Green Chemistry

Accepted Manuscript

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ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9GC00289H

Journal Name

ARTICLE

Uncatalyzed, on water oxygenative cleavage of inert C-N bond with concomitant 8, 7-amino shift in 8-aminoquinoline derivatives†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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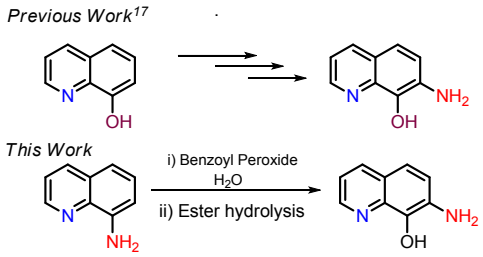
Oxygenative cleavage of inert C_{Ar}-NH_2 bond with concomitant 1, 2 amine migration in 8-aminoquinoline derivatives is reported in water at room temperature. The reaction is highly atom- and step-economical as both C- and N-containing fragments of the C-N bond cleavage are incorporated into the target molecule and is effected without the need for *N*-oxide. The reaction is scalable to gram level and the products are useful as electrophilic partners for coupling reactions, ligands in catalysis and bioactive compounds.

Introduction,

The abundant sources of C-N bond and the facile metalation of the inert C-N bond into more active C-M or N-M species via transition metal catalysis has attracted tremendous attention among chemists.[1] In the absence of transition metal catalysts, C-N bond could be cleaved and transformed through radical and cationic intermediates. The cleavage of C-N bond of a primary amine (R-NH_2) is the most challenging task as NH_2 is a poor leaving group and hence require highly reactive cationic intermediates such as diazonium/ammonium salts in which the elimination of electronically neutral di nitrogen and amine moiety facilitates the C-N bond cleavage process.[2]

Figure 1. Synthesis of 7-aminoquinolin-8-ol.



Tedious nitration-hydrogenation sequence is the traditional choice to access aryl amines directly until the invention of Buchwarld-Hartwig amination of aromatic halides with ammonia.[3] Other groups including Ullman, Chan-Evans-Lam, Chang[4] also studied C-H aminations extensively.[5] The amide radical mediated direct aromatic ring amination by aqueous ammonia with platinum loaded TiO_2 catalyst is known to produce less than 10% yields.[6]

Transposition and migration of functional groups are effective tools in organic chemistry to achieve the synthesis of difficult targets in a single step reaction.[7,8] 1,2-Amino shift was reported in a rare biotransformation of amino acids under complex enzyme catalysis by the cooperative action of aminomutases, coenzyme B-12, and vitamin B-6.[9a,b] A Cu(I) catalysed 1,3-amino migration via a highly reactive ketenimine intermediate was also achieved by Talukdar *etal.,* in the formation of acrylamidines[9c] and more recently, Guan and co-workers reported copper catalyzed oxidative cyclization/1,2-amino migration via aziridinium intermediate for the synthesis of substituted pyrroles,[9d] however, to our knowledge amino migration in aromatic systems is unprecedented.

Given the importance and versatility of quinoline derivatives as bioactive natural products, pharmaceuticals, agrochemicals, functional materials, directing group for C-H functionalizations and ligands in transition metal catalysis, the development of efficient and environmentally benign methods for the functionalisation of quinolines is highly warranted. Particularly, 7-substituted 8-hydroxy quinoline (8HQ) derivatives inhibit a 2OG oxygenase, the prolyl hydroxylase containing protein[10a,b] and 7-*N,N*-dimethylamino quinoline derivatives are known as small molecule fluorescent probes for applications in live cell imaging etc.[10c] Due to the innate reactivity of C=N bond or the *N*-adjacent C-H bond, C2 functionalizations of quinolines have been extensively investigated and C8-functionalizations are comparatively less studied.[11a] Recently Sharma *etal.,* reported efficient Rh-catalysed C8-alkenylation and -hydroxy alkylation of quinoline *N*-oxides.[11b, c] Cui and Wu groups investigated decarboxylative C8-acylation of quinoline N-oxides with α-oxocarboxylic acid.[11d] Noteworthy are Ru-catalysed alkenylations reported by Shibata and Rh- and Ir-catalysed iodination and amidation by Chang respectively.[12] In metal

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Electronic Supplementary Information (ESI) available: All optimization tables, Copies of crystallographic data (CCDC 1559199) see. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C9GC00289H

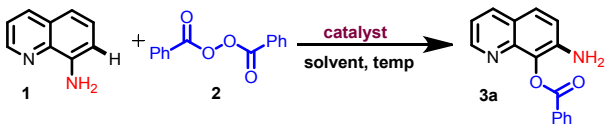
catalysed C8-functionalizations, the oxygen of quinoline *N*-oxide serves as an exocyclic directing group *via* formation of a five membered metallacycle.[13a,b] Further, several reports have been published on Pd-catalysed C2 functionalisation, only one report describes the Pd-catalyzed selective C8-arylation of quinoline *N*-oxides.[13c] However, these procedures are associated with limitations such as high temperature conditions, use of expensive rare metal catalysts, necessitate initial installation and later reduction of the N-O bond affecting overall efficiency of the reaction and thus reduce the synthetic utility. Therefore, C8-functionalisation of unmodified quinolines represents a practical, efficient and step economic method for the generation of important quinoline derivatives. In this context, the only reports available in literature, to the best of our knowledge are published by Chang and Sawamura.[14] While Chang's pioneering work represents the first selective C8-arylation of quinolines, catalysed by Rh(NHC) system in presence of a strong base, Sawamura reported, a selective C8-borylation of quinolines using a heterogeneous Ir-catalyst system based on a silica supported cage type monophosphane ligand SMAP, as a gateway for the construction of a variety of 8-substituted quinolines. Though the C-8 and C-7 direct functionalizations are scarce, C5 functionalizations of 8-aminoquinoline derivatives for the formation of C-X (X= C, N, O, S, P and halo) bonds are extensively investigated.[15] In continuation of our interest on C-H functionalization reactions for the construction of C-C, C-X (X=O, N, Halogen) bonds, and particularly the regioselective introduction of aryls/heteroatoms on THQ/quinoline framework,[16] we herein report our serendipitous invention of an efficient, catalyst free, one step synthesis of 8-benzyloxy, 7-aminoquinoline directly from 8-aminoquinoline in water under extremely mild conditions. The 8-amino group serves as a function as well as functionality, particularly as traceless and migrating directing group. The herculean tasks carried out by the benzoxylation reaction include: 1. selective cleavage of inert C_{Ar}-N bond in presence of C-H, C-O and C-halogen bonds, 2. amine as traceless directing group for benzoxylation (C_{Ar}-N to C_{Ar}-O bond formation), 3. amine migration from C8 to C7, 4. C7-H amination. Interestingly the multiple chemical events such as bond breaking (C-N, C-H), new bonds formation (C-O, C-N) and group migration (-NH_2) occur in the most efficient *i.e.,* open air, room temperature, metal- or catalyst-free, in water as the solvent with high degree of atom- and step-economy. Both the C- and *N*-fragments arising from C-N bond cleavage are incorporated into the target molecule and the reaction proceeds without the necessity to employ quinoline *N*-oxide. Further the aqueous, ambient and open to air conditions qualify the reaction for green technology.

This is the first report on 1,2-amino shift on aryls via oxygenative inert C-N bond cleavage and demonstrates a simultaneous C_{Ar}-N oxygenation and C_{Ar}-H amination that represents an easy entry to 7-amino-8-hydroxy quinoline derivatives.[17] The reaction represents a powerful, straightforward, practical, atom- and step-economic strategy for constructing an otherwise difficult to obtain new organic compounds, following a new chemistry differentiating from conventional organic syntheses.

Results and discussion,

The mechanistic investigations of the chelation assisted, remote C5-benzoxylation of 8-amidoquinoline with benzoyl peroxide previously reported from our group, revealed that 8-aminoquinoline is resistant to 5-oxygenation under the standard reaction conditions.[16e] Realizing the importance of 8 substituted quinolines, we further probed the benzoxylation reaction of 8-aminoquinoline and the new compound obtained, to our perplexity, was 7-amino, 8-benzyloxy quinoline with an intramolecular hydrogen bonding between the amino nitrogen donor and electronegative carbonyl oxygen acceptor. Apparently not only the benzoxylation occurred at 8-position but also triggered a serendipitous encounter of 8-7 amino shift involving multiple bond breaking (C-N, C-H) and formation (C-O and C-N) reactions in one pot.

Table 1. Optimization of reaction conditions[a]



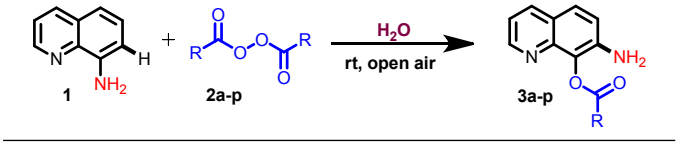
Entry	Catalyst	Temp (°C)	Yield [%][b]
1	$FeCl_3.6H_2O$	90	48
2	$FeCl_3.6H_2O$	reflux	39
3	$FeCl_3.6H_2O$	60	56
4	$FeCl_3.6H_2O$	rt	61
5[c]	$FeCl_3.6H_2O$	0	18
6	$FeCl_3$	rt	58
7	$FeBr_3$	rt	28
8	$Fe(OTf)_3$	rt	36
9	$Fe(acac)_3$	rt	43
10	-	rt	67
11[c]	-	rt	69

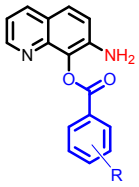
[a]Reagents and conditions: Unless otherwise specified, a mixture of 1 (1.0 mmol) and 2 (1.2 mmol) in water (3.0 mL) was stirred at rt for 16 h in open air. [b]Isolated yield. [c]Portion-wise addition of BPO.

In order to optimize the reaction conditions, we began our study with 8-aminoquinoline (1a) as a model substrate. Stirring a solution of 1a, iron (III) chloride and benzoyl peroxide (BPO) in a toluene solution at 90 °C resulted in formation of the product 3a in 48% yield (Table 1, entry 1). Elevation of the temperature to reflux (110 °C) did not accelerate the course of the reaction, rather decreased product yields (39%) accompanied with the formation of capricious complex mixtures and benzoic acid (Table 1, entry 2) was observed. The product yield improved to 56% when the reaction was conducted at 60 °C (Table 1, entry 3). At ambient temperature, the yield of the product was further improved to 61% (Table 1, entry 4), whereas at 0 °C the yields of 3a diminished to 48% despite ~~of~~ prolonged reaction times (Table 1, entry 5). In the presence of other iron salts the results were not satisfactory (Table 1, entry 6-9), while copper and

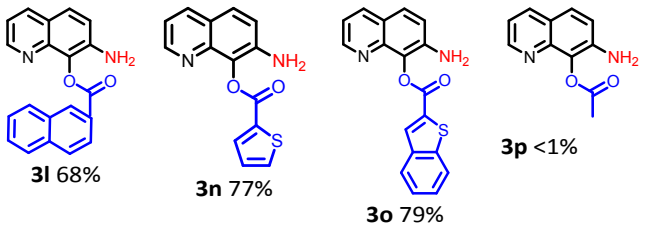
palladium salts inhibited the reaction.[18] Interestingly, significant improvement of the product yield was observed in the absence of any catalyst. However the best yield was obtained under metal free conditions with water as a green and universal solvent medium at room temperature. Presumably the hydrogen bonding between water and nitrogen present substrate facilitate faster reaction resulting in better yields compared to ACN and THF. [18] BPO was added to the reaction mixture in portionwise (1.2 mmol, 2×0.6 equiv/0.5 h). Among the choice of benzoxylation sources, BPO was found to be the most effective.[18] 1,10-Phenanthroline, 4,4'-bipyridine, 2,2'-bipyridine, Proline did not affect the reaction indicating the absence of additive effect.[18] The effect of co-oxidant and other reaction conditions were also investigated.[18] Finally stirring a solution of 1a and BPO (portionwise addition) at room temperature in H_2O for 16 h in open air was found to be optimum.

Figure 2. Acyl peroxide substrate scope of migration reaction.[a]





R = H, **3a** 69%
R = 2-Me, **3b** 75%
R = 3-Me, **3c** 76%
R = 4-Me, **3d** 80%
R =3,5-dimethyl **3e** 78%
R = 4-OMe, **3f** 80%
R = 4-F, **3g** 74%
R = 2-Br, **3h** 66%
R = 4-Br, **3i** 68%
R = 4-I, **3j** 61%
R = 4-Ph, **3k** 71%
R = 4-NO_2, **3m** <1%



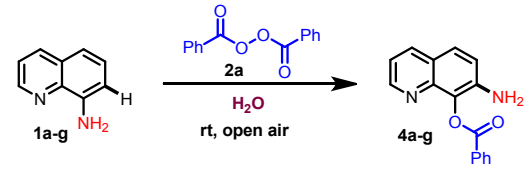
3l 68%
3n 77%
3o 79%
3p <1%

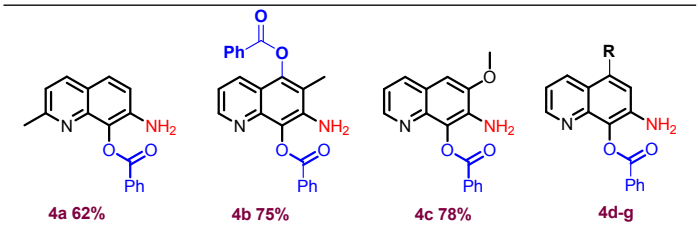
[a]The reaction was performed with 1 (1.0 equiv.) and 2 (1.2 equiv, 2×0.6 equiv/0.5 h) in H_2O (3 mL) at the room temperature for 16 h. under an open air atmosphere. All reported yields are isolated yields.

With the optimized conditions in hand, the substrate scope of the reaction was investigated (Fig 2). We examined various e-withdrawing, -donating and -neutral substituted benzoyl peroxides as oxygenating reagents. Good yields of the C8-oxygenated products were often achieved when unsubstituted and electron-donating moieties including methyl and methoxy groups were present on the aryl ring of the BPO (Fig 2, 3a-3f). The C8-oxygenation reaction tolerated halogen substituents on benzoyl peroxide and produced moderate yields of the products (Fig 2, 3g–3j). Biphenyl and naphthyl peroxides also underwent smooth reaction affording a moderate yield of the corresponding 8-oxygenated, 8-7 amino shift products (Fig 2, 3k, 3l). Further, the reaction proceeded with heteroaryl acyl peroxides as well affording the products in good yields (Fig 2, 3n, 3o).

8-Aminoquinoline was subjected to transition metal free oxygenation-amino migration reaction with mixed peroxide under standard reaction conditions employing aryl-alkyl acyl peroxides i.e., benzyl acetyl- and benzyl *t*-butyl peroxides. In both the cases the products obtained were found to be corresponding to the arylacyl 8-oxygenated 7-amino product 3a in 38% yield while the formation of the alkyl acyloxy product was not observed.[18] Acetyl peroxide and TBHP failed to afford the expected oxygenated product under standard reaction conditions.[18]

Figure 3. Quinoline substrate scope for migration reaction.[a]





4a 62%
4b 75%
4c 78%
4d-g

R =Cl, **4d** 60%
R =I, **4e**54%
R=Ts,**4f** 62%
R=NO_2,**4g**<1 %

[a]The reaction was performed with 1 (1.0 equiv.) and 2 (1.2 equiv, 2×0.6 equiv/0.5 h) in H_2O (3 mL) at the room temperature for 16 h. under an open air atmosphere. All reported yields are isolated yields.

We also subjected the electrophilic partner (phenyl boronic acid) and electron rich substrates (β-napthol, benzimidazole and indole) for the migration reaction with 8-aminoquinoline under standard reaction conditions and failed to achieve C-C bond forming reaction products at 8 position.[18]

The electronically differentiated substrate scope for quinoline variation was also investigated. The e-donating groups i.e., methyl and methoxy substituents present on quinoline influence the migration reaction and produced good yields of the products (Fig 3, 4a-c). C6-Methoxy, 8-amino quinoline substrate provided a challenging contiguously trisubstituted quinoline 4c in 78% yield. It is interesting to note that good leaving groups (Cl, I, Ts) are unaffected and selective oxygenative cleavage of inert C-N bond occurs to deliver the corresponding 8-benzoxylated and 8,7 amino shift products with moderate yields (Fig 3, 4d-f). Further 5-halo/tosyl groups serve as good handles and potential points of departure for introducing new functionalities. However the strong electron withdrawing nitro group at 5-position of quinolone ring (4g) inhibited the 8-oxygenation reaction. The 5, 7-substitutions on quinolones 5a and 5b are detrimental for the benzoxylation reaction probably due to steric crowding. The –NH_2 group at 3-(heterocyclic ring) 5c or 6-position (carbocyclic ring) 5d are

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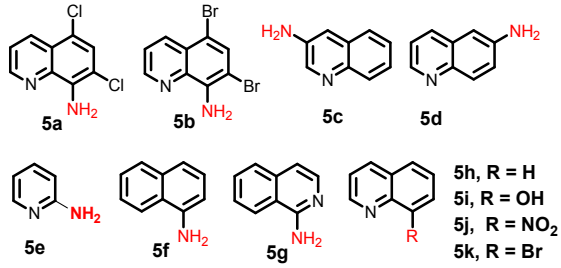
unaffected, indicating the importance of the 8-amino group as efficient traceless directing as well as migrating group (Fig 4). The amine group containing substrates 5e-g, quinoline and other 8-hydroxy, 8-NO_2, 8-halo quinolines are unreactive towards the benzoxylation reaction.

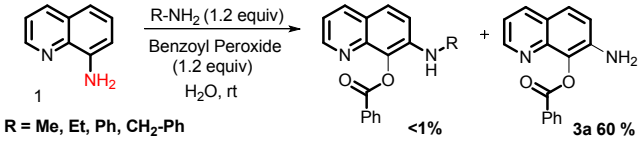
In order to explore the migrating ability, different functionalities on the migrating nitrogen have been evaluated. Amide, sulfonamide (Ms, Ts, Tf), carbamate (Boc, MeOCO), secondary amines with methyl and benzyl substituents (methylamine, benzylamine) and tertiary amine (dimethylamine) as migrating groups are resistant to benzoxylation reaction.[18] Further we tested the reaction in the presence of external alkyl/aryl 1°-amines presuming to obtain 7-alkyl/aryl amino 8-benzoxylated products under the standard reaction conditions, instead the product 3a was obtained in 60% yield (Fig 5).

Figure 4. Substrates Resistant to Migration Reaction.



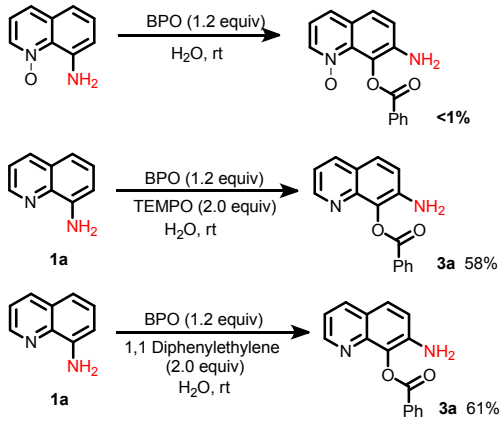
All the new compounds have been fully characterized using ^{1}H-NMR, ^{13}C-NMR, HRMS. Further the structure of the oxygenated product 3d was unambiguously confirmed by single crystal X-ray analysis.[18]

Figure 5. External *N*-alkyl/aryl amine source.



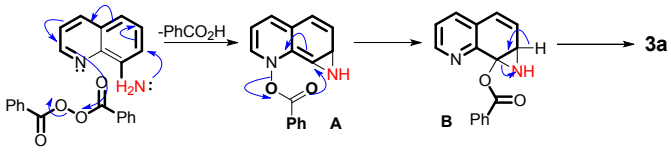
The efficacy of the oxygenative-amino migration reaction is further demonstrated from the formation of hydrolyzed product, 8-hydroxy, 7-amino quinoline directly from 8-amino quinoline in one pot.[18] This class of benzyloxy products and 7-aminoquinolin-8-ol derivatives are known to have applications in catalysis, materials and biology (Fig. 8).[10c,17a] The benzoxylation reaction could be scaled up to 1.0 gram demonstrating the practicality of the process.[18]

Figure 6. Mechanistic Insights.



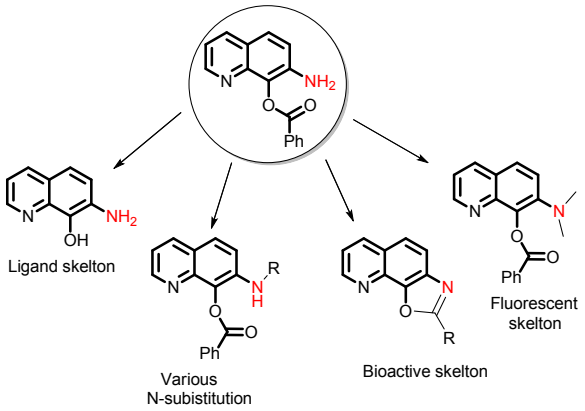
Under the standard reaction conditions, 8-aminoquonoline *N*-oxide failed to afford the corresponding migration product, ruling out the formation of *N*-oxide intermediate.[18] Radical clock experiments conducted in the presence of TEMPO and 1,1-diphenyl ethylene produced comparable product yields of 58% and 61% respectively indicating that the reaction does not proceed through radical pathway (Fig 6). Further, the resistance of the reaction with the substrates 5a-5k (Fig 4) and also failure to incorporate external amines at 7 position (Fig. 5) suggest that unmodified quinoline nitrogen, free amine at C8 and free C7-H in the substrate are essential for the successes of the oxygenative migration reaction.

Figure 7. Proposed Mechanism.



With the support of the above studies and considering the fact that the heteroatom in the quinoline ring has considerable deactivating effect on the ring towards electrophilic attack and at the same time the electron-rich nitrogen atom is the main centre for attack by electrophiles, a tentative domino reaction mechanism as depicted in Fig. 7 has been proposed. The internal 8-amino nucleophile attacks the vicinal C7 forming the tricyclic aziridine which triggers the concomitant nucleophilic attack of the ring nitrogen on benzoyl peroxide with disruption of the aromaticity releasing benzoic acid. The neutral species, *N*-benzoyloxy tricyclic aziridine intermediate (**A**) further undergoes intramolecular rearrangement of the benzyloxy group from the ring nitrogen to C8 through a 6-membered transition state, generating intermediate **B** with a new quaternary carbon. Rearomatization facilitates the breaking of aziridine ring and 8,7 migration of NH_2. Interestingly, though the product appears to be arising from amino migration, apparently the mechanism involves two migrations including benzyloxy migration from nitrogen to C8.

Figure 8. Synthetic applications.



Conclusions

The efficiency of the metal free benzoxylation reaction was demonstrated from the inert C_{Ar}-N bond cleavage, C8-oxyganation and 8, 7 amino shift achieved on inexpensive and commercially available 8-aminoquinoline. These above sequence of events occured in one-pot in the most atom economical incorporation of C- and N-containing fragments resulting from C-N bond cleavage into the target 7-amino, 8-benzyloxy quinoline molecule. The product 7-amino-8-benzyloxy quinoline formation involves multiple bond breaking (C-N, C-H) and bond formation (C-O and C-N) reactions. A tentative mechanism has been proposed wherein the migration of the benzyloxy group from ring nitrogen to C8 and the amine at C8 position, after serving as a directing group for benzoxylation, migrates to the adjacent carbon via tricyclic aziridine intermediate. This is the first report of the most complicated direct conversion of C_{Ar}-N to C_{Ar}-O and 1, 2 amino shift on aryl moiety. Metal-, catalyst-, ligand-, additive-free open air and aqueous reaction conditions, demonstrate the operational simplicity and green protocol of the reaction. This is the shortest and unconventional route to prepare 7-amino, 8-hydroxy quinoline derivatives. Further mechanistic studies are underway.

Experimental

General

All commercially available chemicals were used as received. Benzoyl peroxide was purchased from S.D Fine-Chemicals. Thin-layer chromatography plates were visualized by exposure to UV or Iodine, and/or by immersion in an acidic staining solution of phosphomolybdic acid followed by heating on a hot plate. ^{1}H NMR spectra were obtained with 300, 400 and 500 MHz spectrometers, ^{13}C NMR spectra were obtained with 100 and 125 MHz spectrometers in $CDCl_3$ at 298 K with tetramethylsilane and $CDCl_3$ as the internal standard. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constant, number of hydrogen atoms). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were carried out with a Quattro LC triple-quadrupole mass spectrometer (Micromass, Manchester, UK). High-resolution mass spectra were determined with a Quadrupole time-of-flight (Q-TOF) mass spectrometer (QSTARXL, Applied Biosystems/MDS Sciex, Foster city, USA).

General procedure for the synthesis of 7-aminoquinolin-8-yl benzoate derivatives:

The 25 mL oven dried roundbottom flask was equipped with a magnetic stir bar and charged with charged with 8-aminoquinoline (144 mg, 1.0 mmol) in H_2O (3 mL) and benzoyl peroxide (1.2 mmol, 2×0. 6 equiv/0.5 h), at room temperature for 16 h. The crude compound obtained was washed with a saturated aqueous solution of $NaHCO_3$ to remove the unwanted benzoic acid formed, and then extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate) to obtain the desired product 3a as Pale yellow solid, 182 mg (yield 69%).

General procedure for gram-scale synthesis of compound 3a: Following the same synthetic procedure for compound 3a, the reaction of 8-aminoquinoline (1.0 g, 6.94 mmol) in H_2O (25 mL) and benzoyl peroxide (1.2 equiv, 2×0. 6 equiv/0.5 h), at room temperature for 16 h, to obtain the desired product 3a (yield 65%) as pale yellow solid,

General procedure for the synthesis of acylperoxides: [16e]

Hydrogen peroxide (1.669 g, 35 wt. % in H_2O, 17.18 mmol) was added dropwise over 10 min to a cold (ice bath) solution of acid chloride (30 mmol) in diethyl ether (7 mL), followed by dropwise addition of an aqueous solution of NaOH (1.517g, 37.93mmol, 10 mL) over 20 min. The resulting white precipitate was collected by filtration. After washing with water (3 × 5 mL) and diethyl ether (3 × 5 mL), the solid was crystallized from a cold acetone / water mixture (1: 3 v/v).

Procedure for the synthesis of 6-methoxy-8-nitroquinoline: [19]

To a solution of 4-methoxy-2-nitroaniline (5.09 g, 33.0 mmol, 1.0 equiv) in conc. HCl (40 mL) and conc. H_3PO_4 (15 mL), acrolein (6.5 mL, 97 mmol, 2.9 equiv) was slowly added at 80 °C for 1 h. The mixture was stirred at 95 °C for 6 h, and then cooled to 0 °C. After neutralization with aq. NH_3, the resulting powder was filtered off and dissolved in acetone. The solvent was removed and 6-methoxy-8 nitroquinoline was obtained as a brown solid (4.68 g, 70% yield).

Procedure for the synthesis of 6-methoxyquinolin-8-amine: [19]

A mixture of 6-methoxy-8-nitroquinoline (2.82 g, 13.8 mmol, 1.0 equiv), activated charcoal (1.38 g), iron chloride (448 mg, 2.76

mmol, 0.20 equiv), and hydrazine monohydrate in methanol (80 mL) was stirred at 80 °C for 12 h. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure to give 8-amino-6-methoxyquinoline (2.00 g, 83% yield).

General procedure for synthesis of 5-tosylquinolin-8-amine: [20]

To a 50 mL schlenk tube equipped with a magnetic stir bar was added a mixture of N-(5-tosylquinolin-8-yl)benzamide (8.0 mmol), NaOH (1.0 g, 25 mmol), and EtOH (25.0 mL). Upon completion of the reaction at 90°C for 12 h, the mixture was cooled to room temperature and then diluted with EtOAc (50 mL). The collected organic layer was washed with brine (100 mL), dried with Na_2SO_4, and filtered through a pad of celite the solvent was removed in vacuo by rotary evaporation, and isolated by silica-gel column chromatography, desired product (1.8 g, 83% yield).

7-aminoquinolin-8-yl benzoate (3a): Pale yellow solid, 182.2 mg (yield: 69%), mp: 101-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.95 (s, 1H), 10.47 (s, 1H), 8.80-8.75 (m, 1H), 8.13-8.08 (m, 3H), 7.65-7.60 (m, 1H), 7.59-7.54 (m, 3H), 7.34-7.30 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 148.7, 147.7, 141.1, 136. 1, 133.1, 132.5, 128.9, 127.6, 125.1, 122.6, 119.1, 117.6. ESI-HRMS: calcd for $C_{16}H_{13}O_2N_2$ = 265.09715, Found 265.09705.

7-aminoquinolin-8-yl 2-methylbenzoate (3b): Pale yellow solid, 208.6 mg (yield: 75%), mp: 97-99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.79 (s, 1H), 10.44 (s, 1H), 8.73-8.69 (m, 1H), 8.13-8.07 (m, 1H), 7.76 (d, *J* = 7.62 Hz, 1H), 7.58 (d, *J* = 9.00 Hz, 1H), 7.47-7.42 (m, 1H), 7.36-7.28 (m, 4H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 148.7, 147.8, 140.9, 137.1, 136.0, 134.6, 131.5, 130.9, 127.6, 126.1, 125.2, 122.6, 119.1, 117.9, 20.3. ESI-HRMS: calcd for $C_{17}H_{15}O_2N_2$ = 279.11280, Found 279.11414.

7-aminoquinolin-8-yl 3-methylbenzoate (3c): Pale yellow solid, 211.4 mg (yield: 76%), mp: 86-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.96 (s, 1H), 10.92 (s, 1H), 8.79-8.75 (m, 1H), 8.10-8.06 (m, 1H), 7.91-7.87 (m, 2H), 7.55 (d, *J* = 9.04 Hz, 1H), 7.46 -7.42 (m, 2H), 7.33-7.29 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 148.6, 147.8, 141.0, 138.8, 135.9, 133.2, 128.7, 128.3, 124.9, 124.4, 122.5, 121.5, 119.0, 117.6, 21.36. ESI-HRMS: calcd for $C_{17}H_{15}O_2N_2$ = 279.11280, Found 279.11415.

7-aminoquinolin-8-yl 4-methylbenzoate (3d): Pale yellow solid, 224.5 mg (yield: 80%), mp: 148-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.02 (s, 1H), 10.93 (s, 1H), 8.79-8.71 (m, 1H), 8.11-8.08 (m, 1H), 8.01 (d, *J* = 8.19 Hz, 2H), 7.57-7.54 (m,1H), 7.36 (d, *J* = 7.94 Hz, 2H), 7.34-7.30 (m, 2H), 2.46 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 148.6, 147.7, 143.2, 140.9, 135.9, 130.1, 129.5, 127.5, 124.9, 122.5, 119.0, 117.7, 21.5. ESI-HRMS: calcd for $C_{17}H_{14}O_2N_2$ = 279.1151, Found 279.1149.

7-aminoquinolin-8-yl 3,5-dimethylbenzoate (3e): Pale yellow solid, 227.8 mg (yield: 78%), mp: 143-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.96 (s, 1H), 10.87 (s, 1H), 8.81-8.77 (m, 1H), 8.12-8.07 (m, 1H), 7.72-7.67 (m,1H), 7.56 (d, *J* = 9.04 Hz, 2H), 7.35-7.29 (m, 2H), 7.26-7.23 (m,1H), 2.44 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 148.7, 147.8, 138.6, 136.1, 134.1, 133.1,125.3, 125.0, 122.63, 119.1, 117.8, 21.3. ESI-HRMS: calcd for $C_{18}H_{17}O_2N_2$ = 293.12845, Found 293.12993.

7-aminoquinolin-8-yl 4-methoxybenzoate (3f): Pale yellow solid, 235.3 mg (yield: 80%), mp: 221-223 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.08 (s, 1H), 10.90 (s, 1H), 8.80-8.77 (m, 1H), 8.12-8.07 (m, 3H), 7.56 (d, *J* = 8.85 Hz, 1H), 7.35-7.30 (m, 2H), 7.06 (d, *J* = 8.85 Hz, 2H), 3.91 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 163.1, 148.6, 147.8, 141.1, 136.1, 129.6, 125.3, 124.8, 122.6, 119.1, 117.9, 114.1, 55.5. ESI-HRMS: calcd for $C_{17}H_{15}O_3N_2$ = 295.10772, Found 295.10779.

7-aminoquinolin-8-yl 4-fluorobenzoate (3g): Pale yellow solid, 208.7 mg (yield: 74%), mp: 109-111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.84 (s, 1H), 10.93 (s, 1H), 8.78-8.77 (m, 1H), 8.14-8.10 (m, 3H), 7.57 (d, *J* = 9.00 Hz, 1H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 165.3, 164.1. 148.7, 147.8, 141.0, 136.1, (130.1-130.0 d) 129.2, 125.1, 122.6, 119.1, 117.5, 116.1, 115.9. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2F$ = 283.08773, Found 283.08735.

7-aminoquinolin-8-yl 2-bromobenzoate (3h): Pale yellow solid, 225.7 mg (yield: 66%), mp: 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.48 (s, 1H), 10.58 (s, 1H), 8.73-8.69 (m, 1H), 8.12-8.07 (m, 1H), 7.79-7.72 (m, 2H), 7.60 (d, *J* = 9.04 Hz, 1H), 7.50-7.46 (m, 1H), 7.43-7.39 (m, 1H), 7.35-7.29 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 148.7, 147.8, 140.9, 136. 5, 136.1, 133.9, 132.0, 129.7, 127.6, 125.5, 122.5, 119.9, 119.2, 117.5. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2Br$ = 343.00767, Found 343.00978.

7-aminoquinolin-8-yl 4-bromobenzoate (3i): Pale yellow solid, 232.5 mg (yield: 68%), mp: 178-180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.78 (s, 1H), 10.96 (s, 1H), 8.80-8.77 (m, 1H), 8.13-8.10 (m, 1H), 7.98 (d, *J* = 8.54 Hz, 2H), 7.71 (d, *J* = 8.54 Hz, 2H), 7.58 (d, *J* = 9.00 Hz, 1H), 7.35-7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 148.7, 147.9, 141.0, 136.1, 132.2, 129.2, 127.4, 125.3, 122.6, 119.2, 117.4. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2Br$ = 343.0077, Found 343.0077.

7-aminoquinolin-8-yl 4-iodobenzoate (3j): Pale yellow solid, 238.5 mg (yield: 61%), mp: 141-143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.08 (s, 1H), 10.98 (s, 1H), 8.76-8.72 (m, 1H), 8.31-8.26 (m, 1H), 8.11-8.09 (m, 2H), 7.94-7.91 (m, 1H), 7.65-7.62 (m, 1H), 7.59-7.56 (m, 2H), 7.41-7.37(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 149.2, 148.1, 140.5, 133.3, 132.7, 128.9, 127.6, 124.4, 120.5, 118.5, 93.5. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2I$ = 390.99380, Found 390.99403.

7-aminoquinolin-8-yl [1,1'-biphenyl]-4-carboxylate (3k): Pale yellow solid, 241.5 mg (yield: 71%), mp: > 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.99 (s, 1H), 11.04 (s, 1H), 8.82-8.79 (m, 1H), 8.20 (d, *J* = 8.43 Hz, 2H), 8.14-8.10 (m, 1H) 7.80 (d, *J* = 8.55 Hz, 2H), 7.69-7.66 (m, 2H), 7.58 (d, *J* = 9.04 Hz, 1H), 7.52-7.48 (m, 2H), 7.45-7.40 (m, 1H), 7.36-7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 148.7, 147.9, 145.3, 141.2, 139.8, 136.2, 131.8, 128.9, 128.2, 127.6, 127.3, 125.1, 122.7, 119.2, 117.8. ESI-HRMS: calcd for $C_{22}H_{17}O_2N_2$ = 341.12845, Found 341.12846.

7-aminoquinolin-8-yl 2-naphthoate (3l): Pale yellow solid, 213.6 mg (yield: 68%), mp: 210-212 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.02 (s, 1H), 11.10 (s, 1H), 8.81-8.79 (m, 1H), 8.62 (s, 1H), 8.12-8.08 (m, 2H), 8.04-7.98 (m, 2H), 7.92-7.89 (m, 1H), 7.62-7.54 (m, 3H), 7.35-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 148.7, 147.8, 141.1, 136.1, 135.1, 132.5, 130.1, 129.2, 128.8, 128.2, 127.7, 126.1, 125.1, 123.4, 122.6, 119.1, 117.7. ESI-HRMS: calcd for $C_{20}H_{15}O_2N_2$ = 315.11280, Found 315.11459.

7-aminoquinolin-8-yl thiophene-3-carboxylate (3n): Pale yellow solid, 207.9 mg (yield: 77%), mp: 185-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.68 (s, 1H), 10.86 (s, 1H), 8.80-8.75 (m, 1H), 8.12-8.08 (m, 1H), 7.92-7.90 (m, 1H), 7.68-7.62 (m, 1H), 7.57-7.54 (m, 1H), 7.34-7.30 (m, 2H) 7.23-7.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 148.6, 147.5, 140.7, 137.6, 136.1, 131.9, 129.7, 128.1, 124.9, 122.5, 119.1, 117.3. ESI-HRMS: calcd for $C_{14}H_{11}O_2N_2S$ = 271.05357, Found. 271.05486.

7-aminoquinolin-8-yl benzo[b]thiophene-2-carboxylate (3o): Pale yellow solid, 252.8 mg (yield: 79%), mp: 193-195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.62 (s, 1H), 11.02 (s, 1H), 8.86-8.82 (m, 1H), 7.98-7.92 (m, 2H), 7.59 (d, *J* = 8.92 Hz, 1H), 7.51-7.45 (m, 2H), 7.32-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 148.8, 147.8, 141.6, 140.9, 139.0, 137.1, 136.2, 127.0, 126.9, 125.4, 125.3, 125.2, 122.8, 122.7, 122.6, 119.28, 117.4.

7-amino-2-methylquinolin-8-yl benzoate (4a): Pale yellow solid, 172.4 mg (yield: 62%), mp: 140-142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.94 (s, 1H), 11.06 (s, 1H), 8.12-8.09 (m, 2H), 7.95 (d, *J* = 8.24 Hz, 1H), 7.64-7.60 (m, 1H), 7.59 -7.55 (m, 2H), 7.48 (d, *J* = 8.85 Hz, 1H), 7.25-7.23 (m, 1H), 7.17 (d, *J* = 8.24 Hz, 1H) 2.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 1, 157.6, 147.7, 140.4, 136.1, 133.2, 132.4, 128.9, 128.3, 127. 5, 124.7, 121.2, 120.5, 119.7, 117.1, 25.3.

7-amino-6-methylquinoline-5,8-diyl dibenzoate (4b): Pale yellow solid, 208.6 mg (yield: 75%), mp: 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$+CD_2Cl_2): δ = 12.28 (s, 1H), 10.90 (s, 1H), 8.78-8.73 (m, 1H), 8.38-8.30 (m, 2H), 8.15-8.11 (m, 2H), 8.05-8.01 (m, 1H), 7.76-7.69 (m, 1H), 7.64-7.55 (m, 5H) 7.31-7.27 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 164.56, 148.3, 147.6, 141.6, 139.4, 134.1, 133.1, 132.5, 130.4, 130.16, 128.9, 128.83, 128.60, 127.7, 123.8, 119.3, 116.9, 116.0, 10.86. ESI-HRMS: calcd for $C_{24}H_{19}O_4N_2$ = 399.13393, Found. 399.13677.

7-amino-6-methoxyquinolin-8-yl benzoate (4c): Pale yellow solid, 229.4 mg (yield: 78%), mp: 220-222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.34 (s, 1H), 10.97 (s, 1H), 8.69-8.64 (m, 1H), 8.15-8.10 (m, 2H), 8.04-8.00 (m, 1H), 7.64-7.56 (m, 3H), 7.34-7.28 (m, 1H) 6.96-6.90 (m, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 151.5, 146.1, 140.6, 137.1, 134.5, 132.6, 130.4, 129.9, 128.9, 127.7, 122.9, 119.7, 118.1, 101.7, 56.1. ESI-HRMS: calcd for $C_{17}H_{15}O_3N_2$ = 295.10772, Found. 295.10948.

7-amino-5-chloroquinolin-8-yl benzoate (4d): Pale yellow solid, 178.8 mg (yield: 60%), mp: 151-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.14 (s, 1H), 10.93 (s, 1H), 8.89-8.81 (m, 1H), 8.49 (d, *J* = 8.43 Hz, 1H), 8.11 (d, *J* = 7.70 Hz, 2H), 7.68-7.57 (m, 3H), 7.47-7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 149.3, 147.6, 141.1, 133.4, 132.8, 132.7, 128.9, 127.6, 122.4, 120.6, 119.7, 117.0. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2Cl$ = 299.05818, Found. 299.05993.

7-amino-5-iodoquinolin-8-yl benzoate (4e): Pale yellow solid, 210.6 mg (yield: 54%), mp: 203-205 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.08 (s, 1H), 10.98 (s, 1H), 8.75-8.72 (m, 1H), 8.30-8.26 (m, 1H), 8.11-8.09 (m, 2H), 7.93 (s, 1H), 7.66-7.62 (m, 1H), 7.59-7.56 (m, 2H), 7.41-7.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 149.2, 148.0, 140.6, 140.5, 133.3, 132.7, 128.9, 127.6, 124.4, 122.5, 120.6, 118.5, 93.5. ESI-HRMS: calcd for $C_{16}H_{12}O_2N_2I$ = 390.99380, Found. 390.99691.

7-amino-5-tosylquinolin-8-yl benzoate (4f): Pale yellow solid, 259.2 mg (yield: 62%), mp: 235-237 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.12 (s, 1H), 11.19 (s, 1H), 9.04-9.01 (m, 1H), 8.83-8.79 (m, 1H), 8.25-8.23 (m, 1H), 8.12-8.09 (m, 2H), 7.86 (d, *J* = 8.43 Hz, 2H), 7.67-7.64 (m, 1H), 7.61-7.58 (m, 2H), 7.51-7.49 (m, 1H), 7.45-7.41 (m, 1H), 7.29 (d, *J* = 7.94 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 149.1, 146.0, 144.4, 140.9, 138.2, 133.6, 133.1, 132.4, 129.9, 129.0, 128.4, 127.7, 127.5, 126.3, 122.5, 120.6, 118.5, 21.5. ESI-HRMS: calcd for $C_{23}H_{19}O_4N_2S$ = 419.10600, Found 419.10891.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Vinayak Botla thanks the University Grant Commission (UGC), New Delhi for the award of Senior Research Fellowship (SRF). We thank Dr. B. V Rao, Dr. S. Raghavan for discussions and Dr. B. Sridhar for his support in X-ray crystallography analysis.

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View Article Online
DOI: 10.1039/C9GC00289H

Uncatalyzed, on water oxygenative cleavage of inert C-N bond with concomitant 8, 7-aminoshift in 8-aminoquinoline derivatives.

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The Oxygenative cleavage of inert C_{Ar}-NH_2 bond with concomitant 1, 2 amine migration in 8-aminoquinoline derivatives is reported. An efficient, catalyst free, one step synthesis of 8-benzyloxy, 7-aminoquinoline directly from 8-aminoquinoline in water at room temperature under extremely mild conditions with high degree of atom- and step-economy.