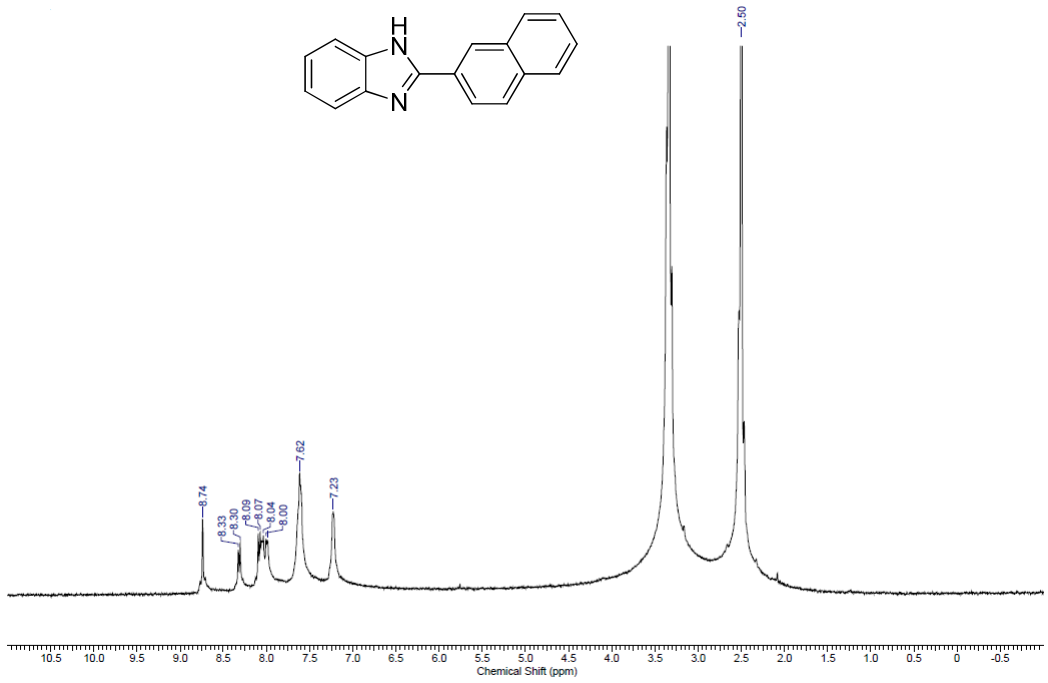
j) ^{1}H NMR spectrum of **5j**



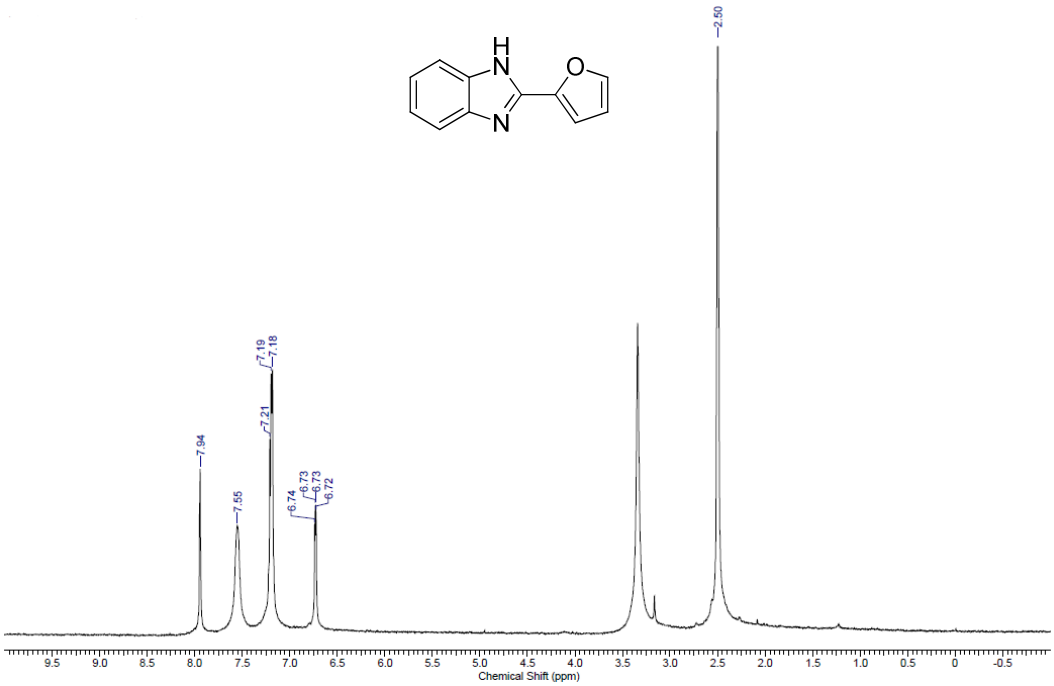
k) ^{1}H NMR spectrum of **5k**



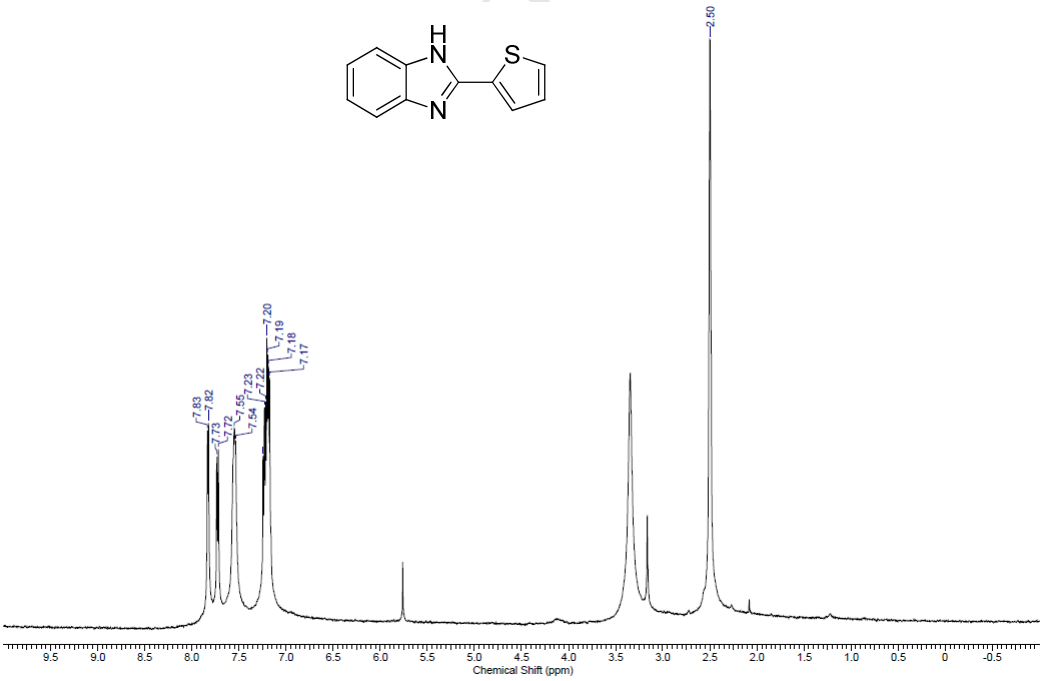
l) ^{1}H NMR spectrum of **5l**



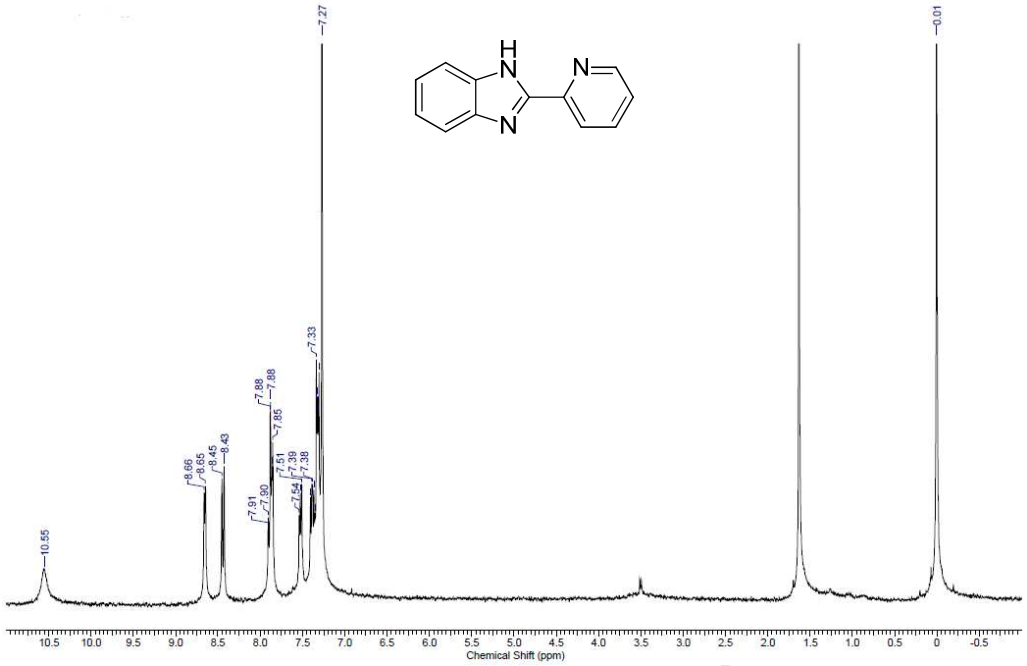
m) ^{1}H NMR spectrum of **5m**



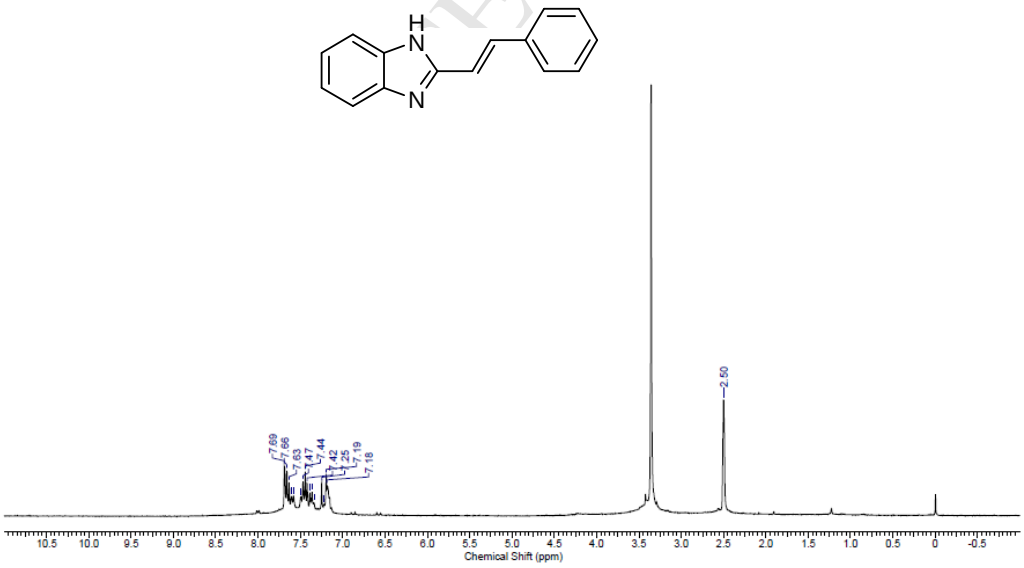
n) ^{1}H NMR spectrum of **5n**



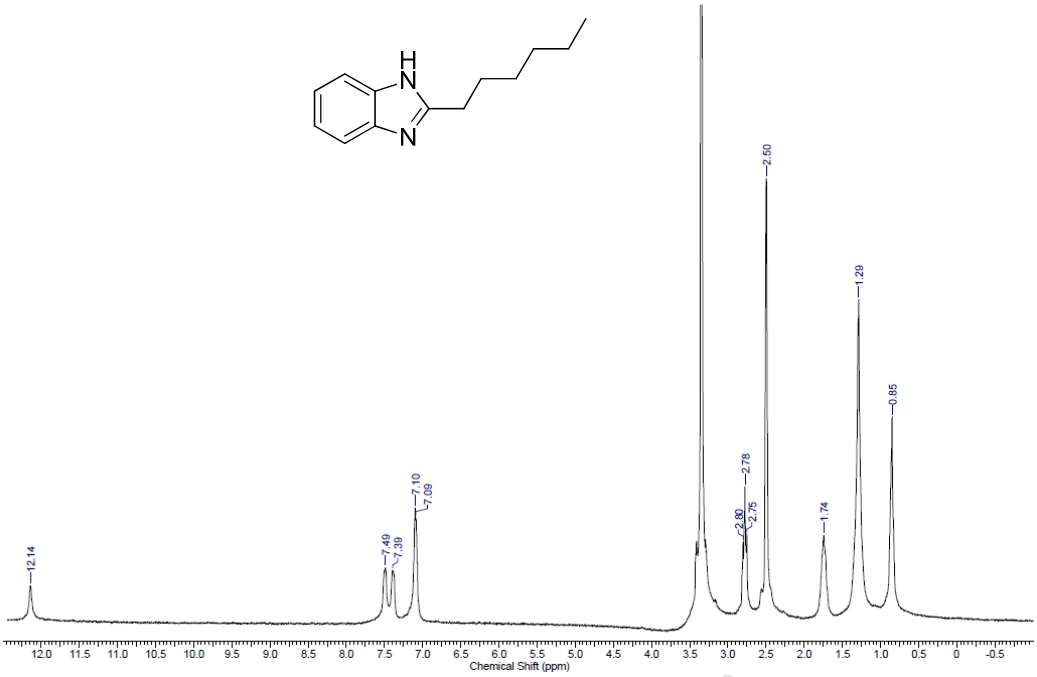
o) ^{1}H NMR spectrum of **5o**



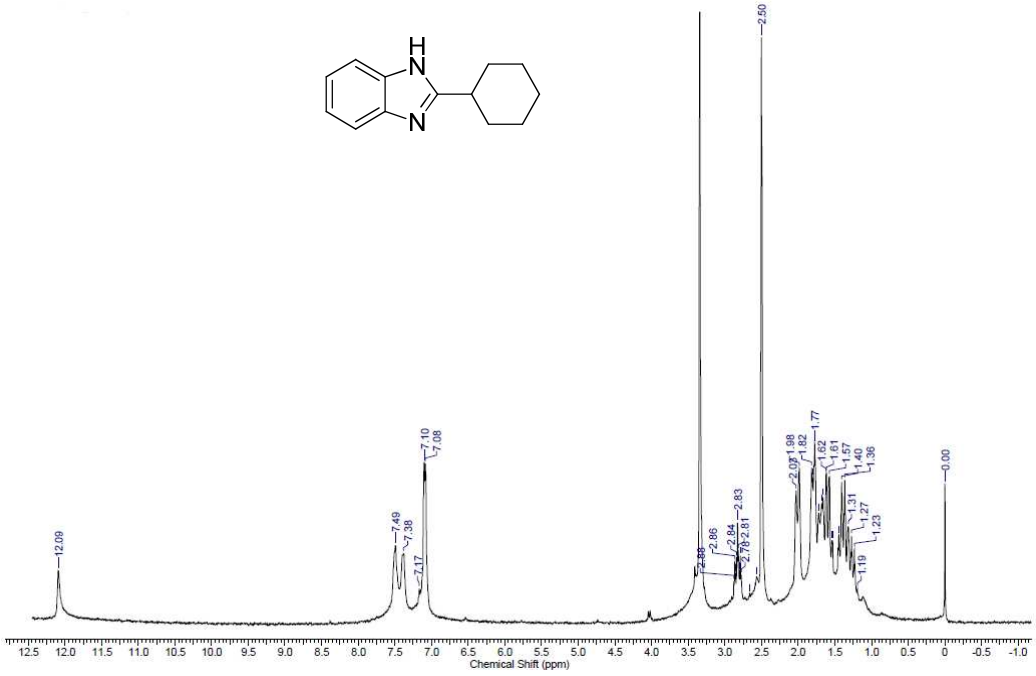
p) ^{1}H NMR spectrum of **5p**



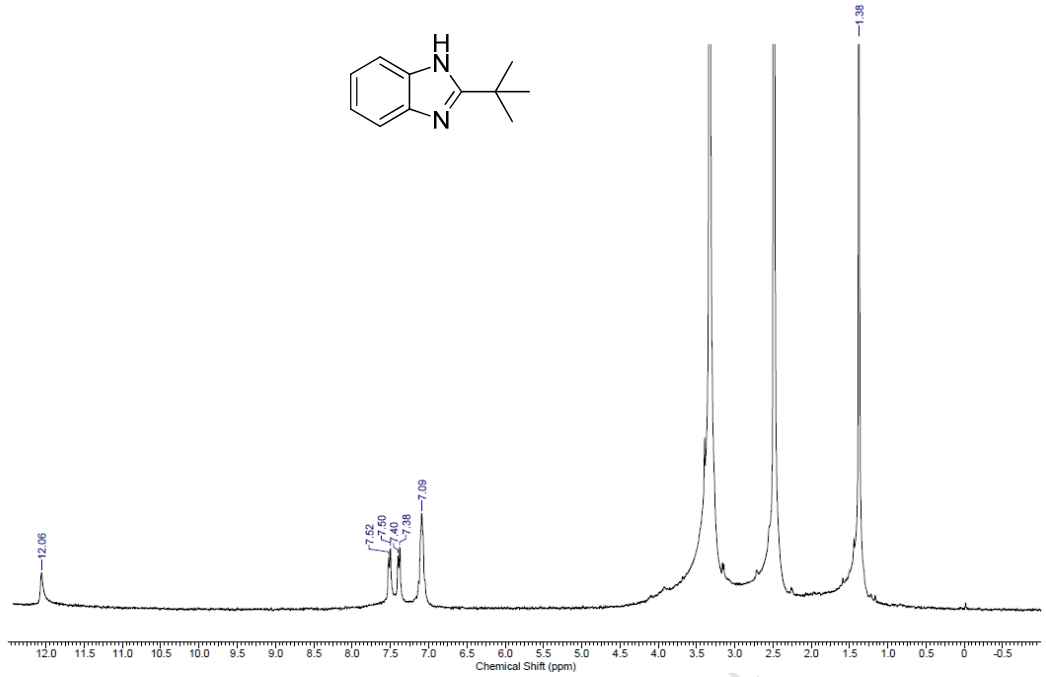
q) ^{1}H NMR spectrum of **5q**



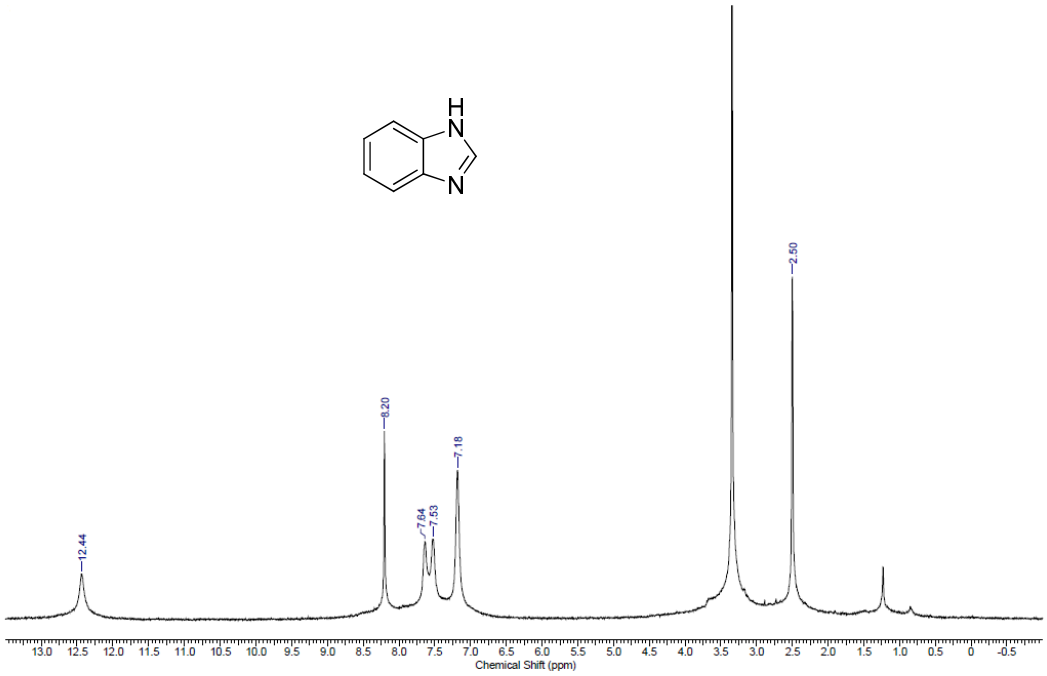
r) ^{1}H NMR spectrum of **5r**



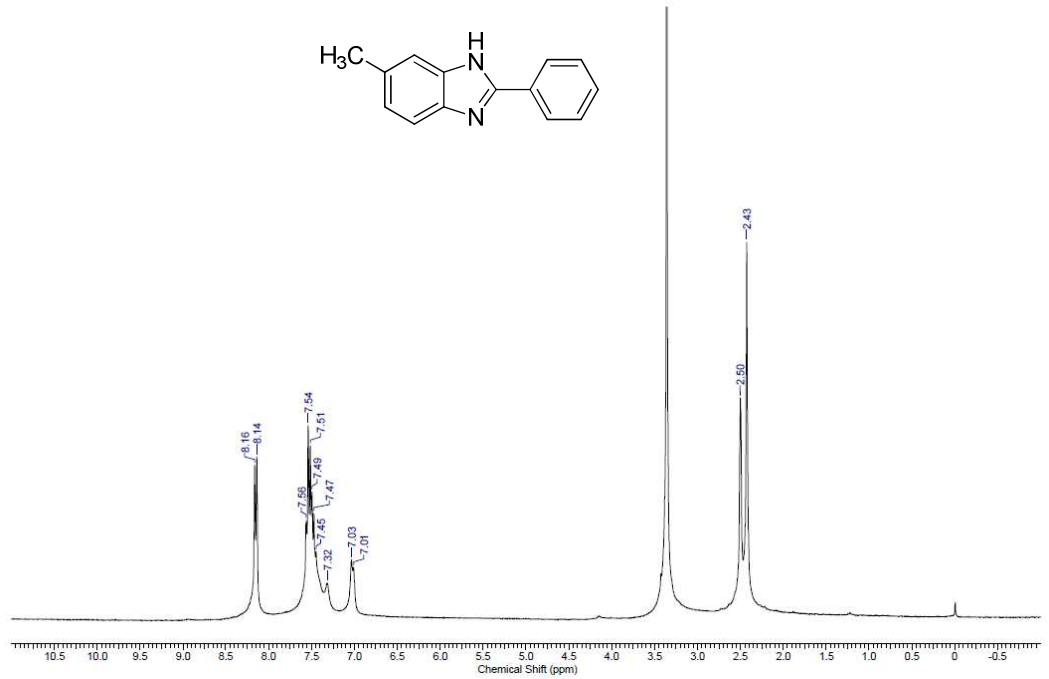
s) ^{1}H NMR spectrum of **5s**



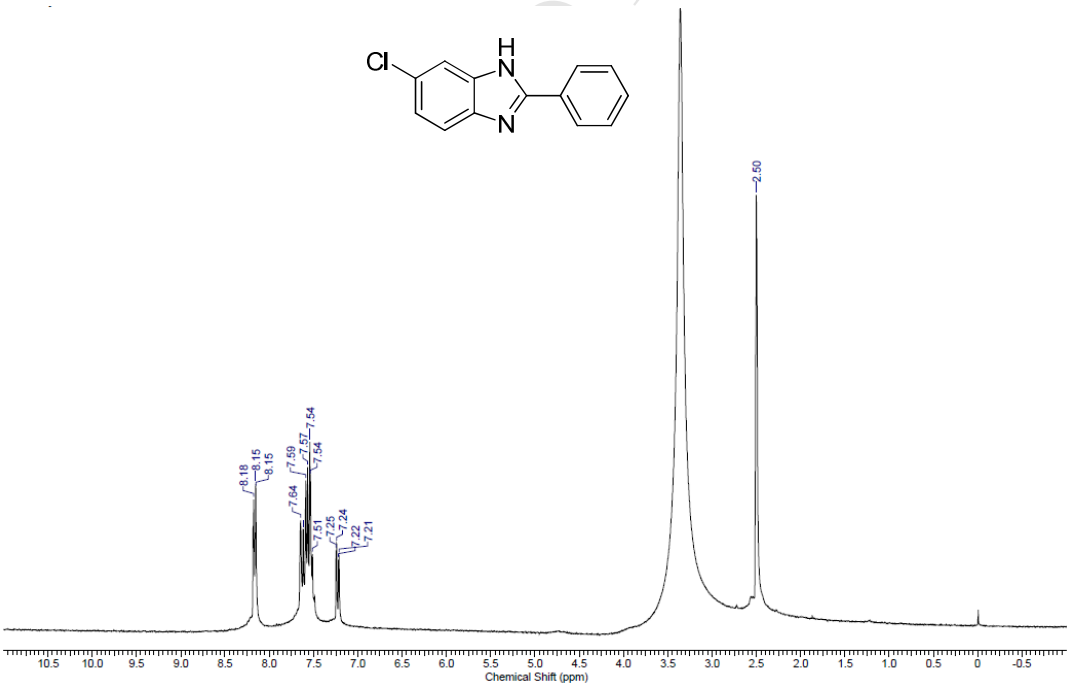
t) ^{1}H NMR spectrum of **5t**



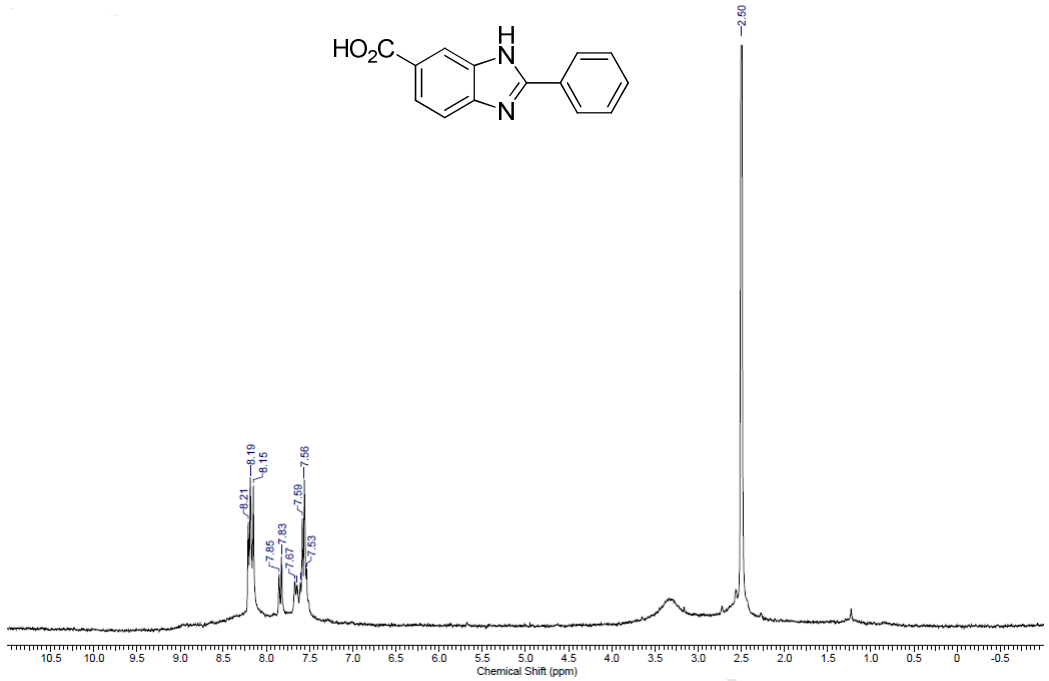
u) ^{1}H NMR spectrum of **5u**



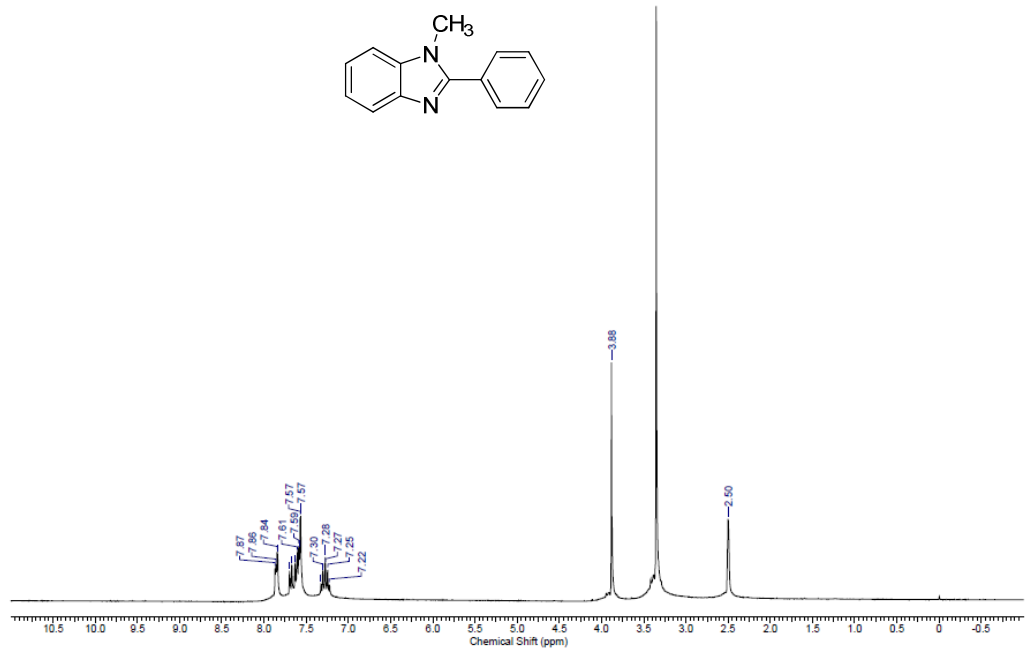
v) ^{1}H NMR spectrum of **5v**



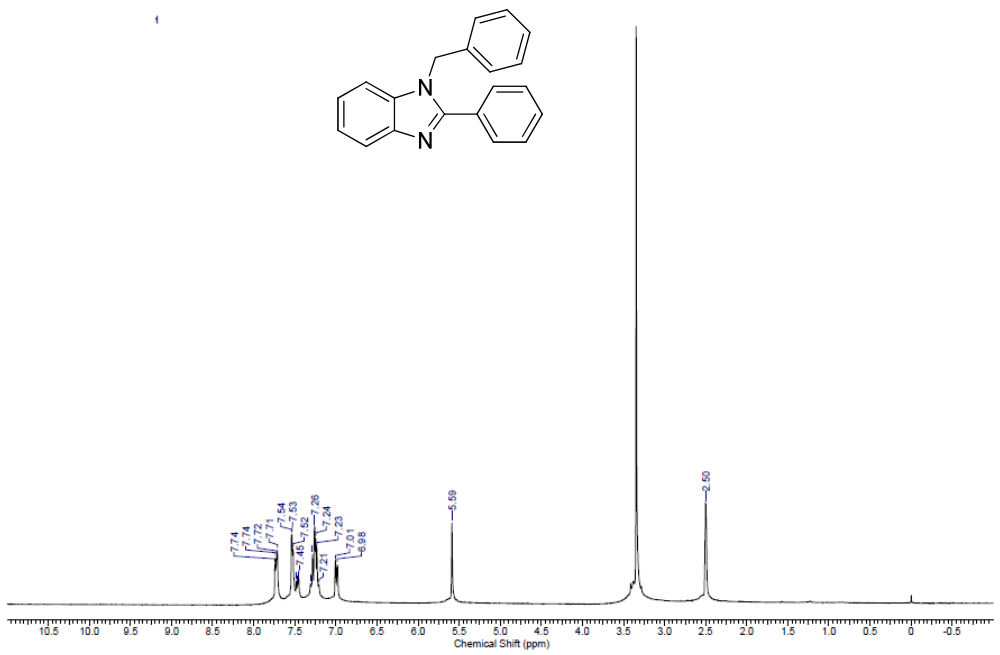
w) ^{1}H NMR spectrum of **5w**



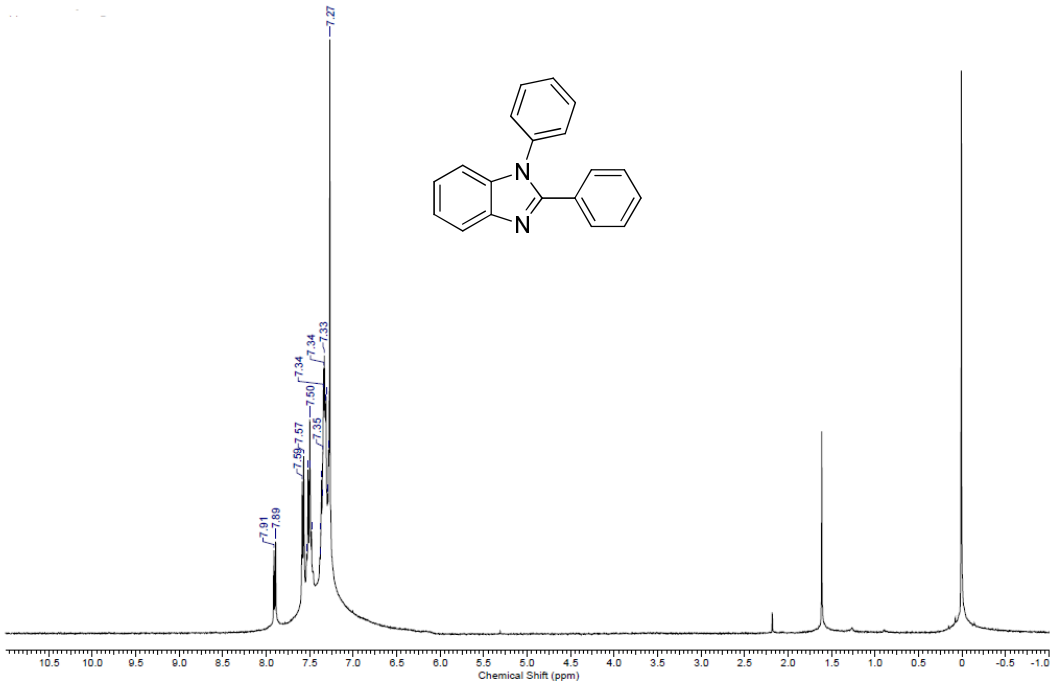
x) ^{1}H NMR spectrum of **5x**



y) ^{1}H NMR spectrum of **7a**



z) ^{1}H NMR spectrum of **5y**



4. References

1. Ebenezer,W. J.; Hutchings, M. G.; Jones, K.; Lambert, D. A.; Watt, I. *Tetrahedron Lett.* **2007**, *48*, 1641.

2. Chattopadhyay, P.; Rai, R.; Pandey, P. S. *Synth. Commun.* **2006**, *36*, 1857.

3. Chen, C.; Chen, C.; Li, B.; Tao, J.; Peng, J. *Molecules* **2012**, *17*, 12506.

4. Kazerouni, M. R.; Bamoniri, A.; Mirjalili, B. F. *Chem. Heterocyclic Compd.* **2014**, *50*, 35.

5. Tushar, M.; Dhimant, K.; Kapse, G. K.; Hugar, M. H. *J. Appl. Chem.* **2013**, *2*, 50.

6. Li, G.; Wang, J.; Yuan, B.; Zhang, D.; Lin, Z.; Li, P.; Huang, H. *Tetrahedron Lett.* **2013**, *54*, 6934.

7. Weires, N. A.; Boster, J.; Magolan, J. *Eur. J. Org. Chem.* **2012**, 6508.

8. Xue, D.; Long, Y.-Q. *J. Org. Chem.* **2014**, *79*, 4727.

9. Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577.

10. Graham, T. H.; Liu, W.; Shen, D.-M. *Org. Lett.* **2011**, *13*, 6232-6235.

11. Shargi, H.; Aberi, M.; Doroodmand, M. M. *J. Iran Chem. Soc.* **2012**, *9*, 189.

12. Shelkar, R.; Sarode, S.; Nagarkar, J. *Tetrahedron Lett.* **2013**, *54*, 6986.

13. Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, W. *J. Org. Chem.* **2011**, *76*, 716.