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ARTICLE TYPE

"All-water" chemistry of tandem *N*-alkylation-reduction-condensation for synthesis of *N*-arylmethyl-2-substituted benzimidazoles

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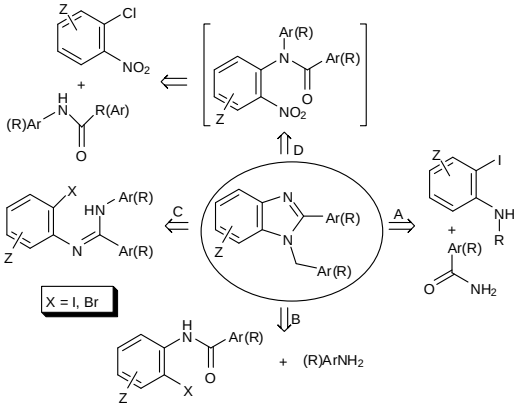
Water-assisted tandem *N*-alkylation-reduction-condensation process has been devised as a new synthetic route for one-pot synthesis of *N*-arylmethyl-2-substituted benzimidazoles. Water plays the crucial and indispensable role through hydrogen bond mediated 'electrophile-nucleophile dual activation' in promoting selective *N*-monobenzylation of *o*-nitroanilines as an alternative to the transition metal-based chemistry for C-N bond formation (amination) and forms the basis of disposing the substituents on the benzimidazole moiety in regiodefined manner. Water also exerts beneficial effect in the condensation of *N*-mono-benzylated *o*-phenylenediamines with aldehydes. The water-assisted C-N bond formation chemistry led to metal/base-free synthesis of *N*-monobenzylated *o*-nitroanilines and *N*-monobenzylated *o*-phenylenediamines. The indispensable/advantageous role of water in the various stage of the *N*-alkylation-reduction-condensation process exemplifies an 'all-water' chemistry for the synthesis of the *N*-arylmethyl-2-substituted benzimidazoles.

Introduction

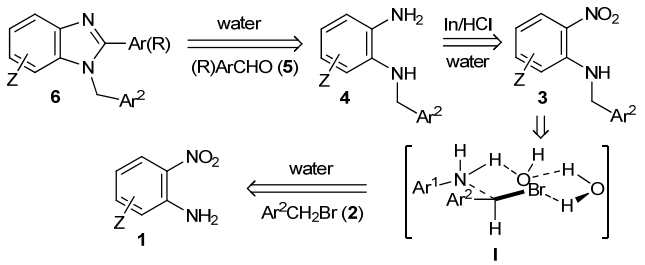
The broad range of biological activities[1] exhibited by compounds bearing the 1,2-disubstituted benzimidazole scaffold makes them a much demanded synthetic targets. However, regiospecific synthesis of 1,2-disubstituted benzimidazoles remains a synthetic challenge. The limited synthetic strategies adopted the transition metal-catalysed aryl-amination (C-N bond formation) chemistry (Scheme 1) that include intermolecular coupling of (i) *o*-iodo-*N*-alkylaniline with amide[2] (Route A), (ii) *o*-iodo/bromoanilides with alkyl/aryl amines[3] (Route B), and (iii) intramolecular coupling of *Z*-*N*'-(*o*-halophenyl)-*N*-alkyl/phenyl)amidines[4] (Route C), and (iv) intramolecular reductive cyclisation of *o*-nitroanilides formed in situ by palladium-catalysed reaction of *o*-nitrochlorobenzenes with amides in the presence of suitable ligands[5] (Route D). These require special efforts to prepare the starting materials. The origin of regiodefined disposition of the substitutents in the respective position of the benzimidazole scaffold resides on the aryl-amination stage that necessitates the use of transition metal catalysts and the efficiency of this critical step is dependent on the presence of specific and costly ligands and appropriately chosen bases. Herein we demonstrate a new 'all water' strategy of tandem *N*-alkylation-reduction-condensation for a convenient and clean synthesis of regiodefined 1,2-disubstituted benzimidazoles.

In designing the new synthetic route we realised that in the reported procedures[2-5] the transition-metal catalysed aryl-amination step is critical and the controlling event for incorporation of the substituents on the benzimidazole moiety in regiodefined fashion and is presumed to occur through metallation of the aromatic-halogen bond (electrophilic activation) followed by coordination of the metal centre with the amine/amide nitrogen and NH proton abstraction by the base (nucleophilic activation) for the concomitant C-N bond formation (amination).[6]



Scheme 1. Reported synthetic strategies of regiodefined 1,2-disubstituted benzimidazoles.

Herein we describe a metal and base-free route (Scheme 2) through exploitation of the hydrogen bond mediated 'electrophile-nucleophile dual activation' ability of water[7] in the relevent C-N bond forming step towards the development of an 'all-water' chemistry.

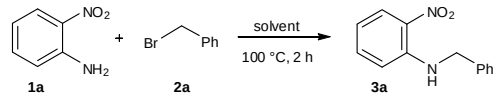


Scheme 2. An 'all water' strategy for formation of 1,2-disubstituted benzimidazoles in regiodefined fashion.

Results and Discussion

In a model study, selective *N*-monobenzylation of *o*-nitroaniline (**1a**) was tried with benzyl bromide (**2a**) in various solvents (Table 1). The *N*-phenylmethyl-*o*-nitroaniline (**3a**) was obtained in excellent yields (96-98%) in tap/normal water, pure water, and ultra pure water and the comparable results suggested that the *N*-alkylation is not influenced by any dissolved metallic/organic impurities.

Table 1. Influence of the reaction medium for a metal/catalyst and base-free selective *N*-monobenzylation of **1a** with **2a**.[a]



1a **2a** **3a**

Entry	Solvent	α[b]	β[b]	Yield (%)[c]
1	Tap water	1.17	0.18	98
2	Pure water[d]	1.17	0.18	98
3	Ultra-pure water[e]	1.17	0.18	96
4	MeOH	0.93	0.62	55
5	EtOH	0.83	0.77	64
6	^{i}PrOH	0.76	0.95	60
7	^{t}BuOH	0.68	1.01	65
8	TFE	1.51	0.00	60
9	HFIP	1.96	0.00	65
10	DCE	0.00	0.00	35
11	THF	0.00	0.55	28
12	Dioxane	0.00	0.37	41
13	Acetone	0.08	0.48	25
14	$MeNO_2$	0.22	0.00	40
15	DMF	0.00	0.69	43
16	DMA	0.00	0.76	50
17	Formamide	0.71	0.00	46
18	Toluene	0.00	0.11	35
19	Hexane	0.00	0.00	trace
20	Neat	---	---	trace

[a]**1a** (1 mmol) was treated with **2a** (1.5 mmol, 1.5 equiv) in various solvents (2 mL), except for entry 20, under heating at 100 °C (oil bath) for 2 h. [b]Ref 8. [c]Isolated yield of **3a**. [d]The pure water was obtained by purification of normal/tap water through reverse osmosis and ionic/organic removal and has the resistivity of 15 MΩ at 25 °C. [e]The ultrapure water was obtained by further subjecting pure water to UV treatment (185/254 nm), deionization and ultra membrane filtration (0.01 µm) under pressure up to 145 psi (10 bar) and has the resistivity of 18.2 MΩ at 25 °C.

The specific assistance by water in promoting the metal/base-free selective *N*-monobenzylation is revealed by the fact that **3a** was not formed under neat condition (entry 20, table 1) and poor results were obtained in hydrocarbon, halogenated hydrocarbon, ethereal, and aprotic polar solvents (entries 10-19, table 1). Alcohols (protic polar solvents) gave moderate results (entries 4-9, table 1). The role of water in promoting the C-N bond formation (amination) can be envisaged by its ability to form hydrogen bond (HB) with the NH_2 hydrogen of **1a** (nucleophilic activation). The second molecule of the water dimer in turn forms HB with the Br atom of **2a** (electrophilic activation) and brings the benzylic carbon in close proximity to the amino nitrogen of **1a** in the intermediate **I** (Scheme 2). Therefore, the implication of the reaction medium in assisting the *N*-alkylation would be governed by effective formation of the H-bonded adduct **I** (Scheme 2) due to their hydrogen bond donor (HBD) (α scale) and hydrogen bond acceptor (HBA) (β scale) properties.[8] This is reflected by the excellent results obtained in water (entries 1-3, table 1). The inferior yields obtained in TFE/HFIP (entries 8 and 9, table 1) despite of their better α values could be due to the poor HBA property.

To determine the best operative reaction condition, the reaction of **1a** was carried out with **2a** under variation of different reaction parameters such as the molar equiv of **2a**, amount of water as the reaction medium, temperature, and time (Table 2). The best result was obtained by treatment of **1a** with 1.2 molar equiv of **2a** in water (2 mL) at 100°C for 1.5 h (entry 1, Table 2).

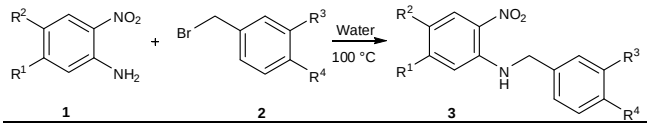
Table 2. Reaction of **1a** with **2a** in water under different experimental conditions.[a]

Entry	Amt of **2a** (equiv)[b]	Amt of water (mL)	Temp (°C)[c]	Time (h)	Yield (%)[d]
1	1	2	100	2	90
2	1.2	2	100	2	96
3	1.5	2	100	2	96
4	1.2	1	100	2	88
5	1.2	2	100	2	96
6	1.2	5	100	2	96
7	1.2	2	rt[e]	2	0
8	1.2	2	60	2	0
9	1.2	2	80	2	35
10	1.2	2	100	1	80
11	1.2	2	100	1.5	96

[a]**1a** (1 mmol) was treated with different amount of **2a** in varying amount of water under varied experimental condtions (e.g., change of temperature and reaction time. [b]Molar equiv with respect to **1a**. [c]Oil bath). [d]Isolated yield of **3a**. [e]~30-35.

The synthetic potential of the water-assisted selective *N*-monobenzylation for the preparation of *N*-monoarylmethylated *o*-nitroanilines is demonstrated by the reaction of a few substituted *o*-nitroanilines **1** with substituted benzyl bromides **2** to form **3** (Table 3).

Table 3. Water-assisted metal-free selective *N*-mono-alkylation of *o*-nitroanilines **1** with benzyl bromides **2**.[a]



1 **2** **3**

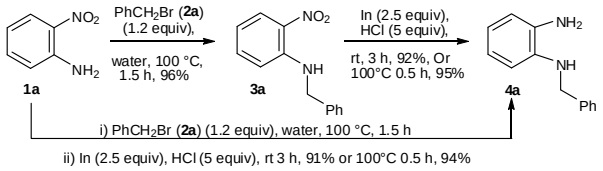
Entry	R^1	R^2	R^3	R^4	Yield (%)[b]
1	H	H	H	H	96
2	H	Me	H	H	96
3	H	Cl	H	H	95
4	Me	H	H	H	96
5	Cl	H	H	H	95
6	H	H	OMe	H	96
7	H	H	H	F	96
8	H	H	H	I	95

[a]**1** (1 mmol) was treated with **2** (1.2 mmol, 1.2 equiv) in water (2 mL) at 100 °C (oil bath) for 1.5 h. [b]Isolated yield of **3**.

We observed that there are insufficient literature reports on the preparation of *N*-monobenzylated-*o*-nitroanilines. The reported procedures for *N*-benzylation of *o*-nitroanilines with benzyl bromide (2 equiv) requires the use of NaH (3 equiv) in THF under reflux for 4 h to afford the *N*-monobenzylated-*o*-nitroaniline in 5-14% yields along with side product.[9] Benzylation with benzyl chloroformate in the presence of Et_3N (3 equiv) in dry DCM requires heating under reflux for 2 days.[10] Thus, the water-assisted selective *N*-alkylation offers a transition metal and

base-free protocol to prepare *N*-monobenzylated-*o*-nitroanilines. However, the use of other alkyl bromides (non-benzylic) was not effective.

The treatment of **3a** with In (2.5 equiv) and HCl (5 equiv)[11] in water afforded 2-*N*-phenylmethylaniline **4a** in 92 and 95% yields at rt and 100 °C after 3 and 0.5 h, respectively, (Scheme 3). The cascade *N*-alkylation-reduction performed in one-pot reaction afforded **4a** in comparable yields.



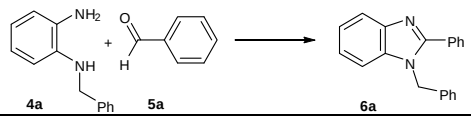
Scheme 3. Tandem *N*-benzylation-reduction strategy for 'all-water' synthesis of *N*-mono-benzylated *o*-phenylenediamine.

The treatment of **3a** with In (2.5 equiv) and HOAc (6 equiv) without any water afforded **4a** in 15 and 10% yields after 0.5 h at 100 °C and 3 h at rt, respectively. This further highlights the beneficial effect of water as the redox potential is influenced by the solvent[12] The better solvation of the In^{+3} cation in water makes the electron transfer from In metal for reduction of the nitro group more efficient.

We observed that in the direct alkylation, reaction of **2a** with excess (4.4 equiv) of **1a** in the presence of K_2CO_3 (2.8 equiv) for 20 h at rt affords moderate yields (~50%).[13] Therefore, this new strategy of tandem *N*-alkytaion-reduction constitutes an efficient route for the preparation of mono-*N*-benzylated-*o*-phenylenediamines.

To assess any beneficial role of water in the final cyclocondensation, **4a** was treated with benzaldehyde (**5a**) in various solvents in the absence of any catalyst. A 90% yield of 1-phenylmethyl-2-phenylbenzimidazole (**6a**) was obtained in water at 80 °C (entry 3, Table 4). Comparable results were obtained in MeOH and EtOH but other organic solvents (aprotic polar, ethereal, hydrocarbon, and halogenated hydrocarbon) gave poor yields (Table 4).

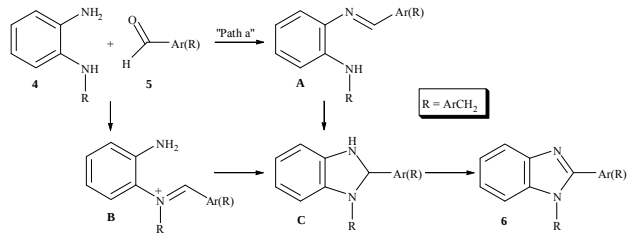
Table 4. Influence of the reaction medium and the indium metal or $InCl_3$ during the reaction of *N*-phenylmethyl-*o*-phenylenediamine **4a** with benzaldehyde **5a** to form **6a**.



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	Water	rt	2	30
2	Water	60	2	75
3	Water	80	2	90
4	EtOH	80	2	91
5	MeOH	80	2	89
6	Toluene	80	2	65
7	1,4-Dioxane	80	2	71
8	THF	80	2	60
9	DMF	80	2	63

[a]**4a** (1 mmol) was treated with **5a** (1 mmol, 1 equiv) in the appropriate solvent (2 mL) under different reaction conditions. [b]Isolated yield of **6a**.

The reaction may proceed by two pathways: a) via imine **A** formation 'path a' or via (b) immonium intermediate **B** formation 'path b' (Scheme 4).



Scheme 4. The possible routes of cyclo-condensation step.

To understand whether the reaction proceeds through 'path a' or 'path b' the progress of the reaction of **4a** (R = CH_2Ph) with **5a** (Ar = Ph) in water was monitored by ^1H NMR. The appearance of the signal at δ 8.6 in the sample after 15 and 30 min reaction suggested the formation of the imine. This signal as well as the aldehyde proton signal at δ 10.8 disappeared after 2 h (Figure 1).

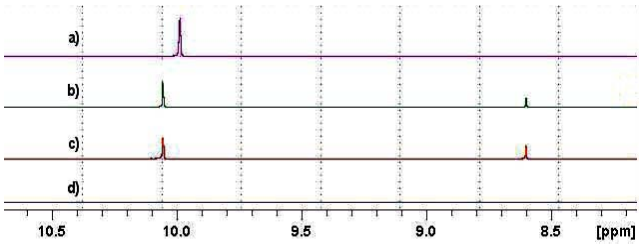
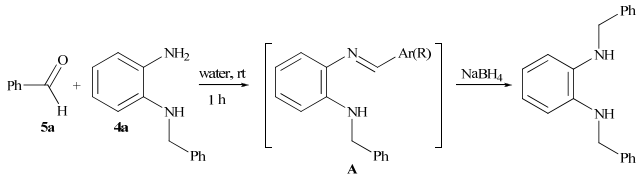


Figure 1. Time dependent NMR study (8.1-10.6 δ) for reaction of **4a** (1 mmol) with **5a** (1 mmol) in water (2 mL): (a) Benzaldehyde; (b) Reaction mixture after 15 min; (c) Reaction mixture after 30 min; (d) Reaction mixture after 2 h.

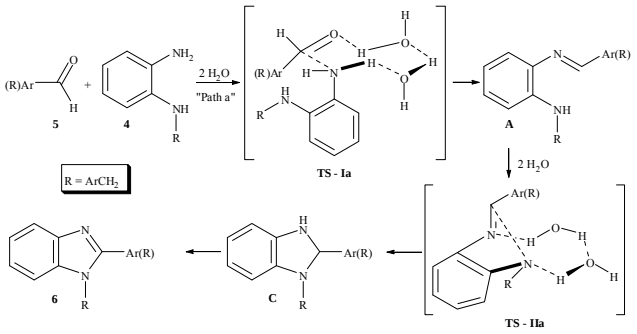
This suggested that the reaction proceeds via the imine formation 'path a' and was further confirmed by treatment of the reaction mixture after 1 h with $NaBH_4$ that formed *N*,*N*'-bisbenzylated *o*-phenylenediamine (Scheme 5).



Scheme 5. Proof of concept for intermediacy of the imine **A** during the progress of the reaction **4a** with **5a** via 'path a'

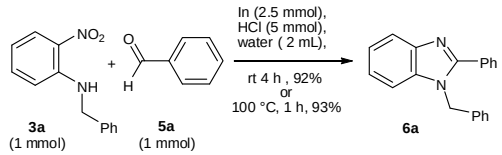
The role of water in the cyclocondensation can be attributed to its 'electrophile-nucleophile dual activation'[7] ability. Water forms HB with the aldehyde carbonyl oxygen (electrophilic activation). The second molecule of the water dimer in turn forms HB with one of the NH_2 hydrogens of **4a** (nucleophilic activation) through the transient species **TS-Ia** to form the imine (Scheme 6). Intramolecular nucleophilic attack of the adjacent NH group to the C=N is facilitated by water via 'electrophile (C=N) and nucleophile (NH) dual activation' through the hydrogen bonded assembly **TS-IIa** to form the imidazoline which on dehydrogenation forms the 1,2-disubstituted benzimidazole (Scheme 6). The better HBD value of water compared to that of other organic solvents makes the electrophilic activation more effective in water. The good HB acceptor value of water also

contributes in making the amino/imino nitrogens better nucleophile, through HB formation with the water oxygen, compared to other organic solvents. The alcohols (EtOH and MeOH) that are also good HB donors as well as HB acceptors gave next best results. Further beneficial effect in using water may also be visualized through the ease of oxidative conversion of the intermittently formed dihydrobenzimidazole **C** (Scheme 4 and Scheme 6) to **6** as water has been found to promote the conversion of benzothiazoline to benzothiazole.[7c]



Scheme 6. The role of water in the cyclo-condensation step.

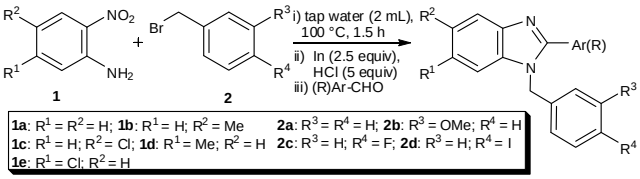
A tandem nitro reduction-condensation is achieved by the treatment of **3a** with In/HCl in water followed by **5a** to afford **6a** (Scheme 7).

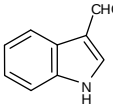
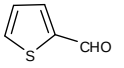
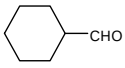
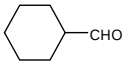
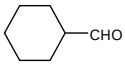
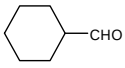
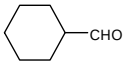
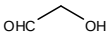


Scheme 7. Tandem reduction-condensation for regiospecific *N*-arylmethyl-2-arylbenzimidazole synthesis in water.

The 'all water' one-pot *N*-alkylation-reduction-condensation cascade was adopted for the regiospecific synthesis of *N*-arylmethyl-2-substituted benzimidazoles by sequential treatment of *o*-nitroanilines with benzyl bromides in water under heating followed by treatment with In/HCl and aldehydes (Table 5).

Table 5. The 'all water' *N*-alkylation-reduction-condensation cascade for regiospecific synthesis of *N*-arylmethyl-2-substituted benzimidazoles.[a]



Entry	1	2	Aldehyde	Time (h)[b]	Yield (%)[c]
1	**1a**	**2a**	R^1= R^2= R^3= R^4= H	3	89
2	**1a**	**2a**	R^1= R^2= R^4= H; R^3= Me	3	88
3	**1a**	**2a**	R^1= R^3= H; R^2= R^4= OMe	3	86
4	**1a**	**2a**	R^1= R^2= OMe; R^3= R^4= H	3	85
5	**1a**	**2a**	R^1= R^4= H; R^2= OH; R^3= OMe	3	87
6	**1a**	**2a**	R^1= R^2= R^4= H; R^3= OBn	3	88
7	**1a**	**2a**	R^1= R^2= R^4= H; R^3= Cl	3	90
8	**1a**	**2c**	R^1= R^2= R^3= R^4= H	3	88
9	**1a**	**2b**	R^1= R^2= R^3= R^4= H	3	86
10	**1a**	**2d**	R^1= R^2= R^3= R^4= H	3	87
11	**1b**	**2a**	R^1= R^2= R^3= R^4= H	3	90
12	**1b**	**2a**	R^1= R^1= R^4= H; R^3= Me	3	90
13	**1b**	**2a**	R^1= R^1= R^4= H; R^3= OBn	3	90
14	**1b**	**2a**	R^1= R^1= R^4= H; R^3= Cl	3	90
15	**1c**	**2a**	R^1= R^2= R^3= R^4= H	3	88
16	**1c**	**2a**	R^1= R^1= R^4= H; R^3= Me	3	87
17	**1c**	**2a**	R^1= R^1= R^4= H; R^3= OBn	3	88
18	**1c**	**2a**	R^1= R^1= R^4= H; R^3= Cl	3	89
19	**1d**	**2a**	R^1= R^2= R^3= R^4= H	3	90
20	**1d**	**2a**	R^1= R^1= R^4= H; R^3= Me	3	88
21	**1d**	**2a**	R^1= R^1= R^4= H; R^3= OBn	3	89
22	**1d**	**2a**	R^1= R^1= R^4= H; R^3= Cl	3	86
23	**1e**	**2a**	R^1= R^2= R^3= R^4= H	3	89
24	**1e**	**2a**	R^1= R^1= R^4= H; R^3= Me	3	87
25	**1e**	**2a**	R^1= R^1= R^4= H; R^3= OBn	3	88
26	**1e**	**2a**	R^1= R^1= R^4= H; R^3= Cl	3	89
27	**1a**	**2a**		3	84
28	**1a**	**2a**		3	85
29	**1a**	**2a**		3.5	88
30	**1b**	**2a**		3.5	89
31	**1c**	**2a**		3.5	86
32	**1d**	**2a**		3	87
33	**1e**	**2a**		3.5	88
34	**1a**	**2a**		4	82

[a]**1** (2 mmol) was treated with **2** (2.4 mmol, 1.2 equiv) in water (4 mL) at 100 °C (oil bath) for 1.5 h followed by addition of In (5 mmol, 2.5 equiv), HCl (5 mL 2 N aq HCl, 10 mmol, 5 equiv) and the aldehyde (2 mmol, 1equiv) for the remaining time. [b]Total time for the one-pot reaction. [c]Isolated yield of the 1,2-disubstituted benzimidazole.

Conclusions

A new strategy for water-assisted tandem *N*-alkylation-reduction-condensation process has been demonstrated for synthesis of *N*-arylmethylated-2-substituted benzimidazoles. Water plays the crucial and indispensable role of hydrogen bond mediated 'electrophilie nucleophile dual activation' during the selective *N*-monoalkylation of *o*-nitroanilines that forms the basis of regiodefined installation of the substituents in the respective position in the benzimidazole framework and offers alternative to the transition metal based C-N bond formation amination chemistry. The beneficial role of using water is also realised during the nitro reduction and the final condensation steps that make this synthetic strategy an 'all-water' chemistry. Further findings are (i) base-free synthesis of mono-*N*-benzylated *o*-nitroanilines and (ii) base-free tandem *N*-alkylation-reduction protocol for one-pot synthesis of mono-*N*-benzylated-*o*-phenylenediamines.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Spectral data and scanned NMR spectra]. See DOI: 10.1039/b000000x/

‡ **Experimental section:** The glassware to be used in reactions was thoroughly washed and dried in an oven and the experiments were carried out with required precautions. Chemicals and all solvents were commercially available and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using Me_3SiCl as an internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in Hz. ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CDCl_3$ at 77.00 ppm. Splitting pattern were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded under APCI mode of ionisation. Accurate mass measurements were performed on a Q-TOF instrument calibrated internall with sodium formate. Infra-red (IR) spectra were recorded in the range 4000-600 cm^{-1} either as neat for liquid or KBr pellets for solid samples. Purity compounds were checked on the silica gel GF-254 under UV at 254 nm. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Typical procedure for the selective *N*-mono-benzylation. *N*-Phenylmethyl-2-nitroaniline (3a) (Entry 1, Table 3): The mixture of *o*-nitroaniline **1a** (276 mg, 2 mmol) and benzyl bromide **2a** (407 mg, 2.4 mmol, 1.2 equiv) in water (4 mL) was stirred magnetically at 100 °C (oil-bath) for 1.5 h (TLC). The reaction mixture was cooled to rt and treated with $NaHCO_3$ (170 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$) and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane:EtOAc, 90:10) to obtain analytically pure **3a** (437 mg, 96%); Red solid; mp = 74-76 °C; IR (Neat) *ν*: 3435, 2940, 1618, 1573, 1510, 1350, 1262, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.42 (brs, 1H), 8.19-8.17 (m, 1H), 7.54-7.16 (m, 6H), 6.80 (d, *J* = 8.60 Hz, 1H), 6.67-6.63 (m, 1H), 4.53 (d, *J* = 5.64 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.3, 137.4, 136.3, 132.2, 128.9, 127.7, 127.1, 126.9, 115.7, 114.2, 47.1; MS (+pAPCI) m/z: 229.5 (MH^+), identical with those of an authentic compound.[14]

Typical procedure for the synthesis of N^1-benzylbenzene-1,2-diamine (4a) at 100 °C: To the mixture of *N*-benzyl-2-nitroaniline **3a** (456 mg, 2 mmol) in water (4 mL) was added In (574 mg, 5 mmol, 2.5 equiv), HCl (5 mL 2N aq HCl, 10 mmol, 5 equiv) and stirred magnetically at 100 °C (oil-bath) for 0.5 h (TLC). The reaction mixture was cooled to room temperature, treated with $NaHCO_3$ (170 mg), and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$) and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane:EtOAc, 90:10) to obtain analytically pure **4a** (376 mg, 95%); Low melting solid; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = 7.21-7.45 (m, 5 H; Ar-H), 6.79 (t, *J* = 7.2 Hz, 1H; Ar-H), 6.65-6.72 (m, 3 H; Ar-H), 4.29 (s, 2 H; CH_2), 3.39 (bd, s, 3 H, NH); MS (+pAPCI) *m/z*: 199.4 (MH^+), identical with those of an authentic compound.[13]

Typical procedure for the synthesis of N^1-benzylbenzene-1,2-diamine at rt: To the mixture of *N*-benzyl-2-nitroaniline **3a** (456 mg, 2 mmol) in water (4 mL) was added In (574 mg, 5 mmol, 2.5 equiv), HCl (5 mL 2 N aq HCl, 10 mmol, 5 equiv) and stirred magnetically at rt for 3 h (TLC). The reaction mixture was treated with $NaHCO_3$ (170 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane:EtOAc, 90:10) to obtain analytically pure product (364 mg, 92%).

Typical procedure for the synthesis of 1,2-disubstituted benzimidazole 6a by tandem reduction-condensation process of *N*-benzyl-2-nitroaniline 3a with benzaldehyde 5a in the presence of In/HCl in water at 100 °C: To the mixture of *N*-benzyl-2-nitroaniline **3a** (456 mg, 2 mmol) in water (4 mL) was added In (574 mg, 5 mmol, 2.5 equiv), HCl (5 mL 2 N aq HCl, 10 mmol, 5 equiv) and stirred magnetically at 100 °C (oil-bath) for 0.5 h (TLC). Benzaldehyde **5a** (212 mg, 2 mmol, 1 equiv) was added and the stirring was continued for another 30 min. The reaction mixture was cooled to rt and treated with $NaHCO_3$ (140 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 85:15) to obtain analytically pure **6a** as a white solid (528 mg, 93%). mp = 131-132 °C; IR (Neat) *ν*: 3030, 2949, 1608, 1464, 1453, 1365, 1255, 1162 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz) δ: 7.91-7.89 (m, 1H), 7.73-7.72 (m, 2H), 7.71-7.70 (m, 3H), 7.54-7.45 (m, 3H), 7.38-7.23 (m, 3H), 7.13 (d, *J* = 7.68 Hz, 2H), 5.49 (s, 2H); MS (+pAPCI) m/z: 285.3 (MH^+), identical with those of an authentic compound. [15]

Typical procedure for the synthesis of 1,2-disubstituted benzimidazole 6a by tandem reduction-condensation of *N*-benzyl-2-nitroaniline 3a and benzaldehyde 5a in presence of In/HCl in water at rt: To the mixture of *N*-benzyl-2-nitroaniline **3a** (456 mg, 2 mmol) in water (4 mL) was added In (574 mg, 5 mmol, 2.5 equiv), HCl (5 mL 2 N aq HCl, 10 mmol, 5 equiv) and stirred magnetically at rt for 3 h (TLC). Benzaldehyde **5a** (212 mg, 2 mmol, 1 equiv) was added and the stirring was continued for another 1 h. The reaction mixture was treated with $NaHCO_3$ (140 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 85:15) to obtain analytically pure **6a** as white solid (522 mg, 92%).

Typical procedure for the synthesis of 1,2-disubstituted benzimidazole 6a by tandem reduction-condensation of *N*-benzyl-2-nitroaniline 3a and benzaldehyde 4a in the presence of In/HOAc at 100 °C: The mixture of *N*-benzyl-2-nitroaniline **3a** (456 mg, 2 mmol) and In (574 mg, 5 mmol, 2.5 equiv), HOAc (0.6 mL, 10 mmol, 5 equiv) was stirred magnetically at 100 °C (oil-bath) for 0.5 h (TLC). Benzaldehyde **5a** (212 mg, 2 mmol, 1 equiv) was added and the stirring was continued for another 30 min. The reaction mixture was cooled to rt and treated with $NaHCO_3$ (140 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 85:15) to obtain analytically pure **6a** as white solid (85 mg, 15%).

Typical procedure for tandem *N*-alkylation-reduction-condensation process for the synthesis of 1,2-disubstituted benzimidazole (1-Benzyl-2-phenyl-1H-benzimidazole (6a); Entry 1, Table 5): The mixture of *o*-nitroaniline **1a** (276 mg, 2 mmol) and benzyl bromide **2a** (407 mg, 2.4 mmol, 1.2 equiv) in water (4 mL) was stirred magnetically at 100 °C (oil-bath) for 1.5 h (TLC) followed by addition of In (574 mg, 5 mmol, 2.5 equiv), HCl (5 mL 2N aq HCl, 10 mmol, 5 equiv) and continued stirring for further 30 min. Benzaldehyde **5a** (212 mg, 2 mmol, 1 equiv) was added and the stirring was continued for another 30 min. The reaction mixture was cooled to room temperature and treated with $NaHCO_3$ (140 mg) and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 85:15) to obtain analytically pure **6a** as white solid (511 mg, 90%).

1 **Angiotensin II receptor antagonist:** Y. Kohara, K. Kubo, E. Imamiya, T. Wada, Y. Inada and T. Naka, *J. Med. Chem.* 1996, **39**, 5228; **Neuropeptide Y Y1 receptor antagonist:** H. Zarrinmayeh, A.

M. Nunes, P. L. Ornstein, D. M. Zimmerman, M. B. Arnold, D. A. Schober, S. L. Gackenheimer, R. F. Bruns, P. A. Hipskind, T. C. Britton, B. E. Cantrell and D. R. Gehlert, *J. Med. Chem*. 1998, **41**, 2709; **Factor Xa inhibitor:** Z. S. Zhao, D. O. Arnaiz, B. Griedel, S. Sakata, J. L. Dallas, M. Whitlow, L. Trinh, J. Post, A.Liang, M. M. Morrissey and K. J.Shaw, *Bioorg. Med. Chem. Lett*. 2000, **10**, 963; **Antiallergic 5-Lipoxygenase inhibitor:** H. Nakano, T. Inoue, N. Kawasaki, H. Miyakata, H. Matsumoto, T. Taguch, N. Inagaki, H. Nagai and T. Satog, *Bioorg. Med. Chem.* 2000, **8**, 373; **Antibacterial:** H. Göker, C. Kuş, D. W. Boykin, S. Yildiz and N. Altanlar, *Bioorg. Med. Chem.* 2002, **10**, 2589; **Burkitt's lymphoma promotion inhibitors:** M. M. Ramla, M. A. Omar, H. Tokuda and H. I. El-Diwani, *Bioorg. Med. Chem*. 2007, **15**, 6489; **Antimicrobial and antiviral:** D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq and J. Balzarini, *J. Enz. Inhibit. Med. Chem*. 2009, **24**, 1161; **Antiparasitic:** J. Pérez-Villanueva, R. Santos, A. Hernández-Campos, M. A. Giulianotti, R. Castillo and J. L. Medina-Franco, *Med. Chem. Commun*. 2011, **2**, 44.

2 B. Zou, Q. Yuan and D. Ma, *Angew. Chem. Int. Ed.* 2007, **46**, 2598.

3 (a) N. Zheng and S. L. Buchwald, *Org. Lett*. 2007, **9**, 4749; (b) N. Zheng, K. W. Anderson, X. Huang, N. H. Nguyen and S. L. Buchwald, *Angew. Chem. Int. Ed.* 2007, **46**, 7509.

4 (a) C. T. Brain and J. T. Steer, *J. Org. Chem*. 2003, **68**, 6814; (b) P. Saha, M. A. Ali, P. Ghosh and T. Punniyamurthy, *Org. Biomol. Chem*. 2010, **8**, 5692.

5 J. Alonso, N. Halland, M. Nazaré, O. R'kyek, M. Urmann and A. Lindenschmidt, *Eur. J. Org. Chem.* 2011, 234.

6 S. Shekhar, P. Rydberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter and S. L. Buchwald, *J. Am. Chem. Soc*. 2006, **128**, 3584.

7 (a) S. V. Chankeshwara and A. K.Chakraborti, *Org. Lett.* 2006, **8**, 3259; (b) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.* 2006, **8**, 2433; (c) A. K. Chakraborti, S. Rudrawar, K. B. Jadhav, G. Kaur and S. V. Chankeshwara, *Green Chem*. 2007, **9**, 1335; (d) N. Parikh, D. Kumar, S. Raha Roy and A. K. Chakraborti, *J. Chem. Soc. Chem. Commun*. 2011, **47**, 1797.

8 M. J. Kamlet, J.-M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem*. 1983, **48**, 2877.

9 J. M. Gardiner, C. R. Loyns, C. H. Schwalbe, G. C. Barrett and P. R. Lowe, *Tetrahedron* 1995, **51**, 4101.

10 H. Pati, P. Weisbruch, A. Lemon and M. Lee, *Synth Commun.* 2004, **34**, 933.

11 J. G. Lee, K. I. Choi, H. Y. Koh, Y. Kim, Y. Kang and Y. S. Cho, *Synthesis* 2001, 81.

12 N. G. Connelly and W. E. Geiger, *Chem. Rev*. 1996, **96**, 877.

13 P. Chattopadhyay, R. Rai and P. S. Pandey, *Synth.Commun.* 2006, **36**, 1857.

14 J. W. Hubbard, A. M. Piegols and B. C. G. Söderberg, *Tetrahedron* 2007, **63**, 7077.

15 R. Varala, A. Nasreen, R. Enugala and S. R. T.Adapa, *Tetrahedron Lett*. 2007, **48**, 69.

"All-water" chemistry of tandem *N*-alkylation-reduction-condensation for synthesis of *N*-arylmethyl-2-substituted benzimidazoles

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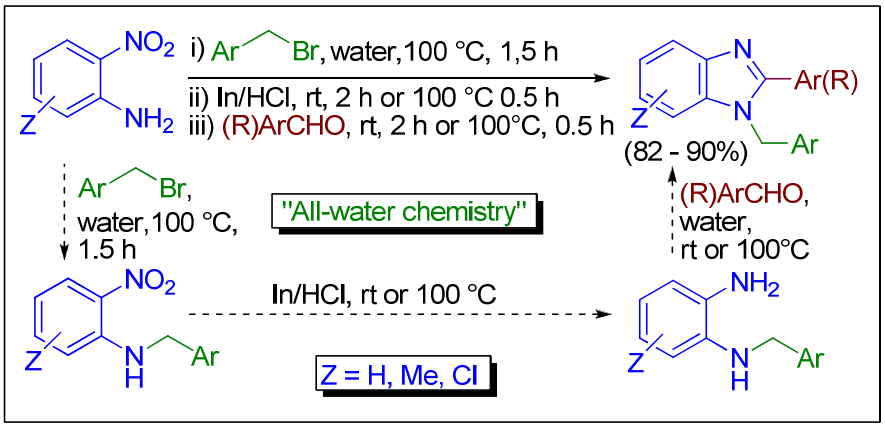

A strategy of 'all water chemistry' of tandem *N*-alkylation-reduction-cyclisation is reported for synthesis of 1-arylmethyl-2-substituted benzimidazoles in regiodefined manner.