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DBSA mediated chemoselective synthesis of 2-substituted benzimidazoles in aqueous media

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ABSTRACT

An efficient synthetic method has been developed for the facile synthesis of 2-substituted benzimidazoles in organized aqueous media in the presence of a surfactant (viz. DBSA) as catalyst and I_2 as co-catalyst. The method described has the advantages of operational simplicity, excellent yields, high chemoselectivity, and clean and green reaction profile.

Benzimidazole is a ubiquitous heterocyclic moiety in natural and synthetic compounds. Benzimidazole derivatives with substituents particularly at N-1 and/or C-2 positions have received paramount interest in recent times because of their broad range of biological functions[1] and pharmacological applications.[2] They are an integral part of various clinical medicines as well, for example 2-substituted benzimidazole, Esomeprazole[3] is an anti-ulcerative drug and Albendazole[4] is used to treat parasitic diseases, whereas, 1,2-substituted benzimidazole, Astemizole is an antihistamine drug.[5] In addition, they are important intermediates in many organic reactions[6] and structural subunits (or major components) of many functional materials.[7] This has led to the development of several methods for the synthesis of benzmidazole derivatives in recent times. The traditional methods for the synthesis of benzimidazoles involve the condensation of an *o*-diaminoarene with a carboxylic acid or its derivatives under harsh dehydrating conditions.[8] Several alternative approaches such as reductive cyclization reaction of *o*-nitroaniline with aldehydes,[9] palladium catalyzed tandem carbonylation–cyclization reaction of *o*-diaminoarene,[10] iron(II) bromide catalyzed coupling of 2-azidoarylimine,[11] rhodium catalyzed hydroformylation reaction of *N*-alkenyl phenylenediamines,[12] solid-phase supported synthesis,[13] Cu_2O catalyzed cascade reaction between *o*-haloaniline and amidine hydrochlorides[14] etc., have also been developed for the synthesis of benzimidazole derivatives. However, dehydrative Schiff's base formation followed by oxidative cyclization in the same pot involving *o*-diaminoarene and aldehydes turned out to be the most popular method for the synthesis of 2-substituted benzimidazoles, **3**[15] and, 1,2-disubstituted benzimidazoles, **4**.[16] The reported procedures for this protocol involved a wide spectrum of reagents such as $In(OTf)_3$,[15a] $Sm(OTf)_3$,[15b] WO_x/ZrO_2,[15d] H_2O_2/CAN,[15e] *p*-TsOH/DMF[15j] for 2-substituted benzimidazoles and $HClO_4$–SiO_2,[16a] proline,[16c] Zn-proline,[16d] and oxalic acid[16e] for 1,2-disubstituted benzimidazoles. Interestingly, acid catalyzed conditions favor 2-substituted benzimidazoles over 1,2-disubstituted benzimidazoles in most of the cases.[15a,b,j] However, most of the methods use considerable amounts of hazardous organic solvents for reaction and extraction processes, which are not environmentally benign. Moreover, several of these reactions were carried out at higher temperatures and using costly reagents. In the last few years, several eco-friendly methods have been reported for 1,2-disubstituted benzimidazoles[17] but similar methods for the selective synthesis of 2-substituted benzimidazoles are rare.[17f,18]

As the use of large volumes of volatile hazardous organic solvents in industrial processes poses a serious threat to the environment, development of novel, milder, and sustainable synthetic processes involving environmentally-friendly solvents and nontoxic reagents has become imperative. One of the most sustainable alternatives to organic solvents is water, which has gained increasing popularity due to being inexpensive, non-toxic, nonflammable, widely abundant in nature, and environmentally benign. The problem of insolubility and hydrolytic decomposition of many organic compounds in water may be solved by the use

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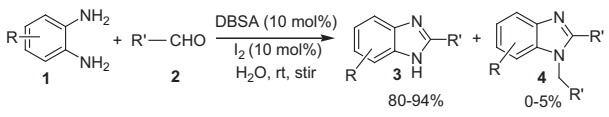
of surface-active compounds. They form a colloidal, micellar, or other organized phase and thereby, solubilize the organic reagents inside the hydrophobic interior of the organized aqueous media and allow the reaction to occur. The use of surfactants as catalysts is widespread, and has been investigated in detail for various reactions in aqueous media.[19,20] In particular, dehydration reactions, which otherwise need anhydrous conditions and thus one of the most challenging tasks to accomplish in water, have been successfully carried out by our group[21] and others[22] in aqueous media in the presence of surfactants. Synthesis of benzimidazoles involves a dehydration step and micellar condition has been successfully utilized, separately, by Bahrami et al.[17f] and Ghosh and co-workers[17g] for the construction of this heterocyclic system in the presence of mildly basic SDS as catalyst. It is interesting to note that both the methods predominantly yield 1,2-disubstituted benzimidazoles. As the literature survey reveals that acidic catalysts favor 2-substituted benzimidazoles over 1,2-disubstituted benzimidazoles,[15a,b,j] we assumed, acidic surfactant, DBSA (dodecylbenzenesulfonic acid) could be effective in achieving selectivity toward 2-substituted benzimidazole derivatives. As part of our continued efforts on the development of safe and 'green' protocols for organic reactions in aqueous media,[21] we report herein, DBSA catalyzed chemoselective synthesis of 2-substituted benzimidazoles in aqueous media in which iodine acts as co-catalyst to enhance selectivity of the desired product (Scheme 1). The primary roles of DBSA are (a) to assist in solubilizing the organic substrates in aqueous media by forming micelles or other organized phase and (b) to act as a catalyst to promote condensation of *o*-diaminoarene with the aldehyde.

We started our work with a focus on optimizing the reaction conditions. In this direction, the formation of the emulsion droplets was confirmed by taking optical micrograph of different surfactants containing aqueous solutions of reactants before the reaction would actually proceed (Fig. 1a). Dynamic light scattering (DLS) experiments of those solutions revealed that the corresponding size of emulsion droplets is in the nanometer range (Fig. 1b). We screened catalytic activity of six surfactants on a model reaction between equimolar mixture of *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) to find out the best catalyst that induces higher selectivity to 2-phenylbenzimidazoles. To our delight, all six surfactants (DBSA, SDS, CTAB, Triton X100, Tween 20, and Tween 80) could catalyze the above reaction at a variable rate to produce the desired products (**3a** and **4a)** in different proportions indicating a micellar condition is useful to carry out this condensation reaction (Table 1). As expected, DBSA showed highest selectivity (Table 1, entry 1) among all toward 2-phenylbenzimidazole (**3a**) with about 10% of undesired 1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole (**4a**). At elevated temperatures, the rate of the reaction was increased with slightdrop in the selectivity (Table 1, entry 2). SDS was found to be the most suitable catalyst in terms of time required for the completion of the reaction with much reduced selectivity toward 2-phenylbenzimidazole (**3a**) (Table 1, entry 4). The reaction was slower and selectivity was poor for other cases (Table 1, entries 6–9). We also examined the chemoselectivity of SDS and DBSA on the same reaction upon the addition of 2 equiv of benzaldehyde at one portion. In case of SDS as catalyst, the result was close to what is reported by others[17f] showing pronounced selectivity toward 1,2-disubstituted benzimidazole (**4a**) but about 10% of 2-phenylbenzimidazole (**3a**) was also obtained (Table 1, entry 5). On the other hand, the reaction was relatively slow in the presence of DBSA producing nearly equal proportion of both **3a** and **4a** even after 6 h (Table 1, entry 3). From the above results we inferred that acidic nature of DBSA and slow reaction rate are helpful for the formation of 2-substituted benzimidazoles.



Scheme 1. DBSA catalyzed synthesis of 2-substituted benzimidazoles.

The excellent chemoselectivity induced by DBSA inspired us to investigate this transformation in detail. Formation of some amount of undesired 1,2-disubstituted benzimidazole was still our concern. Literature survey revealed that use of oxidizing agent under micellar condition[17f] increases selectivity toward 2-substituted benzimidazoles by quick conversion of monoimine into the aromatic system before diimine would form, which is the intermediate of 1,2-disubstituted benzimidazole.[16a] In this regard, various nonhazardous, easily available, cheap oxidizing agents are chosen to accelerate oxidative aromatization process from monoimine and thereby, minimize formation of **4a**. Initially, stoichiometric amounts of oxidizing agents such as I_2, H_2O_2, *p*-benzoquinone, ammonium persulfate, and oxone were used separately for condensation of equimolar mixture of *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) in the presence of 10 mol % of DBSA in water to find out their influence in the final outcome on the product ratio (Table 2). Selectivity was improved at various extents toward the formation of **3a** in each case. However, both hydrogen peroxide and iodine were found equally suitable to bring about higher selectivity as well as to reduce reaction time (Table 2, entries 1 and 5). A few more reactions were carried out with different aromatic aldehydes under same condition in the presence of both I_2 and H_2O_2,[23] and based on the observed selectivity and considering the fact that iodine is milder and easier to handle, it was selected as an additive for further study. We presumed that the role of iodine could be twofold: (a) to act as Lewis acid to increase electrophilicity of the imine bond and thus, facilitate cyclization process and (b) to oxidize dihydroimidazole to corresponding aromatic system. In order to optimize the amount of iodine required for this condensation, we carried out reactions with various proportions of iodine at substoichiometric level keeping other conditions same. We were delighted to observe that use of 10 mol % of iodine is equally effective as that of stoichiometric amount to impose similar selectivity toward 2-phenylbenzimidazole (Table 2, entry 7). This indicates that the primary role of iodine is to act as Lewis acid[24] to expedite cyclization process and presumably, oxidation is mostly done by the dissolved oxygen[15h,18a] in the system. We also examined that use of more than 10% of DBSA does not enhance chemoselectivity (or yield) (Table 2, entry 8). Neither the use of less than 10% of DBSA is suitable for this transformation (Table 2, entry 9). Therefore, we decided to use 10 mol % of iodine as co-catalyst along with DBSA (10 mol %) for this condensation reaction to achieve highest chemoselectivity toward 2-substituted benzimidazoles.

To test the generality of this method, a series of aromatic aldehydes was treated with various *o*-diaminoarenes under optimal reaction conditions.[25] The developed process was found to be excellent in terms of yield and selectivity resulting in a variety of 2-substituted benzimidazoles in very high yield (Table 3). The aldehydes with electron donating (Table 3, entries 6, 7, 24, 31, etc.) as well as with electron withdrawing groups (Table 2, entries 2, 15, 22, 30, etc.) participated in the reaction uniformly with no significant distinction with regard to the yields of the target products. Similarly, no distinct substituent effect was observed on the yields of 2-substituted benzimidazoles by varying substituents in *o*-diaminoarenes. Even sensitive substrates like furfuraldehyde (Table 3, entries 9, 19 and 25) produced the desired product without any difficulty. The present method was fairly applicable to aliphatic aldehydes as well (Table 3, entry 11, 28, etc.). However, reactions were sluggish for water soluble aldehydes viz.

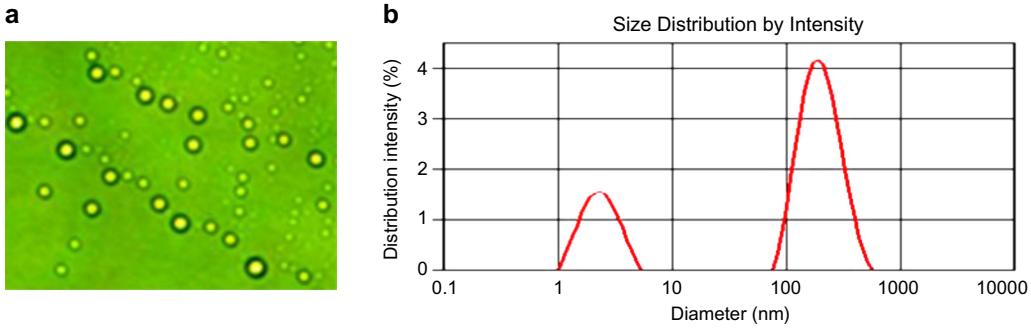
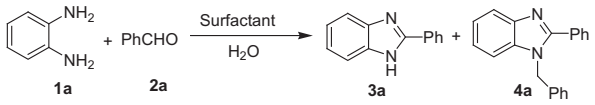


Figure 1. (a) A typical optical micrograph of vesicles formed in an aqueous solution of DBSA, *o*-diaminoarene and benzaldehyde. (b) DLS data of DBSA showing formation of aggregates.

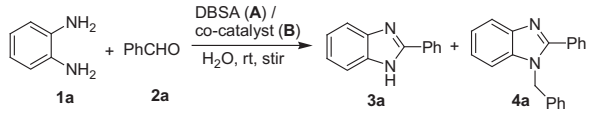
Table 1
Catalytic activity of different surfactants on benzimidazole formation



Entry	Surfactant[a] (10 mol %)	No. of equiv of PhCHO	*T* (°C)	Time (h)	Yield of **3a** (%)	Yield of **4a** (%)
1	DBSA	1.0	rt	6.0	72	10
2	DBSA	1.0	55	2.0	68	13
3	DBSA	2.0	rt	6.0	52	44
4	SDS	1.0	rt	1.0	44	26
5	SDS	2.0	rt	0.5	10	78
6	CTAB	1.0	55	6.0	32	24[b]
7	Triton X100	1.0	rt	3.0	48	25
8	Tween 20	1.0	rt	6.0	42	28
9	Tween 80	1.0	rt	6.0	39	26[b]

[a] The reaction was carried out between 0.5 mmol of *o*-phenylenediamine (**1a**) and 0.5 mmol of benzaldehyde (**2a**) in the presence of 0.05 mmol of surfactants in 2 mL of water.
[b] 12–15% of *o*-phenylenediamine was isolated along with the products.

Table 2
Effect of co-catalysts and optimization of the reaction condition



Entry	mol % of **A**	Co-catalyst (**B**)	mol % of **B**	Time (h)	Yield of **3a** (%)	Yield of **4a** (%)
1	10	H_2O_2	100	2	90	3
2	10	*p*-Benzoquinone	100	5	82	5
3	10	Oxone	100	4	78	6
4	10	$(NH_4)_2S_2O_8$	100	4	75	8
5	10	I_2	100	1.5	89	0[a]
6	10	I_2	20	2	88	0[a]
7	10	I_2	10	2	92	0[a]
8	20	I_2	20	2	88	0[a]
9	5	I_2	05	6	74	6

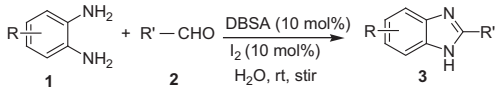
[a] No trace of **4a** was found in the TLC.

butyraldehyde (Table 3, entry 12), which is quite expected as they will hardly stay inside the micelles. Apparently, the nature and position of the substitutions in the aryl rings did not have great influence on the reactivity. Most of the reactions were completed within 3 h. Only aldehyde with strong electron withdrawing group reacted relatively faster (Table 2, entries 2, 15, 30, etc.) and reaction was little slow for an aldehyde with strong electron donating group (Table 2, entries 6, 7, 24, 31, etc.), as expected.

Based on the above results a plausible mechanism has been proposed, which is believed to be the major pathway for this dehydrative condensation followed by cyclization reaction (Scheme 2). The reaction is initiated by the formation of a Schiff's base when an aldehyde molecule comes in contact with an *o*-diaminoarenes inside the hydrophobic core of the micelle. This step is always inclined toward product as the water molecule is ejected out of the hydrophobic core as soon as it is formed. Next, iodine acts as a Lewis acid to make a partial bond with imine to increase its electrophilicity and facilitates attack of the other amino group to the imine carbon resulting in the formation of dihydrobenzimidazole. In the final step the dihydrobenzimidazole gets oxidized to the product by the dissolved oxygen in water (Scheme 3).

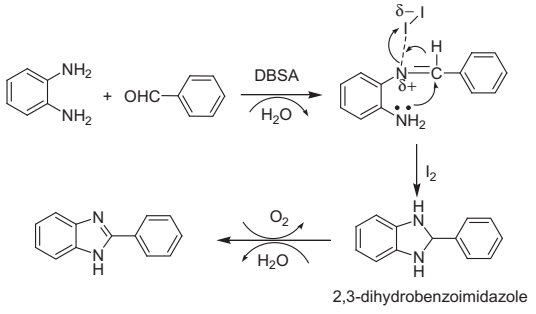
In order to expand the scope of this method we treated *o*-diaminoarene with 2-formylchromone in 1:1 ratio under similar conditions, which resulted in the formation of a macro-heterocyclic

Table 3
DBSA–I_2 catalyzed synthesis of 2-substituted benzimidazoles

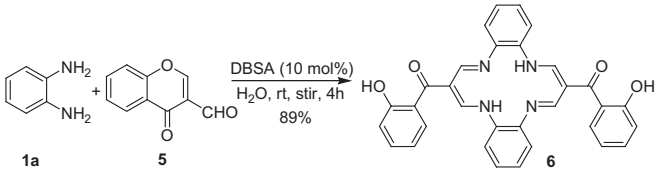


Entry	R	R′	Time (h)	Yield of **3**[a] (%)	Ref.
1	H	Ph	2.0	92[b]	15d
2	H	4-$NO_2C_6H_4$	1.0	94[b]	15d
3	H	3-ClC_6H_4	3.0	80[c]	11
4	H	4-ClC_6H_4	2.5	89[c]	15d
5	H	4-BrC_6H_4	2.0	87[c]	11
6	H	2-OHC_6H_4	3.0	84[c]	15d
7	H	4-$OCH_3C_6H_4$	5.0	86[c]	15d
8	H	C_6H_5–CH=CH–	2.0	84[d]	15a
9	H	Furan-2-yl	4.0	80[d]	15d
10	H	Pyrrole-2-yl	2.0	90[b]	
11	H	Thiophene-2-yl	2.5	88[c]	15i
12	H	*n*-Bu	12.0	12[e,f]	17f
13	H	Cyclohexyl	6.0	82[c,f]	18a
14	4-Methyl	Ph	2.0	91[b]	17f
15	4-Methyl	4-$NO_2C_6H_4$	1.0	93[b]	14
16	4-Methyl	3-ClC_6H_4	3.0	79[c]	26a
17	4-Methyl	4-ClC_6H_4	2.0	82[c]	26a
18	4-Methyl	2-OHC_6H_4	3.0	84[c]	15h
19	4-Methyl	Furan-2-yl	4.0	81[d]	
20	4-Methyl	Thiophene-2-yl	2.5	86[c]	29
21	4-Nitro	Ph	2.5	94[b]	16f
22	4-Nitro	4-$NO_2C_6H_4$	2.0	91[b]	
23	4-Nitro	2-OHC_6H_4	4.0	90[b]	26b
24	4-Nitro	4-$OCH_3C_6H_4$	6.0	92[b]	26b
25	4-Nitro	Furan-2-yl	4.0	83[d]	29
26	4-Nitro	Pyrrole-2-yl	2.5	88[d]	
27	4-Nitro	Thiophene-2-yl	3.0	86[c]	
28	4-Nitro	Cyclohexyl	6.0	81[c,f]	
29	4-Chloro	Ph	2.0	89[c]	14
30	4-Chloro	4-$NO_2C_6H_4$	1.5	90[b]	
31	4-Chloro	4-$OCH_3C_6H_4$	5.0	93[b]	

[a] All yields refer to isolated product, characterized by melting point, ^{1}H NMR and mass, and also ^{13}C NMR and HRMS for new entries.
[b] Isolated as sole product.
[c] 3–5% of 1,2-Disubstituted benzimidazole was also isolated.
[d] Trace amounts of other products were isolated, which could not be purified and characterized.
[e] Isolated yield of the product after 12 h.
[f] The reactions are carried out at 40 °C.



Scheme 2. Plausible mechanistic pathway.



Scheme 3. DBSA catalyzed synthesis of dibenzotetraaza-[14]-annulene derivative (**6**).

system, 2,3:9,10-dibenzo-6,13-disalicyloyl-1,8-dihydro-1,4,8,11-tetraaza[14]annulene (**6**) in a very high yield. Tetraaza-[14]-annulenes like analogous systems, porphyrins, and phthalocyanines, have a vast range of applications.[27] However, their syntheses are generally carried out in organic media at elevated temperatures.[28] The present method appeared to be a potential route to construct this important macrocyclic framework in an environmentally friendly and sustainable manner. A detailed study on the synthesis of these systems will be published elsewhere.

In conclusion, a practical and 'green' method has been demonstrated for the chemoselective synthesis of 2-substituted benzimidazoles in organized aqueous media in the presence of DBSA as catalyst and iodine as co-catalyst. A broad range of 2-substituted benzimidazoles have been synthesized from*o*-diaminoarenes and a variety of aldehydes using this method. The operational simplicity, excellent yields of the products, and high chemoselectivity are some of the merits of this method, and furthermore, this method is cheap, safe, and environmentally benign.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.147.

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23. Reactions are separately carried out with *o*-phenylenediamine and *p*-methoxybenzaldehyde/*p*-nitrobenzaldehyde in the presence of 10 mol % of DBSA and 1 equiv. of either H_2O_2 or I_2. The yields of corresponding 2-arylbenzimidazoles are as follows. For I_2, *p*-OMe: 86%, *p*-NO_2: 94%. For H_2O_2, *p*-OMe: 84%, *p*-NO_2: 88%.
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25. *General procedure for the syntheses of 2-substituted benzimidazoles:* To a solution of DBSA (0.05 mmol) in H_2O (2 mL) were added an amine (0.5 mmol) and iodine (0.05 mmol). An aldehyde (0.5 mmol) was added portionwise at room temperature. The reaction was stirred at room temperature for several hours (see Table 3). The progress of the reaction was monitored by TLC. The completion of the reaction was indicated by separation of the organic phase from aqueous media. The aqueous layer was decanted. The organic part was taken in ethyl acetate, washed with saturated $NaHCO_3$, water, brine and then dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified by silica gel chromatography.
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29. *The physical data of some of the compounds are provided below.* 5-Methyl-2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole (Table 3, entry 20): Yellow color solid, mp 226–227 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.38 (s, 3H), 6.97 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.19–7.52 (m, 2H), 7.66 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 2.8 Hz, 1H), 12.74 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 21.9, 111.2, 118.6, 123.8, 126.9 (2C), 128. 7 (2C), 129.0 (2C), 134.4, 147.1; HRMS (ESI): m/z calcd for $C_{12}H_{11}N_2S$ $[M+H]^+$ 215.0643, found 215.0642. *2-(Furan-2-yl)-5-nitro-1H-benzo[d]imidazole (Table 3, entry 25):* Almond color solid, mp 222–223 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 6.75 (dd, J_1 = 1.5 Hz, J_2 = 3.4 Hz, 1H), 7.31 (d, J = 3.4 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 8.00 (s, 1H), 8.07 (dd, J_1 = 2.1 Hz, J_2 = 8.9 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 113.3 (3C), 118.6, 143.3, 145.0 (2C), 146.4 (2C), 148.1, 148.3; HRMS (ESI): m/z calcd for $C_{11}H_8N_3O_3$ $[M+H]^+$ 230.0566, found 230.0564. *2,3:9,10-Dibenzo-6,13-disalicyloyl-1,8-dihydro-1,4,8,11-tetraaza[14]annulene (6):*[28c]Red crystalline solid, mp 225–226 °C, ^{1}H NMR (300 MHz, Py-d_5): δ (ppm) 7.04 (dd, J_1 = 3.6 Hz, J_2 = 6.0 Hz, 4H), 7.09 (dt, J_1 = 1.2, J_2 = 7.5, 2H), 7.28–7.32 (m, 6H), 7.48 (dt, J_1 = 1.2, J_2 = 7.5, 2H), 7.86 (dd, J_1 = 1.0 Hz, J_2 = 7.5 Hz, 2H), 8.92 (d, J = 6.3 Hz, 4H), 12.30 (br s, 2H, NH), 14.51 (t, J_1 = 6.3 Hz, exchangeable, 2H, OH); ^{13}C NMR (75 MHz, Py-d_5): δ (ppm) 111.0, 116.2, 118.1, 120.02, 123.2, 127.1, 131.6, 133.5, 137.6, 153.6, 158.7, 194.8; Mass spectrum (ESI–MS): m/z 529.00 $[M+H]^+$.