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Metal-free Regioselective Formation of C-N and C-O Bonds with the Utilization of Diaryliodonium Salts in Water: Facile Synthesis of *N*-Arylquinolones and Aryloxyquinolines

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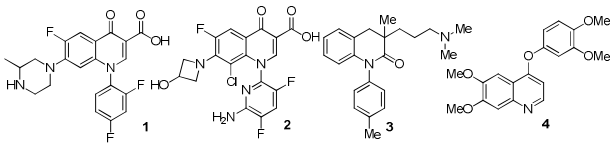
Regioselective construction of crucial C-N and C-O bonds leading to *N*-arylquinolones and aryloxyquinolines have been accomplished by employing easily accessible diaryliodonium salts and quinolones in water under metal- and ligand-free conditions. This operationally simple strategy is significant due to mild reaction conditions, high product yields, recyclability of released iodoarenes and scalable to gram level. The practical utility of the developed protocol was proved by arylation of medicinally important heterocycles like acridin-9(10*H*)-one, 3-methylquinoxalin-2(1*H*)-one and 1*H*-benzo[*d*]imidazol-2(3*H*)-one.

C–N and C–O bonds forming reactions have received wider attention in organic synthesis due to their utilities in preparation of diverse bioactive heterocycles.[1] Recognized and predominant classical name reactions in organic chemistry for the formation of C-N and C-O bonds are Ullmann reaction, Chan-Lam coupling, and Buchwald–Hartwig coupling.[2] Very recently, Miura *et al.* have developed a transition-metal catalyzed elegant method to prepare various carbazoles.[3] Fu group disclosed a copper-catalyzed synthesis of tetrahydroisoquinolino[2,1-a]quinazolinones *via* C-N bond formation.[4] Similarly, Lautens and co-workers reported Rh/Pd-catalyzed preparation of chiral dihydrobenzofuran frameworks through the formation of C-O bond.[5] Especially, *N* -/*O*-arylquinolone and quinoline derivatives are endowed with antibacterial, antiulcer, antitumor (**1** and **2**), inhibition of selective serotonin-norepinephrine reuptake **3** and PDGFR kinase **4** activities (Fig.1).[6]



Temafloxacin (antibacterial potency) | **Defloxacin (antibacterial potency)** | **Selective serotonin norepinephrine reuptake inhibitor** | **PDGFR Kinase inhibitor**

Fig.1 Examples of bioactive arylquinolones and aryloxyquinolines

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In recent past, diaryliodonium salts have been successfully used by synthetic chemists as mild and environmentally benign arylating agents due to their high reactivity, stability and low toxicity.[7] They are often employed in the organic synthesis mainly for the arylation of azaheterocycles.[8] For example, very recently, a domino approach for *N*-/*C*-arylation *via in situ* generation of a directing group in the presence of $[RuCl_2(p\text{-cymene})]_2$ has been developed by Greaney and co-workers.[9] Likewise, *N*-arylation of 2-pyridones with diaryliodonium salts occurred at room temperature in the presence of CuCl.[10] Kang et al. described the *N*-arylation of azoles, lactams and primary amides with catalytic CuI or $Cu(acac)_2$ in the presence of Na_2CO_3 or K_2CO_3 base.[11] Independently, Chen and Greaney co-workers achieved *N*-arylindoles by a copper-catalyzed reaction of indoles with diaryliodonium salts.[12] Similarly, *β*-aryloxy carbonyl compounds were prepared by Liu group involving a copper iodide-catalyzed arylation of enolates with diaryliodonium salts.[13] Selective monoarylation of vicinal diols was achieved by using diaryliodonium salts in the presence of a copper(II) catalyst.[14] However, metal (Pd, Ru, Ir, Cu etc.) catalyzed reactions require the removal of remaining metal traces from the final products which possess an exorbitant challenge in medicinal chemistry.[15]

Recently, arylation under greener reaction conditions has become an emerging area of broad research by avoiding unsuitable metal catalysts, ligands, and environmentally unfavorable organic solvents. Many metal-free methods have been disclosed for the preparation of tertiary amides,[16] *N*-aryloxyimides and aryloxyamines,[17] aryl ethers[18] and alkylaryl ethers[19] by employing diaryliodonium salts. Similarly, amination,[20] *N*-arylation of pyrazoles[21] and indolines[22] with diaryliodonium salts have been developed under metal-free conditions. Additionally, *N*-arylanilines have also been achieved by the use of diaryliodonium salts at higher temperature (130 °C) under metal-free conditions.[23] Nevertheless, the *N*-/*O*-arylation of quinolones are still unexplored in water under metal-free conditions. Aiming to develop efficient and eco-friendly protocols for the arylation of bioactive heterocycles, in this paper we wish to report a metal-free *N*-/*O*-arylation of quinolones using diaryliodonium salts in an aqueous medium.

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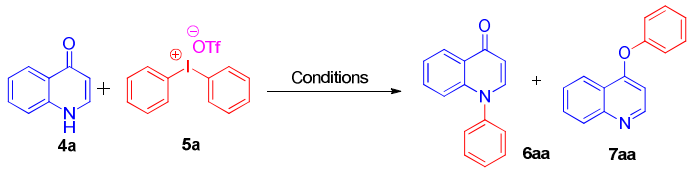
Water has dielectric constant 78 at 25 °C, which reduces with the increment in temperature. Hence, water at an elevated temperature can behave as a pseudo-organic solvent and it can be a benign replacement for an organic solvent. Water as a solvent has attracted much interest due to readily availablity appealing properties such as inexpensive, nontoxicity, nonflammability. The use of neat water helps to reduce the production of organic solvent waste during the organic synthesis and also simplify the workup procedures.[24] Additionally to improve the significance of synthetic protocol in terms of short reaction time and high product yield is extremely desirable. Ascribed to the selective mode of heating, Microwave (MW) radiations widely interacts with polar molecules due to differences in the dielectric properties.[25] Thus, MW heating has become a co-operative process because it allows quick and convenient superheating which dramatically diminishes reaction time under sealed vessel conditions with low-energy consumption. MW heating increases product yield and purity by avoiding unwanted side reactions.

Encouraged from our successful exploration of diaryliodonium salts in the synthesis of 2-arylindoles,[26] diarylsulfones,[27] arylazaheterocycles,[28] diverse biaryls[29] and aryloxyquinolines[30] herein, we report a rapid and metal-free regioselective arylation of quinolones **4** using diaryliodonium salts **5** in water.

At the outset of the study, we selected 4-quinolone (**4a**) and diphenyliodonium triflate (**5a**) as test substrates to prepare *N*-phenylquinolin-4(1*H*)-one (**6aa**) under conventional heating as well as MW irradiation. Results of this investigation are presented in Table 1. Treatment of **4a** with **5a** in the presence of NaOH (3.0 equiv) in DMSO at 80 °C produced the 4-phenoxyquinoline **7aa** (Table 1, entry 1). Changing the base from NaOH to cesium carbonate, potassium carbonate and potassium *t*-butoxide led to a mixture of regioisomers **6aa** and **7aa** (Table 1, entries 2-4). Screening of various solvents such as DMSO, PEG-400, and toluene revealed that the reaction in PEG-400 in the presence of NaOH or *t*-BuOK, produced **6aa** in 45% and 40% yields (Table 1, entries 5 and 6). Only trace amount of **7aa** could be produced, when the reaction was performed in toluene using NaOH or NaH as a base (Table 1, entries 7 and 8). Consequently, use of polar protic solvent, water and potassium hydroxide as a base indeed improved the efficiency of reaction to afford **6aa** in 87% yield (Table 1, entry 9). Later, the reaction of **4a** and **5a** using sodium hydroxide as a base in water produced highest 91% yield of **6aa** under MW irradiation (30 min) whereas conventional heating provided **6aa** in 85% yield after 3h (Table 1, entry 10). Varying the base from NaOH to K_2CO_3 and K_3PO_4 delivered **6aa** in reduced yields (Table 1, entries 11 and 12). Increasing reaction temperature from 80 to 100 °C didn't affect the outcome of the reaction, but the yield of **6aa** was significantly dropped at reduced temperature (60 °C) (Table 1, entries 13 and 14). Finally, we found that 80 °C was the optimum temperature for the satisfactory yield of **6aa.**

Table 1 Optimization of reaction conditions for *N*-arylation of quinolin-4(1*H*)-one[a]



4a 5a 6aa 7aa

					Conventional heating		MW Irradiation		
Entry	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]		Time (min)	Yield (%)[b]	
					6aa	**7aa**		**6aa**	**7aa**
1	NaOH	DMSO	80	10	-	20	60	-	25
2	Cs_2CO_3	DMSO	80	10	10	40	60	15	50
3	K_2CO_3	DMSO	80	10	10	40	60	10	45
4	*t*-BuOK	DMSO	80	10	15	30	60	15	40
5	NaOH	PEG-400	80	10	40	-	60	45	-
6	*t*-BuOK	PEG-400	80	10	30	-	60	40	-
7	NaOH	Toluene	80	10	-	Trace	60	-	Trace
8	NaH	Toluene	80	10	-	Trace	60	-	Trace
9	KOH	Water	80	04	80	-	35	87	-
10	**NaOH**	**Water**	**80**	**03**	**85**	**-**	**30**	**91**	**-**
11	K_2CO_3	Water	80	10	25	-	60	35	-
12	K_3PO_4	Water	80	10	30	-	60	35	-
13	NaOH	Water	100	10	85	-	30	91	-
14	NaOH	Water	60	10	60	-	60	67	-
15	-	Water	100	10	NR	-	60	NR	-

[a]Reaction conditions: **4a** (0.68 mmol), **5a** (0.68 mmol), NaOH (2.04 mmol, 3.0 equiv) in water (1 mL) at 80 °C (30 min). [b]Isolated yield of product. NR = no reaction

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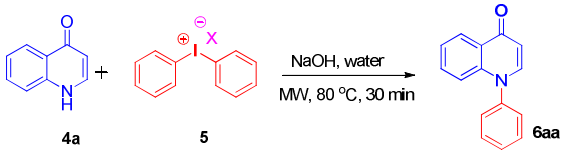
Table 2 Effect of counter anion in *N*-arylation of **4a**[a]



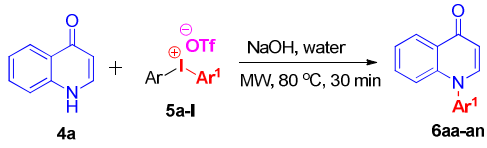
Entry	X	Time (min.)	Yield (%)[b]
1	OTf	30	91
2	BF_4	35	90
3	PF_6	40	89
4	Br	40	80
5	OTs	60	35

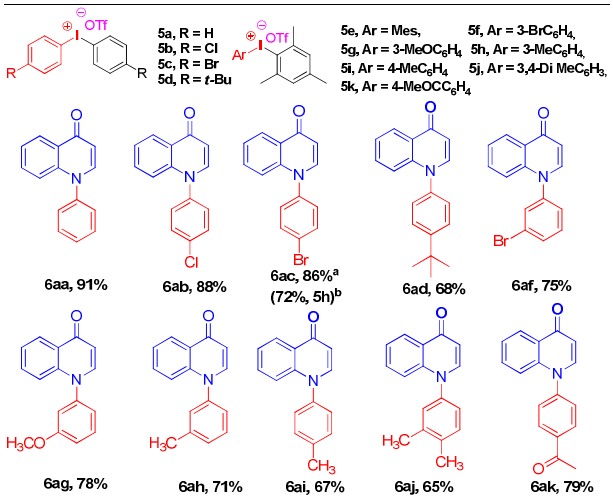
[a]Reaction conditions: **4a** (0.68 mmol), **5** (0.68 mmol), NaOH (2.04 mmol) in water (1 mL) at 80 °C (30 min). [b]Isolated yields of **6aa**.

A control experiment confirmed that no **6aa** was furnished in the absence of a base (Table 1, entry 15). Next, we examined the influence of counterion in diphenyliodonium salt. Utilizing diphenyliodonium salts **5** bearing OTf, BF_4 and PF_6 counteranions rapidly afforded the desired product **6aa** in excellent yields (Table 2, entries 1-3). Marginally low yield (80%) was observed in case of diphenyliodonium bromide (Table 2, entry 4). Use of diphenyliodonium tosylate produced **6aa** in poor yield (Table 2, entry 5). Relatively better coordinating and nucleophilic nature of tosylate ion when compared to counter ions OTf, PF_6 and BF_4 in diaryliodonium salts are probably responsible for the reduced reactivity of diaryliodonium tosylate. Similar observation has also been disclosed by Nagorny group.[31] Generality of the optimized protocol was investigated by arylation of quinolone **4a** with a variety of electron-rich and electron-deficient diaryl-iodonium salts **5**. Reaction with electron-neutral and halogens (Cl and Br) bearing diaryliodonium salts (**5a-c**, **5f**) either at *meta*- or *para*-positions afforded the corresponding *N*-arylquinolones (**6aa-ac, 6af**) in excellent 75-91% yields. Halo-substituted derivatives could be potential precursors for further synthetic manipulations to access useful compounds. Notably, heating the reaction mixture of **4a** and **5c** for 5h at 80 °C produced **6ac** in 72% yield. Diaryliodonium salts (**5d, 5e**, **5g-j**) with electron-donating substituents had little influence on product yield, whereas, diaryliodonium salt **5k** with an electron-deficient group easily delivered **6ak** in 79% yield. Unfortunately, sterically hindered bis(mesityl)iodonium triflate (**5e**) failed to afford the corresponding *N*-arylquinolone. Particularly, unsymmetrical mesityl(aryl)iodonium salts (**5e-k)** are frequently used due to their easy preparation, high yields, use of cheap iodomesitylene, wide substrate scope and selective transfer of an aryl ring.[32] Accordingly, we utilized unsymmetrical diaryliodonium salts **5** for *N*-arylation of **4a**. Delightfully, the electron-deficient or sterically less hindered aryl moiety was selectively transferred to generate **6af-ak** (Table 3) with the concomitant release of iodomesitylene. This unusual selectivity could be due to an unfavorable steric hinderance between bulkier incoming mesityl moiety and C8-hydrogen of quinolone, which is in agreement with the recent reports on iodonium salts-promoted arylation.[33]

To test the versatility of this protocol, we further explored the optimized reaction conditions for the *N*-arylation of analogue 4-methylquinolin-2(1*H*)-one (**4b**) utilizing diaryliodonium salts **5** in

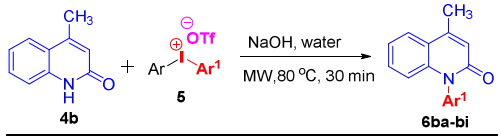
Table 3 *N*-Arylation of quinolin-4(1*H*)-one[a]

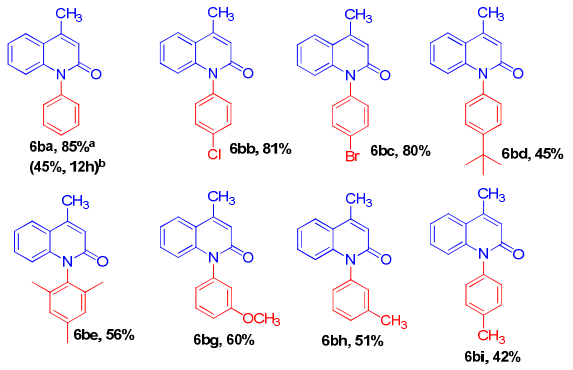




[a]Reaction conditions: **4a** (0.68 mmol), **5** (0.68 mmol), NaOH (2.04 mmol) in water (1 mL) at 80 °C (30 min). [b]Reaction was performed under conventional heating mode. [c]Isolated product yield.

Table 4 *N*-Arylation of 4-methylquinolin-2(1*H*)-one[a]





[a]Reaction conditions: **4b** (0.62 mmol), **5** (0.62 mmol), NaOH (1.86 mmol) in water (1 mL) at 80 °C (30 min). [b]Reaction was performed under conventional heating mode.[c]Isolated product yield.

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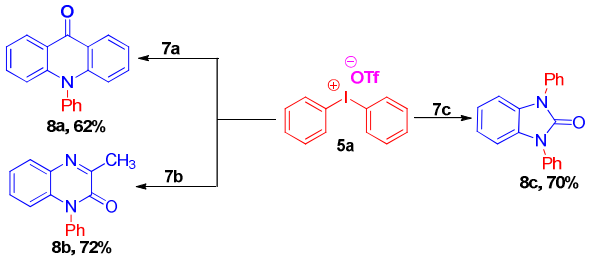
the presence of sodium hydroxide in water. Reaction of **4b** with **5a** resulted **6ba** (85%) under the optimized MW irradiation. But, under heating at 80 °C same reaction afforded **6ba** in 45% yield after 12h. Further, we successfully achieved the desired *N*-aryl-4-methylquinolin-2(1*H*)-ones (**6ba-bi**) in moderate to good yields (42-85%) under MW irradiation at 80 °C for 30 min as illustrated in Table 4. Diaryliodonium salts **5** possessing electronically neutral and halo substituents, produced the corresponding products **6ba-bc** in better yields than with the electronically-rich substituents (**6bd, 6be** and **6bg-bi**).

Next, we focused our attention to arylate pharmaceutically relevant heterocycles, for examples, acridin-9(10*H*)-one (**7a**), quinoxalin-2(1*H*)-one (**7b**) and 1*H*-benzo[*d*]imidazol-2(3*H*)-one (**7c**) which are well-known for their antiviral, antitumor, anti-HIV, anticancer, antimalarial, antibiotic and antifungal activities.[34] Usually arylations of these heterocycles **7a-c** are achieved in the presence of copper catalysts (CuI, $Cu(OAc)_2$).[35] Reaction of **7a** with **5a** in water exclusively produced *N*-phenylacridone (**8a**) probably due to the existence of 9-acridone **7a** in –NH form in an aqueous medium.[36] Furthermore, reactions of **5a** with **7b** and **7c** afforded **8b** and **8c** in 72% and 70% yields, respectively.

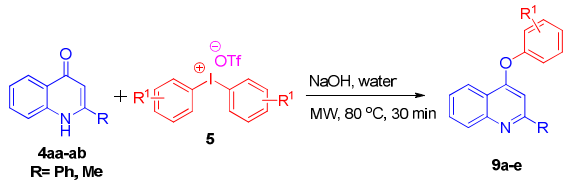
Table 5 *N*-Arylation of medicinally significant heterocycles

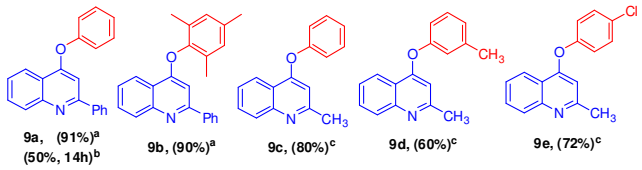


[a]Reaction conditions: **7** (0.51 mmol), **5a** (0.51 mmol), NaOH (1.53 mmol) in water (1.0 mL) at 80 °C (30 min.) [b]Isolated product yield.

Next, the reaction of 2-phenylquinolin-4(1*H*)-one **4aa** with **5a** furnished unexpected 4-phenoxyquinoline **9a** instead of *N*-arylated quinolone (Table 6). Structure of **9a** was unambiguously confirmed by comparing its melting point and NMR (^{1}H and ^{13}C) and IR spectral data as reported in the literature.[30, 37] Under the identified conditions, reaction of **4aa** with **5a** under conventional heating (14h) produced **9a** only in 50% yield. Moreover, bis(mesityl)iodonium salt was also smoothly transferred the mesityl group to afford 4-mesityloxyquinoline **9b** in excellent yield (**90%**). To further investigate the role of C2-substituent in quinolin-4(1*H*)-one, reaction of 2-methylquinolin-4(1*H*)-one **4ab** with diaryiodonium salts **5** was performed. Under the optimized reaction conditions, corresponding *O*-arylated products **9c-e** were successfully achieved in good yields (60-80%). Interestingly, C2-substituent in quinolin-4(1*H*)-ones **4aa-ab** were found to play an important role in controlling the selectivity to exclusively generate the aryloxyquinolines **9a-e**. Increase in steric demand at C2-position of quinolone is believed to hinder the *N*-arylation to afford 4-aryloxyquinolines **9a-e**.[10] In case of unsymmetrical iodonium salts, for example, reaction of **4aa** with mesityl(phenyl)iodonium triflate

Table 6 Regioselective *O*-arylation of quinolin-4(1*H*)-one[a,c]

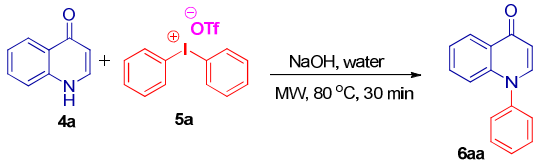




[a]Reaction conditions: **4aa** (0.45 mmol), **5** (0.45 mmol), NaOH (1.35 mmol) in water (1.0) mL at 80 °C, 30 min. [b]Reaction was performed under conventional heating mode. [c]**4ab** (0.62 mmol), **5** (0.62 mmol), NaOH (1.86 mmol) water (1.0 mL) at 80 °C (30 min). [d]Isolated product yield.

produced a mixture of 4-phenoxy-2-phenylquinoline (**9a,** 40%) and 4-(mesityloxy)-2-phenyl-quinoline (**9b,** 60%).

It is noteworthy to mention that the reaction of **4a** with iodobenzene under the optimized conditions could not afford **6aa**, which indicates the greater reactivity of diphenyliodonium triflate. To illustrate the usefulness of this strategy, gram-scale synthesis of **6aa** was accomplished from the reaction of **4a** (1.0 g, 6.9 mmol) and **5a** (2.98 g, 6.9 mmol). *N*-Phenylquinolin-4(1*H*)-one **6aa** was obtained in 86% yield as depicted in Scheme 1. Released iodobenzene was recovered in 90% yield and reused to achieve diaryliodonium salt **5a**.



1 g, 6.9 mmol 1.31 g, 86%

Scheme 1 Gram scale synthesis of **6aa**

Based on the formation of *N*-arylquinolones **6** and 4-aryloxy-quinolines **9** and literature precedence,[38] a plausible pathway for the formation of **6** and **9** is illustrated in Scheme 2. In basic solution, quinolones may exist in keto-enol tautomeric forms **A** and **B** which may be influenced by two crucial parameters including, solvent and steric factor. Tautomerization of quinolone may exhibit ambident nucleophilicity and facilitates attack through oxygen or nitrogen atom. It is believed that in aqueous medium, keto form of quinolone may get stabilized by water molecules through hydrogen-bonding and hinders the reactivity of oxygen atom. Consequently, available -NH in **4a** exclusively reacts with the diaryliodonium salts to generate **6** as the sole product.[39] With the presence of 2-methyl or 2-phenyl in **4**, steric factor likely to dominate over solvent effect and might be responsible for the exclusive formation of **9**.[10, 40] Initial deprotonation of quinolone may generate reactive species **A** or **B** which reacts with diaryliodonium salt (Ar_2IOTf) to form a T-shape intermediate **C** or **D**. 1,2-Phenyl migration in **C** or **D** believed to facilitate the formation of arylquinolones **6** or aryloxyquinolines **9**.

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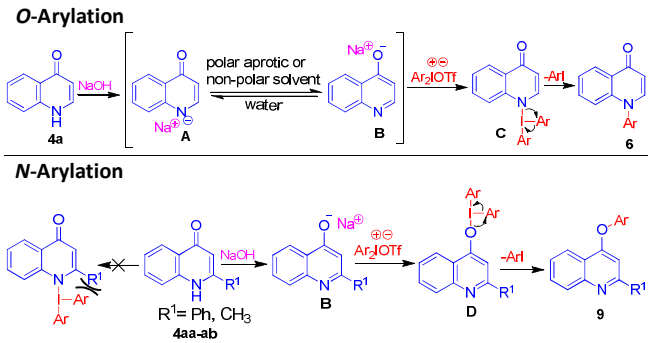

Scheme 2 Putative mechanism for arylation of quinolones

To conclude, we have disclosed a novel straightforward metal- and ligand-free regioselective synthesis of *N*-arylquinolones and 4-aryloxyquinolines in aqueous medium. This protocol utilized easily accessible, environmentally safe and stable solids diaryliodonium salts as versatile arylating agents. Diaryliodonium salts with electron-donating as well as electron-withdrawing groups delivered the desired products in good to excellent yields (42-91%). Highlights of the present strategy include operationally simple, short reaction times, compatible to arylate other heterocycles such as acridin-9(10*H*)-one, 3-methylquinoxalin-2(1*H*)-one and 1*H* benzo[*d*]imid-azol-2(3*H*)-one, recyclability of the released iodoarenes and gram scale synthesis of *N*-phenylquinolin-4(1*H*)-one. Detailed mechanistic studies and extensions of this protocol to other relevant heterocyclic systems are currently in progress.

Acknowledgements

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