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ARTICLE TYPE

An "all-water" strategy for regiocontrolled synthesis of 2-aryl quinoxalines

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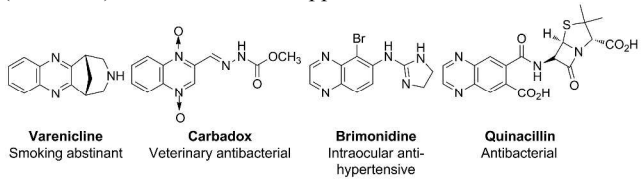
A new synthetic strategy of tandem *N*-aroylmethylation–nitro reduction–cyclocondensation has been developed for the first and generalized regioselective synthesis of 2-aryl quinoxalines adopting "all water chemistry." Water plays the critical role through hydrogen bond driven 'synergistic electrophile-nucleophile dual activation' for chemoselective *N*-aroylmethylation of *o*-nitroanilines, that underlines the origin of the regioselectivity, as the use of organic solvents proved to be ineffective. Water also provides beneficial effects during the nitro reduction and the penultimate cyclocondensation steps.

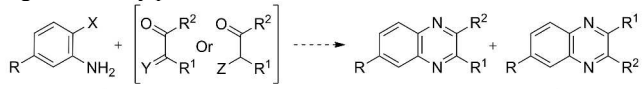
Introduction

Quinoxalines exhibit a wide range of biological activities,[1] represent the essential pharmacophoric feature of various drugs (Scheme 1)[2] and find versatile applications in material sciences.[3]



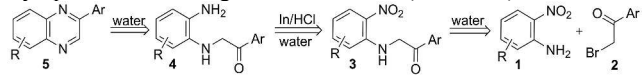
Scheme 1. A few quinoxaline-based drugs.

These have triggered interest to develop synthetic methodologies of quinoxalines that involve the Lewis/Brönsted acid or Lewis base promoted reaction of *o*-phenylenediamines (commercially available or prepared in situ by reduction of the corresponding *o*-nitroanilines or 1,2-dinitrobenzenes) with various coupling partners such as 1,2-diketones (preformed or prepared *in situ* from acetylene derivatives), 1,2-ketomonoximes, α-hydroxyketones/α-haloketones, 1,2-diols, α-methyleno aldehydes/ketones, substituted epoxides, substituted nitroolefins.[4] However, regiocontrolled construction of the quinoxaline scaffold from unsymmetrical substrates (reacting/coupling partners) remains elusive. Some of the reported procedures[5] form regioisomeric mixtures while in all others[4] the regioselectivity issue remained unaddressed/suppressed. It was realized that the reported procedures[4,5] involve simultaneous condensation of 1,2-bisnucleophiles with 1,2-bis-electrophilic coupling partners (Scheme 2) and hence are ought to be associated with the regioselectivity problem.



Scheme 2. Regioselectivity in the synthesis of quinoxalines.

This presses the necessity for a new synthetic design for regioselective construction of the quinoxaline moiety. Herein we present a new strategy of "all-water" tandem *N*-aroylmethylation-reduction-cyclocondensation process for one-pot synthesis of 2-aryl quinoxalines in regiodefined manner (Scheme 3).

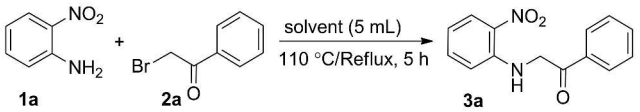


Scheme 3. "All-water" *N*-aroylmethylation-reduction-cyclocondensation strategy for regiocontrolled synthesis of quinoxalines.

Results and Discussion

As the *N*-aroylmethylation is the critical step, to test the feasibility of the metal and base-free C-N bond formation, in a model study *o*-nitroaniline (**1a**) was treated with α-bromoacetophenone (**2a**) (Scheme 3, R = H) in various solvents to form 2-[(2-nitrophenyl)amino]-1-phenylethanone (**3a**) (Table 1). The 2-[(2-nitrophenyl)amino]-1-phenylethanone (**3a**) was obtained in excellent yields (91-92%) in water. The comparable results in tap, pure, and ultra pure water (entries 2-4, Table 1) indicate that the *N*-benzoylmethylation is not influenced by any dissolved metallic/organic impurities. The specific assistance of water in promoting the metal/base free *N*-benzoylmethylation is revealed by the fact that **3a** was formed in poor yield under neat condition (entry 1, Table 1) and in hydrocarbon, halogenated hydrocarbon, ethereal, and aprotic polar solvents (entries 10–20, Table 1). Alcohols (protic polar solvents) gave moderate yields (entries 5–9, Table 1).

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



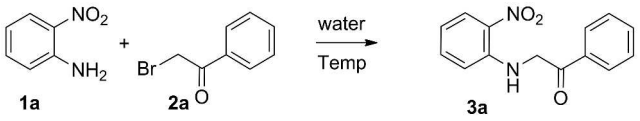
1a 2a 3a

Entry	Solvent	Temp (°C)	α[b]	β[b]	Yield (%)[c]
1	None	110	--	--	7
2	Tap water	Reflux	1.17	0.18	92
3	Pure water[d]	Reflux	1.17	0.18	91
4	Ultra pure water[e]	Reflux	1.17	0.18	92
5	MeOH	Reflux	0.93	0.62	59
6	EtOH	Reflux	0.83	0.77	65
7	^{i}PrOH	Reflux	0.76	0.95	68
8	^{t}BuOH	Reflux	0.68	1.01	74
9	TFE	Reflux	1.51	0.00	50
10	Toluene	Reflux	0.00	0.11	31
11	Hexane	Reflux	0.00	0.00	trace
12	DCE	Reflux	0.00	0.00	35
13	1,4-Dioxane	Reflux	0.00	0.37	55
14	THF	Reflux	0.00	0.55	21
15	Acetone	Reflux	0.08	0.48	13
16	$MeNO_2$	Reflux	0.22	0.00	33
17	DMF	110	0.00	0.69	36
18	DMA	110	0.00	0.76	nil
19	Formamide	110	0.71	0.00	23
20	MeCN	Reflux	0.19	0.31	trace

[a]**1a** (1 mmol) was treated with **2a** (1.5 mmol, 1.5 equiv) in the appropriate solvent (5 mL), except for entry 1, under heating at 110°C (oil bath) for 5 h. [b]The α and β values represent the hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) property of the solvent as provided under Ref 13. [c]Isolated yield. [d]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]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.

Further studies on the variation of different reaction parameters, such as the molar equivalents of **2a**, amount of water, temperature, and time revealed the use of 1.0 molar equivalent of **2a** in water (2 mL/mmol of **1a**) at 110 °C (oil bath) for 3 h to be the optimal condition (entry 19, Table 2).

Table 2. *N*-Benzoylmethylation of *o*-nitroaniline (**1a**) under different condition.[a]



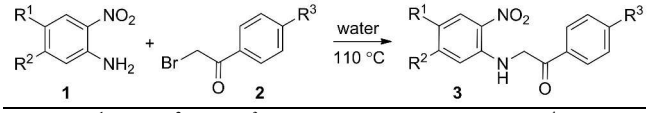
1a 2a 3a

Entry	Water (mL)	Temp (°C)	Time (h)	Equiv of **2a**[b]	Yield (%)[c]
1	5	110	5	1.0	92
2	5	110	5	1.1	92
3	5	110	5	1.2	92
4	5	110	5	1.3	93
5	5	110	5	1.4	92
6	5	110	5	1.5	92
7	0.5	110	5	1.0	68
8	1	110	5	1.0	79
9	2	110	5	1.0	92
10	3	110	5	1.0	92
11	4	110	5	1.0	92
12	2	rt	5	1.0	0
13	2	60	5	1.0	traces
14	2	80	5	1.0	41
15	2	110	5	1.0	92
16	2	120	5	1.0	92
17	2	110	1	1.0	28
18	2	110	2	1.0	75
19	2	110	3	1.0	92
20	2	110	4	1.0	92
21	5	110	2	1.0	84
22	2	rt	12	1.0	nil
23	2	80	8	1.0	35
24	2	120	2	1.0	87

[a]**1a** (1 mmol) was treated with **2a** under different reaction condition in the water as a reaction medium. [b]molar equiv with respect to **1a**. [c]Isolated yield of **3a**.

The synthetic potential of the water-assisted *N*-aroylmethylation of *o*-nitroanilines is demonstrated by the reaction of a few substituted *o*-nitroanilines **1** with substituted α-bromoacetophenones **2** to form **3** (Table 3).

Table 3. The base/catalyst-free *N*-aroylmethylation of different *o*-nitroanilines (**1**) with different α-bromoacetophenones (**2**) in water to form **3**.[a]

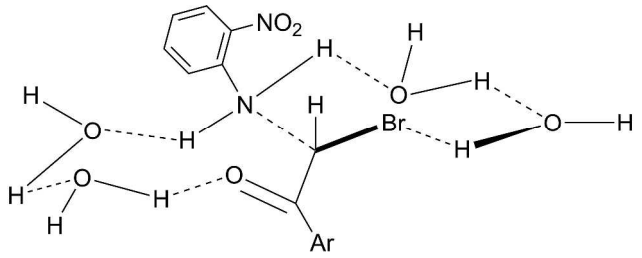


1 2 3

Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]
1	H	H	H	3	92
2	H	H	Cl	3	91
3	Cl	H	H	4	89
4	H	Cl	H	4	90
5	CH_3	H	H	3	92
6	CH_3	H	OMe	3	90

[a]**1** (1 mmol) was treated with **2** (1 mmol, 1 equiv) in water (2 mL) at 110 °C (oil bath) for stipulated time period. [b]Isolated yield of **3**.

The reported method for the preparation of *N*-phenacyl-*o*-nitroanilines involve the use of base in DMF for 48 h.[6] Anilines are known to react with α-halogenated ketones to form indoles.[7] Thus, the results of table 2 exemplify an excellent metal and base-free C-N bond formation protocol for chemoselective synthesis *N*-phenacyl-*o*-nitroanilines. The role of water can be visualized by its ability to form hydrogen bond (HB) with the NH_2 hydrogen of **1** (nucleophilic activation). The second molecule of the water dimer[8] in turn forms HB with the Br atom of **2** (electrophilic activation) and brings the bromomethylene carbon in close proximity to the NH_2 nitrogen of **1** in the H-bonded species (Scheme 4). Further, the carbonyl oxygen of **2** also participates in HB formation with another water dimer in which the second water molecule forms HB with the other NH_2 hydrogen in **1**. The array/network of HBs gives stability[9] to the H-bonded cluster (Scheme 4) and facilitates 'ambiphiphilic nucleophilic-electrophilic dual activation.'[10]



Scheme 4. The envisaged role of water in promoting *N*-aroylmethylation of **1** with **2** to form **3**.

The hydrogen-bond assisted/mediated formation of non-covalent

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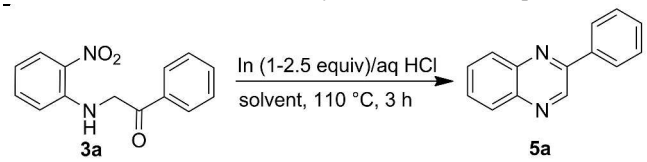
adduct of the reactants and the promoter has been invoked in various organo-catalytic chemical reactions/synthesis.[11]

The physico-chemical parameters (acceptor/donor number etc.) of the solvent often play key role in organic reactions,[12] and the HB involving the reactant and the solvent has significant influence.[13] Therefore, the role of the reaction medium for *N*-aroylmethylation can be visualised through the formation of the HB adducts (Scheme 4) due to the hydrogen bond donor (HBD) (α scale) and hydrogen bond acceptor (HBA) (β scale) properties of the solvent.[14] Although, the HBD property (α value) is expected to play the predominant role in activating the electrophile (**2a**) the HBA ability (β value) is also important as it determines the ability of the solvent to activate the nucleophile (amine nitrogen of **1a**). Therefore, TFE gave inferior results due to its poor β value (entry 9, Table 1).

The reduction of nitro group of **3a** would form the intermediate **4a** which on cyclocondensation would form the 2-phenyl quinoxaline **5a** (Scheme 3, R = H). However, treatment of **3a** with In (2.5 equiv) and 12N HCl (5 equiv)[15] in water (2 mL) afforded **5a** in 24% yield at 110 °C (oil bath) after 3 h (Table 4). Further studies on standardization of the reaction conditions revealed that the best result (90% yield) is obtained in using 5 equiv of 2N HCl (entry 3, Table 4). Organic solvents gave inferior results highlighting the beneficial effect of water on the reduction due to enhanced solvation of the In^{3+} cation in water making the electron transfer more efficient.[16]

Table 4. The effect of solvent and the amount of aq. HCl and In metal on the cascade reduction-cyclocondensation step.[a]



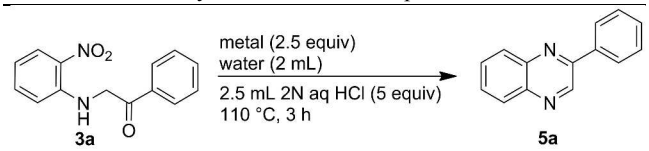
3a **5a**

Entry	Solvent	In metal (mmol)	aq HCl (mL)	Equiv[b]	Yield (%)[c,d]
1	water	2.5	12N (0.4 mL)	5	24
2	water	2.5	6N (0.8 mL)	5	59
3	water	2.5	2N (2.5 mL)	5	90[e,f]
4	water	2.5	2N (2 mL)	4	67
5	water	2.5	2N (1.5 mL)	3	42
6	water	2.5	2N (1 mL)	2	21
7	water	2.0	2N (2.5 mL)	5	64
8	water	1.5	2N (2.5 mL)	5	44
9	EtOH	2.5	12N (0.4 mL)	5	trace
10	Toluene	2.5	12N (0.4 mL)	5	42
11	Toluene	2.5	2N (2.5 mL)	5	27
12	Dioxane	2.5	12N (0.4 mL)	5	nil
13	DCE	2.5	12N (0.4 mL)	5	nil
14	MeCN	2.5	12N (0.4 mL)	5	nil
15	DCE	2.5	12N (0.4 mL)	5	nil
16	THF	2.5	12N (0.4 mL)	5	nil
17	DMF	2.5	12N (0.4 mL)	5	nil
18	none	2.5	2N (2.5 mL)	5	14

[a]To the mixture of **3a** (1 mmol) in water (2 mL, entries 1-6) or the specified organic solvent (4.1 mL, entries 7-15) was added In metal (1.5-2.5 equiv as indicated against each entry) and the indicated amount (in ML) of aq HCl at 110 °C (oil bath) and the mixture was stirred magnetically for 3 h. [b]Molar equiv of HCl. [c]Isolated yield of **5a**. [d]The unreacted **3a** remained unchanged and could be recovered wherever **5a** was formed in poor yields. [e]Only trace amount of **5a** was formed in performing the reaction at room temperature (35-40 °C). [f]**5a** was obtained in 63% yield in performing the reaction at 80 °C.

To find out whether indium metal can be replaced by other less costly metals such as Fe, Zn, Mg, Sn, or $SnCl_2{\cdot}2H_2O$, **3a** was treated with different metals/reducing agent (2.5 equiv) in aq HCl (2N 2.5 mL, 5 equiv) (Table 5).

Table 5. The effect of different metals/reducing agent on the cascade reduction-cycloconden sation step.[a]



3a **5a**

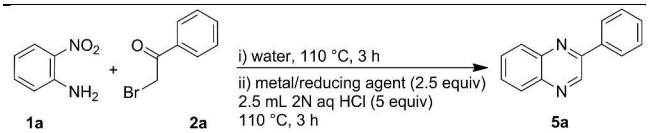
Entry	Metal	Isolated Yield of **5a** (%)
1	In	90
2	Fe	61
3	Zn	trace[b]
4	Mg	trace[b]
5	Al	25[b]
6	Sn	64
7	$SnCl_2{\cdot}2H_2O$	65

[a]To the mixture of **3a** (1 mmol) in water (2 mL) was added metal or the indicated reducing agent (2.5 equiv) and aq HCl (2N, 2.5 mL; 5 equiv) at 110 °C (oil bath) and the mixture was stirred magnetically for 3 h. [b]The unreacted **3a** remained unchanged and could be recovered.

Thus, the use of indium metal provided the best results. The product isolation was found to be tedious in case of aluminium due to gel formation in the reaction mixture. The use of Sn metal or its popularly used salt $SnCl_2{\cdot}2H_2O$ were also less effective.[17]

To determine whether indium metal would offer similar beneficial effect compared to Fe, Zn, Mg, Sn, or $SnCl_2{\cdot}2H_2O$ for the one pot tandem *N*-aroylmethylation-reduction-condensation, **1a** was sequentially treated with **2a** in water followed by different metals/reducing agent (2.5 equiv) in aq HCl (2N 2.5 mL, 5 equiv) to form **5a** (Table 6). The best result was obtained in using indium metal. Herein also poor yields were obtained with Sn metal and $SnCl_2{\cdot}2H_2O$.[17]

Table 6. The effect of different metals/reducing agent on the tandem *N*-aroylmethylation- reduction-cyclocondensation during the reaction of**1a** with **2a** to form **5a**.[a]



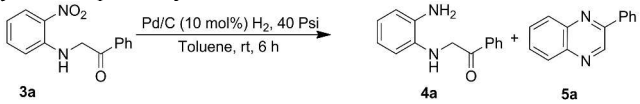
1a **2a** **5a**

Entry	Metal	Isolated Yield of **5a** (%)
1	In	84
2	Fe	59
3	Zn	trace[b]

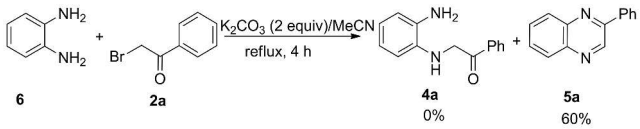
4	Mg	trace[b]
5	Al	15[b]
6	Sn	63
7	$SnCl_2·2H_2O$	57

[a]**1a** (1 mmol) was treated with **2a** in water (2 mL) at 110 °C (oil bath) for 3 h followed by addition of the metal/reducing agent (2.5 equiv) and aq HCl (2N, 2.5 mL; 5 equiv) at 110 °C (oil bath) and the mixture was stirred magnetically for further 3 h. [b]The unreacted **1a** and **2a** remained unchanged.

The poor yields of **5a** obtained in organic solvents (Table 4) during the treatment of **3a** with In/HCl raised the query as to whether the use of aqueous medium exerts beneficial effect only for the nitro reduction or its beneficial effect extends for the subsequent cyclocondensation step as well. To distinguish any role of water in the cyclocondensation of **4a** to **5a**, it was felt necessary to treat the preformed **4a** in water as well as in organic solvents. However **4a** could not be isolated by the In/HCl reduction of **3a**, although the MS spectra of the crude reaction mixture exhibited ion peak corresponding to **4a**. Attempts such as (i) Pd/C mediated hydrogenation of **3a** (Scheme 5), and (ii) reaction of *o*-phenylenediamine (**6**) with **2a** (Scheme 6) were unsuccessful and resulted in the formation of **5a** in 35 and 60% yields, respectively.



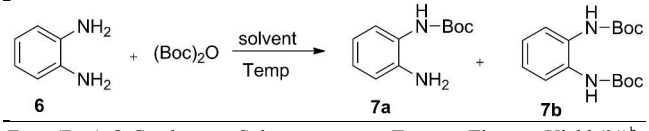
Scheme 5. Pd-Catalysed hyrogenation of 2-[(2-nitrophenyl)amino]-1-phenylethanone (**3a**).



Scheme 6. Reaction of *o*-phenylenediaimine (**6**) with *α*-bromoacetophenone (**2a**).

Thus, it was planned to prepare **8a** [pro-**4a**] which would generate **4a** in-situ through *N*-Boc deprotection under acid/metal-free condition (Scheme 7). Although a few methods[18] were reported for mono-*N*-Boc formation of **6**, repetition of some of these led to the mixture of the mono- and di-*N*-Boc derivatives of **6** (Table 7).

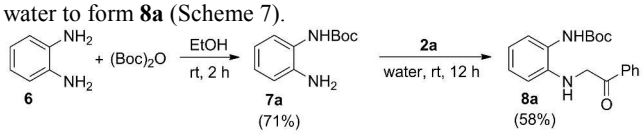
Table 7. Preparation of *tert*-butyl (2-aminophenyl)carbamate (**7a**).[a]



Entry	(Boc)$_2$O (equiv)	Catalyst (mol%)	Solvent (amt)	Temp (^{o}C)	Time (h)	Yield (%)[b] 7a	7b
1	1.2	Gu·HCl[c] (15)	EtOH (1 mL)	35-40	3	52	28
2	1	$LiClO_4$ (20)	DCM (2 mL)	30-40	5	42	23
3	1	none	DCM (1 mL)	0	2	64	21
4	1	Iodine (10)	neat	35-40	4	35	35
5	1	none	EtOH (4 mL)	30	0.5	71	22

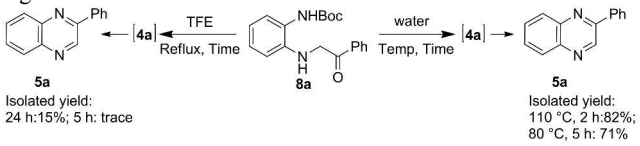
[a]Treatment of **6** (1 mmol) under different reaction condition in different solvents at specified temperature for specified time. [b]Isolated yield.[c]Gu·HCl stands for guanidinium hydrochloride.

The mono-*N*-Boc **7a** was obtained in 71% yield following modification of literature report[18e] and was treated with **2a** in water to form **8a** (Scheme 7).



Scheme 7. Synthesis of **8a**.

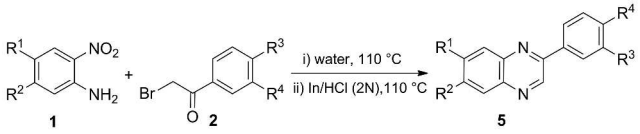
The acid/metal-free *N*-Boc deprotection is reported to take place in water[19] and trifluoroethanol (TFE)[20] under heating. The treatment of **8a** in water 110 °C (oil bath) gave **5a** in 82% yield after 2 h (Scheme 8). This indicated that the cyclocondensation of the in situ formed **4a** to **5a** is promoted by water. However, **5a** was formed in 15% yield by the treatment of **8a** in TFE under reflux for 24 h. No significant amount of **5a** was obtained by the treatment of **8a** in TFE under reflux for 5 h. The treatment of **8a** in water (in place of TFE) under similar condition (80 °C for 5 h) afforded **5a** in 71% yield. Thus, water is the best solvent for the cyclocondensation step due its favourable α and β values that render a better 'dual activation' ability of water compared to organic solvents.



Scheme 8. Acid/metal-free cyclocondensation of **7a** to form **5a**.

The generality of the new strategy of 'all water' one-pot tandem *N*-aryolmethylation-reduction-condensation for synthesis of 2-aryl quinoxalines is demonstrated by sequential treatment of various *o*-nitroanilines with different α-bromoacetophenones in water under heating followed by treatment with In/HCl (2N) (Table 8).

Table 8. 'All water' cascade synthesis of 2-aryl quinoxalines.[a]



Entry	R^1	R^2	R^3	R^4	Time (h)[b]	Yield (%)[c]
1	H	H	H	H	5	86
2	H	H	H	OMe	5	83
3	H	H	OMe	H	5	84
4	H	H	H	Cl	5	82
5	H	H	H	Br	5	84
6	Cl	H	H	H	6	81
7	Cl	H	H	OMe	6	80
8	Cl	H	H	Cl	6	82
9	Cl	H	H	Br	6	80
10	H	Cl	H	H	6	83
11	H	Cl	H	OMe	6	81
12	H	Cl	H	Cl	6	82
13	H	Cl	H	Br	6	83
14	Me	H	H	OMe	5	80
15	Me	H	H	Br	5	80
16	OMe	H	H	H	5	82

[a]**1** (1 mmol) was treated with **2** (1 mmol, 1 equiv) in water (2 mL) at 110 °C (oil bath) for 3 h followed by addition of In (2.5 mmol, 2.5 equiv), 2N HCl (2.5 mL, 5 mmol, 5 equiv) and allowed to proceed for remaining time. [b]Total time for the one-pot reaction.[c] Isolated yield of **5**.

Condensation of *o*-phenylenediamine with phenacyl bromide has been reported in water as well as organic solvents in the presence

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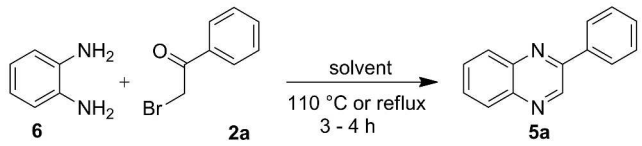
of organic/inorganic catalysts to form 2-phenylqunoxalines.[4a,d-j,5c] However, a catalyst-free protocol in water that would reflect the distinct influence of water in the *N*-aroylmethylation and subsequent cyclo-condensation step is lacking. Thus, to evaluate any distinct advantage of water over organic solvents **6** was treated with **2a** in various solvents in the absence of any added base/acid catalyst at 110 °C (oil bath) (Table 9).

Table 9. Reaction of **6** with **2a** in various solvents under catalyst-free condition.[a]



6 **2a** **5a**

Entry	Solvent	Temp (°C)	Yield (%)[b]
1	Water	80	62
2	Water	Reflux	79,71[c],74[d]
3	EtOH	Reflux	65
4	Toluene	Reflux	40
5	1,4-Dioxane	Reflux	61
6	THF	Reflux	47
7	DMF	110	52
8	MeCN	Reflux	45
9	TFE	Reflux	40

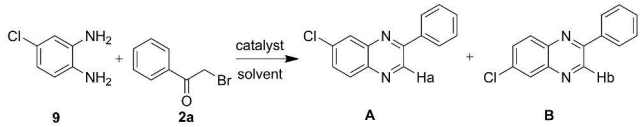
[a]**6** (1 mmol) was treated with **2a** in the specific solvent (2 mL) at 80/110 °C (oil bath temperature) for 4 h (unless specified). [b]Isolated yield of **5a**. [c]The yield of **5a** in performing the reaction for 3 h. [d]The yield of **5a** in performing the reaction for 3 h in the presence of K_2CO_3 (1 equiv).

The best yield obtained in water clearly reflect the distinct advantage of water as the reaction medium for the tandem *N*-aroylmethylation-cyclocondensation. Comparable yield (74%) obtained in performing the reaction in water in the presence of K_2CO_3 (1 equiv) (Table 9, entry 2, footnote d) rules out the possibility of any essential role of the liberated HBr (during the initial *N*-aroylmethylation step) for the final cyclocondensation.

The significant role of the solvent (Table 9) in the final cyclocondensation step can be demonstrated by the best results are obtained in water that acts both as good hydrogen bond donor and hydrogen bond acceptor with the second best results obtained in EtOH. The lesser yield obtained in TFE compared to that in water and EtOH is the clear reflection of the inferior hydrogen bond acceptor ability of TFE. The use of 1,4-dioxane afforded the next best result due to its appreciable hydrogen bond acceptor ability (to activate the amino group of the intermediately formed **4a**). The better result in 1,4-dioxane compared to that of THF could be due to the chelation effect of the two oxygen atoms in the former to form the HB with the NH_2 group more effectively. The inferior yields in DMF, MeCN and toluene are also reflection of the unfavourable hydrogen bond donor/acceptor ability of these solvents.

Although the quinoxaline formation by a direct condensation of **6** with **2a** becomes feasible in water under catalyst-free condition, the reaction of unsymmetrical *o*-phenylenediamine with phenacyl bromide is expected to form regioisomeric quinoxalines as has been observed in one of these reports.[5c] However, the regioselectivity issue remained unaddressed/suppressed in the other reported methodologies.[4a,d-j] To throw light on this regioselectivity issue and establish the distinctiveness of the "all water" strategy of the *N*-aroylmethylation-nitro reduction-cyclocondensation cascade for regioselective synthesis of 2-aryl quinoxalines, the condensation of 4-chloro-1,2-phenylenediamine **9** with phenacyl bromide was performed in water as well as in organic solvents under the reported reaction conditions[4a,d-j,5c] (Table 10). In all of these cases the isolated product on being subjected to ^{1}H NMR analyses revealed to be a mixture of the regioisomeric products. In each case, the pure regioisomers were isolated through flash column chromatography and were identified as **A** and **B** based on the spectral data of authentic compounds (products of entries 6 and 10, respectively, of Table 8) and on comparison with literature reports.[5i,l] On the other hand, the reaction of 4-chloro-2-nitroaniline with phenacyl bromide following the tandem *N*-aroylmethylation-reduction-cyclocondensation strategy resulted in exclusive formation of one of the regioisomeric quinoxalines without any concomitant formation of the other regioisomer (entry 10, Table 8). This clearly demonstrates the distinct advantage of this new synthetic strategy. The unambiguous route of construction of the quinoxaline scaffold under the present method forms the basis of regioselectivity control.

Table 10. Reaction of **I** with **2a** under the reported reaction conditions.[a]



9 **2a** **A** **B**

Entry	Catalyst[b] (mol%)	Solvent	Temp (°C)	Time (h)	(**A**:**B**)[c]	yield (%)[d] **A**	**B**
1	Pyridine (10)	THF	rt	2	20:80	25	45
2	---	PEG-400	80	8	83:17	65	15
3	β-CD (1 equiv)	Water	70	3	79:21	63	21
4	TMSCl (1 equiv)	Water	70	8	86:14	51	12
5	CTAB (20)	Water	10	8	34:65	25	62
6	$HClO_4$-SiO_2 (50 mg)	MeCN	rt	1	22:77	15	63
7	TBAB (20) + K_2CO_3 (2 equiv)	Water	rt-70	4.5	72:28	51	18
8	DABCO (20)	THF	rt	1	32:67	12	62
9	---	Water	110	7	58:42	33	41[e]

[a]**I** (1 mmol) was treated with **2a** under the various reported reaction conditions. [b]Lit ref: 4a, 4e-j, and 5c for entries 1-8, respectively. [c]Regioisomeric distribution based on Ha and Hb proton integration value in the ^{1}H NMR of the crude reaction mixture. [d]Isolated yield after flash column chromatography. [e]Data generated under the condition of the present study.

Conclusions

A new synthetic strategy of 'all water' tandem aroylmethylation-nitro reduction-cyclocondensation is reported for the first and generalized regioselective synthesis of 2-aryl quinoxalines. Water plays the critical role through hydrogen bond driven 'synergistic electrophile nucleophile dual activation' during the *N*-aroylmethylation and provides the basis of quinoxaline formation in regiodefined manner. Water also exerts beneficial effect during the nitro reduction-cyclocondensation cascade and makes this synthetic strategy a true example of 'all-water chemistry.'

Experimental section

General remarks: The glasswares used were 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. The TLC experiments were performed on silica gel GF-254 and visualized under UV at 254 nm. Evaporation of solvent was performed at reduced pressure using a rotary evaporator. Melting points were measured using a melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CHCl_3$: 7.26/77.0) using Me_4Si as an internal standard. The chemical shift (δ) values are given in ppm and *J* values are given in Hz. The ^{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; dt, doublet of triplet and m, multiplet. The mass spectra (MS) were recorded under atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI). The high resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI). The infra-red (IR) spectra were recorded in the range of 4000-600 cm^{-1} as KBr pellets for all solid samples.

Preparation of Pure water (15 MΩ-cm resistivity at 25 °C): The pure water was prepared by subjecting the tap water for reverse osmosis and ionic/organic removal by passing through pre-packed cartridge.

Preparation of Ultrapure water (18.2 MΩ-cm resistivity at 25 °C): The ultrapure water was prepared by subjecting the pure water for UV treatment (185/254 nm UV Lamp), deionization by passing through deionization cartridge followed by ultra membrane filtration (0.01um) under pressures up to 145 psi (10 bar). Ultrapure water (UPW) is generally considered to be ≥ 18.2 MΩ-cm resistivity at 25ºC, low ppt in metals, less than 50 ppt in inorganic anions and ammonia, less than 0.2 ppb in organic anions, and below 1 ppb total organic carbon (TOC) and silica (dissolved and colloidal).

Typical procedure for selective mono-*N*-benzoylmethylation of *o*-nitroaniline (1a): The mixture of *o*-nitroaniline **1a** (138 mg, 1 mmol) and *α*-bromacetophenone **2a** (199 mg, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically at 110 °C (oil-bath). After completion of the reaction (3 h, TLC), the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (95:5) to obtain analytically pure 2-((2-nitrophenyl)amino)-1-phenylethanone (Table 2, Entry 1) (**3a**) as Yellow solid (236 mg, 92 %); mp = 147-149 °C; IR (KBr) ν_{max} = 3433, 2926, 2872, 1735, 1619, 1570, 1514, 1453, 1352, 1259, 1106, 951, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 8.92 (bs, 1H), 8.25 (dd, *J*=1.5, 8.5Hz, 1H), 8.07-8.05 (m, 2H), 7.69-7.65 (m, 1H), 7.58-7.48 (m, 3H), 6.84-6.82 (m, 1H), 6.76-6.72 (m, 1H), 4.80 (d, *J*=4.4Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 192.71, 143.97, 136.22, 134.44, 134.22, 132.70, 129.04, 127.89, 127.08, 115.98, 114.14, 49.42; MS (APCI) m/z: 257 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_{12}N_2O_3Na^+$ [$M+Na^+$], 279.0740; Found 279.0740.

Typical procedure for the cascade reduction-condensation of 3a to 5a: To the mixture of 2-[(2-nitrophenyl)amino]-1-phenylethanone **3a** (256 mg, 1 mmol) in water (2 mL) was added In metal (287 mg, 2.5 mmol, 2.5 equiv) and 2N HCl (2.5 mL, 5 mmol, 5 equiv), and the mixture was stirred magnetically at 110 °C (oil-bath) for 3 h (TLC). The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure **5a** as a pale orange solid (185 mg, 90%)[4a] (Table 4).

Typical procedure for 'all water' one-pot tandem *N*-aryolmethylation-reduction-condensation for synthesis of 2-aryl quinoxalines. Synthesis of 5a: The mixture of *o*-nitroaniline **1a** (138 mg, 1 mmol) and *α*-bromacetophenone **2a** (199 mg, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically at 110 °C (oil-bath) for 3 h followed by addition of In (287 mg, 2.5 mmol, 2.5 equiv), 2N HCl (2.5 mL, 5 mmol, 5 equiv) and the reaction mixture was allowed to stir till the completion of reaction (2 h, TLC). The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was recrystallized from EtOH to afford analytically pure 2-phenylquinoxaline (Table 8, Entry 1) (**5a**) as a pale orange solid (177 mg, 86 %). mp = 75-76 °C; ν_{max} = 3005, 2325, 1275, 1260, 764, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.26 (s, 1H), 8.15-8.05 (m, 4H), 7.72-7.65 (m, 2H), 7.52-7.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 151.68, 143.26, 142.21, 141.53, 136.69, 130.19, 130.13, 129.57, 129.45, 129.07, 127.48; MS (ESI) m/z: 207 $(M+H)^+$.[4a]

In an alternative purification procedure the crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure 2-phenylquinoxaline (Table 8, Entry 1) (**5a**) as a pale orange solid (173 mg, 84 %).

In general, the purification was made by crystallization except for low melting (< 65 °C) compounds wherein the purification was made through column chromatography.

Experimental procedure for the various attempts for the synthesis of 2-((2-aminophenyl)amino)-1-phenylethanone

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(4a):

Pd-Catalysed hydrogenation of 2-[(2-nitrophenyl)amino]-1-phenylethanone (3a) (Scheme 5). Pd/C (5%) (10 mg) was added to the of **3a** (256 mg, 1 mmol) in toluene (10 mL) and kept under H_2 atmosphere at room temperature at 40 psi pressure. After 6 h, the Pd/C was removed by filtration and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure **5a** as a pale orange solid (72 mg, 35%).[4a]

Reaction of *o*-phenylenediaimine (6) with α-bromoacetophenone (2a) (Scheme 6):

To the mixture of *o*-phenylenediaimine (**6**) (108 mg, 1 mmol) and α-bromacetophenone (**2a**) (199 mg, 1 mmol, 1 equiv) in MeCN (2 mL) was added K_2CO_3 (276 mg, 2 mmol, 2 equiv) and stirred magnetically under reflux condition. After completion of the reaction (4 h, TLC), the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure **5a** as a pale orange solid (123 mg, 60%).[4a]

Experimental procedure for the synthesis of *tert*-butyl (2-[(2-oxo-2-phenylethyl) aminophenyl]carbamate (8a) (Scheme 7/Table 7):

Step 1: Preparation of *tert*-butyl (2-aminophenyl) carbamate (7a). *o*-Phenyldiamine (**6**) (108 mg, 1 mmol) was stirred at 30 ºC in absolute EtOH (2 mL), and di-tert-butyl dicarbonate (218 mg, 1.1 mmol, 1.1 equiv), dissolved in absolute EtOH (2 mL), was added dropwise to the reaction mixture. After 30 min, the solvent was evaporated to dryness, and the crude material. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (96:4) to obtain analytically pure *tert*-butyl (2-aminophenyl)carbamate (**7a**) as a white solid (147 mg, 71%); mp = 110-113 °C; IR (KBr) ν_{max} = 3414, 3356, 2973, 1896, 1682, 1595, 1490, 1456, 1387, 1366, 1162, 1054, 1027, 850, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 7.28-7.27 (m, 1H), 7.00 (dt, *J*=1.36, 7.6Hz, 1H), 6.81-6.75 (m, 2H), 6.35 (bs, 1H), 3.75 (bs, 2H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 153.91, 139.99, 126.13, 124.77, 119.56, 117.57, 80.50, 28.35; MS (ESI) m/z: 209 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O_2Na^+$ $[M+Na^+]$, 231.1109; Found 231.1114.[17e]

Di-*tert*-butyl 1,2-phenylenedicarbamate (7b). white solid (65 mg, 22%); mp = 105-106 °C; IR (KBr) ν_{max} = 3307, 2978, 2931, 1699, 1601, 1527, 1457, 1248, 1158, 1049, 1025, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 7.47 (bs, 2H), 7.11 (s, 2H), 6.89 (s, 2H), 1.52 (s, 18H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 153.90, 130.29, 125.31, 124.22, 80.76, 28.46; MS (ESI) m/z: 309 $(M+H)^+$.[17a]

Step 2 (Scheme 7): Synthesis of *tert*-butyl (2-[(2-oxo-2-phenylethyl)aminophenyl]carbamate (8a) from 7a. The mixture of *tert*-butyl2-aminophenylcarbamate (**7a**) (208 mg, 1mmol) and α-bromacetophenone (**2a**) (199 mg, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically at rt. After completion of the reaction (12 h, TLC), the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (94:6) to obtain analytically pure **8a** as a light yellow solid (189 mg, 58 %); mp = 130-132 °C; IR (KBr) ν_{max} = 3368, 2925, 1698, 1607, 1498, 1449, 1356, 1248, 1166, 1048, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 8.03 (d, *J*=7.4Hz, 2H), 7.64 (t, *J*=7.36Hz, 1H), 7.53 (t, *J*=7.72Hz, 2H), 7.39 (t, *J*=7.04Hz, 1H), 7.15-7.11 (m, 1H), 6.81 (t, *J*=7.44Hz, 1H), 6.74 (d, *J*=7.96Hz, 1H), 6.27 (s, 1H), 4.99 (bs, 1H), 4.61 (bs, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 195.22, 154.16, 141.16, 134.93, 133.89, 128.92, 127.78, 126.58, 125.60, 124.68, 118.59, 112.93, 80.57, 50.75, 28.36; MS (ESI) m/z: 237 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{22}N_2O_3Na^+$ $[M+Na^+]$, 349.1528; Found 349.1545.

Experimental procedure for the synthesis of 5a from 8a (Scheme 8): The mixture of *tert*-butyl (2-[(2-oxo-2-phenylethyl)aminophenyl]carbamate (**8a**) (326 mg, 1 mmol) in water (3 mL) was stirred magnetically at 110 °C (oil-bath) After completion of the reaction (2 h, TLC), the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure **5a** as a pale orange solid (168 mg, 82%).[4a]

Experimental procedure for the synthesis of 5a from 8a (Scheme 8): The mixture of *tert*-butyl (2-[(2-oxo-2-phenylethyl)aminophenyl]carbamate (**8a**) (326 mg, 1mmol) in TFE (3 mL) was stirred magnetically at 90 °C (oil-bath). After completion of the reaction (24 h, TLC), the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried (anh Na_2SO_4), filtered, and the filtrate was concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400 mesh size, 500 mg), charged on to a flash chromatography column of silica-gel (230-400 mesh size, 2.5 g), and eluted with hexane-EtOAc (99:1) to obtain analytically pure **5a** as a pale orange solid (31 mg, 15%).[4a]

1-(4-Chlorophenyl)-2-[(2-nitrophenyl)amino]ethanone (Table 3, Entry 2): Yellow solid (266 mg, 91 %); mp = 153-156 °C; ; IR (KBr) ν_{max} = 2981, 1275, 1260, 1054, 1033, 764, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 8.87 (bs, 1H), 8.24 (dd, *J*=1.52,

8.52Hz, 1H), 7.99 (dd, *J*=1.84, 6.8Hz, 2H), 7.53-7.46 (m, 3H), 6.81-6.72 (m, 2H), 4.76 (d, *J*=4.4Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 191.64, 143.86, 140.80, 138.96, 136.24, 129.45, 129.30, 127.17, 116.17, 114.05, 49.43; MS (APCI) m/z: 291 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_{11}ClN_2O_3Na^+$ $[M+Na^+]$, 313.0350; Found 313.0349.

2-[(4-Chloro-2-nitrophenyl)amino]-1-phenylethanone (**Table 3, Entry 3**): Yellow solid (258 mg, 89 %); mp = 158-160 °C; IR (KBr) ν_{max} = 3342, 3005.58, 1691, 1628, 1561.90, 1517, 1402, 1351, 1275, 1261,1156, 1070, 808, 764, 750 cm^{-1};^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 8.89 (bs, 1H), 8.24 (d, *J*=2.36Hz, 1H), 8.04 (d, *J*=7.52Hz, 2H), 7.67 (t, *J*=7.4Hz, 1H), 7.55 (t, *J*=7.76Hz, 2H), 7.44 (dd, *J*=2.36, 9.04Hz, 1H), 6.79 (d, *J*=9.04Hz, 1H), 4.77 (d, *J*=4.24Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 192.30, 142.62, 136.28, 134.38, 134.30, 129.11, 127.92, 126.32, 120.83, 115.54, 49.44; MS (APCI) m/z: 291 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_{11}ClN_2O_3Na^+$ $[M+Na^+]$, 313.0350; Found 313.0350.

2-[(5-Chloro-2-nitrophenyl)amino]-1-phenylethanone (**Table 3, Entry 4**): Yellow solid (262 mg, 90 %); mp = 155-158 °C; IR (KBr) ν_{max} = 3362, 2924, 1695, 1623, 1491, 1275, 1259, , 1078, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.00 (bs, 1H), 8.20 (d, *J*=9.08Hz, 1H), 8.06 (d, *J*=1.2Hz, 2H), 7.69 (t, *J*=7.44Hz, 1H), 7.57 (t, *J*=8Hz, 2H), 6.84 (d, *J*=1.96Hz, 1H), 6.72 (dd, *J*=2, 9.14Hz, 1H), 4.78 (d, *J*=4.28Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 192.12, 144.41, 142.70, 134.41, 134.23, 130.17, 129.28, 129.11, 128.52, 128.32, 127.96, 116.48, 113.71 49.39; MS (ESI) m/z: 291 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_{11}ClN_2O_3Na^+$ $[M+Na^+]$, 313.0350; Found 312.1499.

2-[(4-Methyl-2-nitrophenyl)amino]-1-phenylethanone (**Table 3, Entry 5**): Light yellow solid (248 mg, 92 %); mp = 162-164 °C; IR (KBr) ν_{max} = 3362, 2923, 1742, 1692, 1637, 1561, 1528, 1275, 1155, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 8.78 (bs, 1H), 8.06 (d, *J*=7.56Hz, 3H), 7.67 (t, *J*=7.36Hz, 1H), 7.56 (t, *J*=7.56Hz, 2H), 7.33 (d, *J*=8.52Hz, 1H), 6.75 (d, *J*=8.6Hz, 1H), 4.78 (d, *J*=4.28Hz, 2H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 192.91, 142.19, 137.62, 134.52, 134.17, 132.33, 129.03, 127.89, 126.44, 125.59, 114.12, 49.55, 20.01; MS (APCI) m/z: 271 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{15}H_{14}N_2O_3Na^+$ $[M+Na^+]$, 293.0897; Found 293.0785.

1-(4-Methoxyphenyl)-2-[(4-methyl-2-nitrophenyl)amino]ethanone (**Table 3, Entry 6**): Yellowish orange solid (270 mg, 90 %); mp = 128-130 °C; IR (KBr) ν_{max} = 3364, 2912, 1676, 1632, 1600, 1560, 1524, , 1424, 1348, 1262, 1241, 1181, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 8.75 (bs, 1H), 8.01 (s, 2H), 7.99 (d, *J*=1.96Hz, 1H), 7.28 (dd, *J*=2, 14.5Hz, 1H), 6.99 (d, *J*=1.9Hz, 2H), 6.71 (d, *J*=8.6Hz, 1H), 4.68 (d, *J*=4.4Hz, 2H), 3.88 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 191.31, 164.26, 142.30, 137.59, 132.32, 132.20, 127.51, 126.42, 125.42, 114.18, 113.75, 55.61,49.15, 20.00; MS (ESI) m/z: 301 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_4Na^+$ $[M+Na^+]$, 323.1008; Found 323.1005.

2-(4-Methoxyphenyl)quinoxaline (**Table 8, Entry 2**)[5k]: Light yellow solid (377 mg, 83 %); mp = 97-98 °C; IR (KBr) ν_{max} = 2926, 1606, 1584, 1274, 1252, 1175, 1028, 834, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) *δ*: 9.28 (s, 1H), 8.18-8.07 (m, 4H), 7.76-7.67 (m, 2H), 7.08-7.04 (m, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 161.45, 151.37, 143.04, 142.30, 141.20, 130.14, 129.39, 129.26, 129.07, 129.01, 128.95,114.56, 55.41; MS (ESI) m/z: 237 $(M+H)^+$.

2-(3-Methoxyphenyl)quinoxaline (**Table 8, Entry 3**)[5k]: Light yellowish orange solid (198 mg, 84 %); mp = 87-88 °C; IR (KBr) ν_{max} = 3434, 2918, 2846, 2225, 1733, 1275, 1260, 1022, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.36 (s, 1H), 8.19-8.13 (m, 2H), 7.92 (dd, *J*=1.8,7.64 Hz, 1H), 7.80-7.74 (m, 2H), 7.52-7.48 (m, 1H), 7.22-7.17 (m, 1H), 7.09 (d, *J*=8.24 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 157.40, 152.23, 147.30, 142.71, 141.06, 131.61, 131.44, 129.76, 129.55, 129.37, 129.07,126.56, 121.54, 111.43, 55.65; MS (ESI) m/z: 237 $(M+H)^+$.

2-(4-Chlorophenyl)quinoxaline (**Table 8, Entry 4**)[4a]: Light orange solid (197 mg, 82 %); mp = 120-122 °C; IR (KBr) ν_{max} = 3004, 2325, 1260, 1275, 764, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.31 (s, 1H), 8.19-8.13 (m, 4H), 7.83-7.75 (m, 2H), 7.57-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 150.59, 142.87, 142.22, 141.66, 136.59, 135.19, 130.48, 129.79, 129.60, 129.41, 129.17, 128.78; MS (ESI) m/z: 241 $(M+H)^+$.

2-(4-Bromophenyl)quinoxaline (**Table 8, Entry 5**)[5k]: Light brown solid (238 mg, 84 %); mp = 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) *δ*: 9.29 (s, 1H), 8.15-8.07 (m, 4H), 7.82-7.74 (m, 2H), 7.71-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 150.66, 142.83, 142.22, 141.68, 135.62, 132.80, 130.37, 131.88, 130.52, 129.84, 129.60,129.18, 129.02, 125.00; MS (ESI) m/z: 284 $(M+H)^+$.

7-Chloro-2-phenylquinoxaline (**Table 8, Entry 6**)[5i]: Light orange solid (194 mg, 81 %); mp = 104-106 °C; IR (KBr) ν_{max} = 3047, 2922, 2852. 1606, 1539, 1483,1449, 1404, 1314, 1131, 1073,958, 913,834, 758, 686, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.30 (s, 1H), 8.20-8.14 (m, 3H), 8.04 (d, *J*=8.92Hz, 1H), 7.68 (dd, *J*=2.16, 8.84Hz, 1H), 7.58-7.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 152.48, 143.38, 142.62, 140.07, 136.27, 136.07, 130.56, 130.48, 130.34, 129.21, 128.95, 128.49, 127.84, 127.60; MS (ESI) m/z: 240 $(M)^+$.

7-Chloro-2-(4-methoxyphenyl)quinoxaline (**Table 8, Entry 7**)[5i]: Off-white solid (216 mg, 80 %); mp = 103-105 °C; IR (KBr) ν_{max} = 2922, 1607, 1539, 1487, 1258, 1225, 1181, 1125, 1071, 1025, 957, 914, 841, 827, 750, 571, 515 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.30 (d, *J*=5.92Hz, 1H), 8.19 (dd, *J*=3.04, 8.76Hz, 2H), 8.12 (dd, *J*=2.12, 10.88Hz, 1H), 8.08-8.03 (m, 1H), 7.73-7.66 (m, 1H), 7.10 (d, *J*=8.72Hz, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 161.77, 143.88, 143.15, 135.97, 131.21, 130.61, 130.29, 130.00, 129.10, 128.99, 128.79, 128.28, 128.03, 114.68, 55.49; MS (APCI) m/z: 271 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{15}H_{11}ClN_2ONa^+$ $[M+Na^+]$, 293.0452; Found 293.0452.

7-Chloro-2-(4-chlorophenyl)quinoxaline (**Table 8, Entry 8**): Light orange solid (225 mg, 82 %); mp = 180-182 °C; IR (KBr) ν_{max} = 2922, 1521, 1275, 1260, 1022, 764, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz, TMS) *δ*: 9.30 (s, 1H), 8.18-8.15 (m, 3H), 8.07 (d, *J*=8.92Hz, 1H), 7.72 (dd, *J*=2.32, 8.92Hz, 1H) 7.58-7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 151.30, 142.92, 142.56, 140.17, 137.01, 136.33, 134.70, 131.53, 130.77, 130.39, 129.48, 128.82, 128.73, 128.45; MS (APCI) m/z: 275 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_8Cl_2N_2Na^+$ $[M+Na^+]$, 296.9957; Found 297.1305.

2-(4-Bromophenyl)-7-chloroquinoxaline (**Table 8, Entry 9**)[5c]:

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Light brown solid (256 mg, 80 %); mp = 144-146 °C; IR (KBr) ν_{max} = 2922, 2075, 1633, 1421, 1176, 1075, 957, 880, 835, 775, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 9.28 (s, 1H), 8.13 (d, *J*=2.24Hz, 1H), 8.09-8.04 (m, 3H), 7.72-7.68 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 151.40, 142.89, 142.58, 140.21, 136.37, 135.16, 132.46, 130.82, 130.41, 129.06, 128.97, 128.47, 128.13, 125.44; MS (APCI) m/z: 321 $(M+2H)^+$.

6-Chloro-2-phenylquinoxaline (**Table 8, Entry 10**)[5i]: Colorless crystal (199 mg, 83 %); mp = 125-127 °C; IR (KBr) ν_{max} = 3367, 2162, 1276, 1256, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.34 (s, 1H), 8.21-8.19 (m, 2H), 8.13-8.09 (m, 2H), 7.74 (dd, *J*=2.36, 8.96Hz, 1H), 7.62-7.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 151.95, 144.16, 141.82, 140.85, 136.38, 135.26, 131.34, 130.85, 130.45, 129.24, 128.09, 127.53; MS (APCI) m/z: 241 $(M+H)^+$.

6-Chloro-2-(4-methoxyphenyl)quinoxaline (**Table 8, Entry 11**)[5i]:Off-white solid (219 mg, 81 %); mp = 140-142 °C; IR (KBr) ν_{max} = 2930, 2837, 1674, 1606, 1577, 1538, 1519, 1454, 1309, 1287, 1273, 1257, 1171, 1066, 1026, 957, 827, 764, 750, 570, 515 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.29 (s, 1H), 8.18 (dd, *J*=1.84, 7Hz, 2H), 8.09 (d, *J*=2.2Hz, 1H), 8.05 (d, *J*=8.96Hz, 1H), 7.71 (dd, *J*=2.28, 8.92Hz, 1H), 7.09 (dd, *J*=1.76, 6.92Hz, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 161.68, 151.53, 143.84, 141.42, 140.87, 134.66, 131.18, 130.60, 128.97, 128.86, 128.02, 114.67, 55.46; MS (APCI) m/z: 271 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{15}H_{11}ClN_2ONa^+$ $[M+Na^+]$, 293.0452; Found 293.0451.

6-Chloro-2-(4-chlorophenyl)quinoxaline (**Table 8, Entry 12**): Yellowish orange solid (225 mg, 82 %); mp = 130-132 °C; IR (KBr) ν_{max} = 2917, 2849, 1275, 1260, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.32 (s, 1H), 8.17 (dd, *J*=1.92, 6.72Hz, 2H), 8.14 (d, *J*=2.28Hz, 1H), 8.09 (d, *J*=8.96Hz, 1H), 7.76 (dd, *J*=2.28, 8.96Hz, 1H), 7.57 (dd, *J*=1.96, 6.68Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 150.70, 143.67,141.88, 140.76, 139.29, 136.88, 135.55, 134.77, 131.55, 130.80, 129.49, 128.73, 128.12, 114.07; MS (APCI) m/z: 275 $(M+H)^+$. HRMS (ESI) m/z calcd for$C_{14}H_8Cl_2N_2Na^+$ $[M+Na^+]$, 296.9957; Found 297.1298.

2-(4-Bromophenyl)-6-chloroquinoxaline (**Table 8, Entry 13**): Off-white solid (257 mg, 83 %); mp = 175-177 °C; IR (KBr) ν_{max} = 3049, 2923, 2849, 1604, 1539, 1476, 1328, 1275, 1176, 1004, 919, 825, 750, 569 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.27 (s, 1H), 8.09 (d, *J*=2.24Hz, 1H), 8.06 (d, *J*=8.48Hz, 3H), 7.73-7.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 150.74, 143.61, 141.90, 140.76, 135.58, 135.20, 132.45, 131.56, 130.81, 130.40, 129.04, 128.95, 128.12, 125.29; MS (APCI) m/z: 321 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{14}H_8BrClN_2Na^+$ $[M+Na^+]$, 340.9452; Found 341.1820.

2-(4-Methoxyphenyl)-7-methylquinoxaline (**Table 8, Entry 14**)[4e]: Light yellow solid (200 mg, 80 %); mp = 52-57 °C; IR (KBr) ν_{max} = 2917, 2857, 2307, 1956, 1739, 1618, 1451, 1384, 1179, 1050, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.26 (s, 1H), 8.19-8.16 (m, 2H), 8.01 (dd, *J*=8.52,12.32 Hz, 1H), 7.97 (d, *J*=14.28Hz 1H), 7.62- 7.55 (m, 1H), 7.10 (d, *J*=8.44Hz 2H), 3.92 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 161.30, 142.99, 142.19, 139.57, 132.48, 131.37, 129.51, 128.92, 128.82, 128.58, 128.29, 127.97, 114.56, 55.45, 21.80; MS (ESI) m/z: 251 $(M+H)^+$.

2-(4-Bromophenyl)-7-methylquinoxaline (**Table 8, Entry 15**)[5c]: Yellowish orange (238 mg, 80 %); mp = 96-98 °C; IR (KBr) ν_{max} = 2920, 2851, 1624, 1587, 1488, 1436, 1131, 1072, 1009, 960, 834, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.22 (s, 1H), 8.06 (dd, *J*=1.92, 6.64Hz, 2H), 7.99 (d, *J*=8.56Hz, 1H), 7.91 (s, 1H), 7.68 (dd, *J*=1.84, 6.72Hz, 2H), 7.58 (dd, *J*=1.84, 8.56Hz, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 150.58, 142.31, 141.92, 141.11, 140.21, 135.82, 132.32, 132.18, 128.97, 128.89, 128.66, 128.43, 124.83, 21.91; MS (APCI) m/z: 299 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{15}H_{11}BrN_2Na^+$ $[M+H^+]$, 299.0106; Found 299.0178.

7-Methoxy-2-phenylquinoxaline (**Table 8, Entry 16**)[5i]:Colorless crystal (193 mg, 82 %); mp = 86-88 °C; IR (KBr) ν_{max} = 2917, 2840, 1733, 1459, 1260, 1078, 1025, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, TMS) δ: 9.19 (s, 1H), 8.20-8.18 (m, 2H), 8.02 (d, *J*=9.12Hz, 1H), 7.61-7.54 (m, 3H), 7.45 (d, *J*=2.72Hz, 1H), 7.42 (dd, *J*=2.76, 9.12Hz, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz, TMS) δ: 161.09, 151.98, 143.99, 140.79, 137.81, 137.03, 130.06, 129.14, 127.53, 122.92, 106.90, 55.86; MS (ESI) m/z: 237 $(M+H)^+$.

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Notes and references

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Graphical Abstract

An “all-water” strategy for regiocontrolled synthesis of 2-aryl quinoxalines

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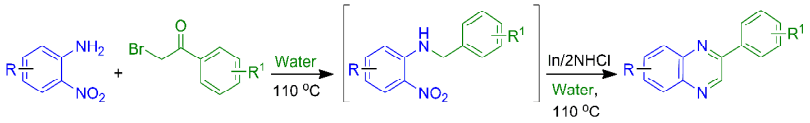

Cascade *N*-aroylmethylation–reduction–condensation process as novel strategy of “all water chemistry” for first generalized regioselective synthesis of 2-aryl quinoxalines.