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Graphical Abstract

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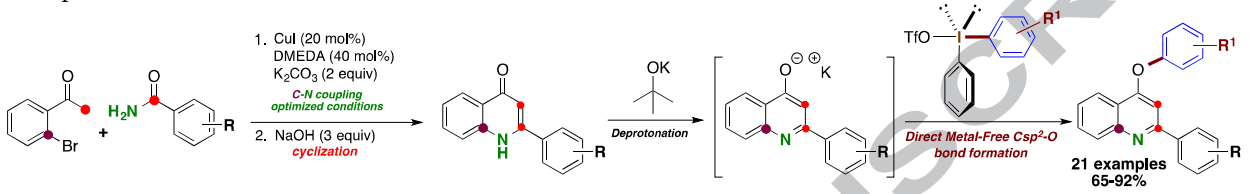

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ABSTRACT

An efficient ligand- and transition metal-free procedure for the direct C_{sp}^2-O bond formation for the arylation of 2-aryl-4-quinolones was developed. The synthesis of the starting quinolones was carried out under our optimized Cu-catalyzed C-N bond formation conditions between 2´-bromoacetophenone and benzamide derivatives followed by cyclization. Easily prepared diaryliodonium salts were used as aryl source. Highly functionalized 4-aryloxyquinolines were obtained in a mild and operationally simple protocol, which involves conventional heating and short periods of time. The method shows good to excellent yields and broad toleration of functional groups like fluorine or trifluoromethyl, which are important in medicinal chemistry. The C_{sp}^2-O bond formation process herein described for the quinolone functionalization offers an excellent non-toxic alternative to the transition metal-catalyzed reactions that not only can potentially contaminate the final compounds but also can be enviromental pollutants.

The quinoline nucleus is an important fragment for the human life.[1] Relevant biological activities like antimalarial,[2] antibacterial,[3] antiparasitary,[4] antifungal,[5] antiinflammatory,[6] analgesic,[7] cardiovascular[8] and hypoglycemic[9] among the most important have been described. It is ubiquitous in nature and usually sought after in medicinal chemistry[10] and organometallic chemistry[11] among other relevant areas. Specifically 2-aryl-4-aryloxy functionalized quinolines represent a tremendously important core in clinical and medicinal research.[12] Essentially, the recent trends about the anti-diabetic,[13] anti-cancer[14] and anti-viral[15] investigation points towards a combined synthetic and computational calculations strategy. In such a way is possible to find easier a properly drug for a plausible treatment in the short- or medium-term. In this sense, the 2-aryl-4-aryloxyquinoline moiety has been widely used (**Figure 1**).

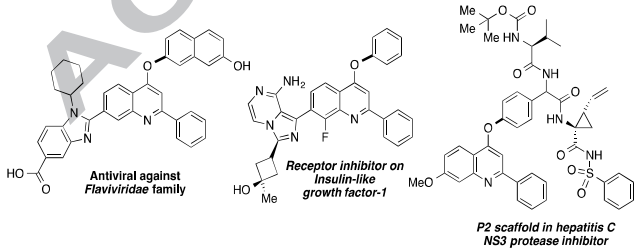

Figure 1. Representative anti-diabetic and anti-viral developed drugs containing the 2-aryl-4-aryloxyquinoline structure.

Representative methods to synthesize 2-aryl-4-aryloxyquinolines involve the starting synthesis of 2-aryl-4-quinolones followed by the change of carbonyl group for the corresponding chlorine or fluorine. Afterwards, a direct nucleophilic aromatic substitution with a naphthol derivative in basic media affords the incorporation of the desired C-O bond in the aryloxy group. This approach is a two-step procedure.[16]

Described protocols for C-O bond formation in aryl derivatives, usually imply the use of Cu-[17] or Pd-catalyzed[18] cross-coupling reactions. These procedures commonly require costly ligands and are often low yielding or not tolerant in presence of heterocyclic groups. Additionally, they can contaminate the final compounds. Recently hypervalent λ^3-iodane[19] derivatives have emerged as an excellent alternative in transition metal-free reactions. Specifically the Olofsson method[20] for the C-O bond formation by using diaryliodonium salts is efficient, mild and shows broad toleration of functional groups, including heterocyclic systems.

In this regard during our quest towards the total synthesis of the naturally occurring graveoline from *Rutta sp.*, we needed the methylation at 4-position in the 2-phenyl-4-quinolone. We questioned ourselves about the use of some other groups like an aryl to be attached in the oxygen of the quinolone for synthesizing analogues of this natural compound. We found in the diaryliodonium chemistry an excellent, direct and non-toxic tool for this transformation. It is important to mention that during the experimental course of our work, Karade[21] and Kumar[22] reported a closely related idea. Karade described the direct arylation of 4-aryl-6-methyl-pyrimidine-2(1*H*)-one derivatives. On the other hand Kumar prepared in one-pot procedure 2- and 4-aryloxyquinolines based on a microwave-assisted *O*-arylation

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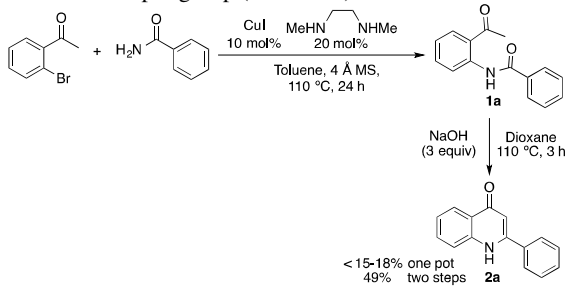
of quinolones. While various diaryliodonium salts were investigated in the preparation of 4-aryloxyquinolines, the synthesis of 2-aryl-4-aryloxyquinolines was limited to one example. In light of the importance of such framework in bioactive compounds, we described herein an easy, mild and efficient procedure for synthesizing in one pot 2-aryl-4-aryloxyquinolines starting from the corresponding functionalized 4-quinolones by using conventional heating and non-symmetrical iodonium salts.

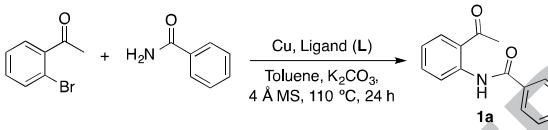
We started with the synthesis of 2-aryl-4-quinolones via an one-pot Buchwald procedure.[23] However after several attempts we could not reproduce the methodology, obtaining only poor yields in the C-N coupling step (**Scheme 1**).



Scheme 1. Synthesis of 2-aryl-4-quinolones by using the Buchwald procedure.

Then we decided to optimize this sequence starting with the C-N coupling to develop a robust and general procedure (**Table 1**).

Table 1. Optimization of the C-N coupling to get acetylphenylbenzamide **1a**.



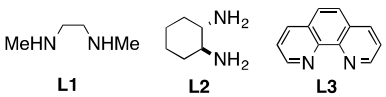
Entry	$PhCONH_2$ (equiv)	Cu (mol%)	L (mol%)	Yield of 1 %[a,b]
1	1.2	CuI (10)	**L1 (20)**	37
2	1.2	CuI (20)	**L1 (40)**	61
3	1.2	CuI (40)	**L1 (80)**	45
4	1.5	CuI (20)	**L1 (40)**	50
5	***2.0***	***CuI (20)***	***L1 (40)***	***67***
6	2.5	CuI (20)	**L1 (40)**	75
7	2.0	CuI (20)	**L3 (40)**	5[c]
8	2.0	CuI (20)	**L2 (40)**	< 5[c]
9	2.0	CuBr (20)	**L1 (40)**	37[c]
10	2.0	$Cu(OAc)_2$ (20)	**L1 (40)**	60[c]
11	2.0	$Cu(OAc)_2$ (20)	**L3 (40)**	13[c]

[a] All of the reactions were carried out using benzamide (1.0 equiv), K_2CO_3 (2 equiv) in toluene (0.3 *M*).

[b] Isolated yields.

[c] The yields were determined using anisole as internal standard.

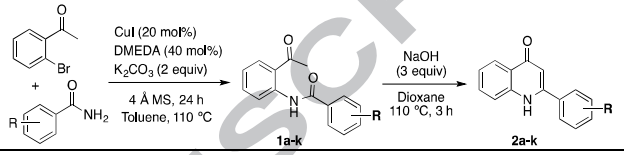
The table illustrates representative experiments. See SI for full details.

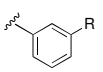
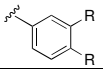
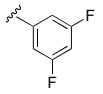
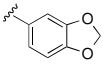


The described conditions[23] gave low to moderate yields (37-61%) even changing the amount of ligand and copper (entries 1-3). Keeping 20 mol% of copper iodide and 40 mol% of DMEDA but increasing the equivalents of benzamide (1.5-2.5) gave rise to significantly better yields (50-75%) (entries 4-6). Some other ligands like *o*-phenathroline, *trans*-1,2-dicyclohexylamine and different copper sources did not produce higher yields (entries 7-11). The optimized conditions for this cross-coupling reaction are described in entry 5. Even though entry 6 shows a slightly better yield, this required a big amount of benzamide (See SI for full details).

With the optimized conditions in hand, we were ready to prepare the series of 2-aryl-4-quinolones (Table 2).

Table 2. Synthesis of 2-aryl-4-quinolones under optimized conditions for the C-N coupling reaction.



Structure	Entry	1a-k, %[a]	-R	2a-k, %[a]
	**1**	**1a**, 67	-H	**2a**, 88
	2	**1b**, 69	-Me	**2b**, 93
	3	**1c**, 70	-OMe	**2c**, 96
	4	**1d**, 62	-Cl	**2d**, 90
	5	**1e**, 65	-F	**2e,** 93
	**6**	**1f**, 70	-Cl	**2f**, 85
	7	**1g**, 68	$-CF_3$	**2g**, 90
	**8**	**1h**, 34	-OMe	**2h**, 91
	9	**1i**, 69	-Cl	**2i**, 93
	**10**	**1j**, 72	3,5-F	**2j**, 87
	**12**	**1k**, 44		**2k**, 91

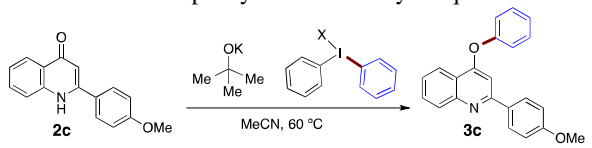
[a] Isolated yields

Several 2-aryl-4-quinolones were synthesized in excellent yields (87-96%) with different groups at the 2-aryl fragment. Thus, electron-donor (entries 2-3, 8 and 12), electron-attractor (entries 4-7, and 9-10) as well as electron-neutral (entry 1) substituents were incorporated. We considered important the former optimization, which was carried out. This in the context to describe a complete, robust and reproducible procedure for the synthesis of highly functionalized 2-aryl-4-aryloxyquinolines starting from simple and/or commercial starting materials.

At this point we were ready to test our hypothesis. Then it was decided to optimize the direct *O*-arylation in **2c** as model. The use of acetonitrile and potssium *tert*-butoxide were the starting conditions based upon previous reports[24] (**Table 3**). Also fixed the reaction temperature at 60 ºC was crucial to get shorter reaction times. Usually overnight period was necessary to complete the starting material at 40 ºC. In the initial screening it was considered the use of hexafluorophosphate, triflate, chlorine and nitrate iodonium salts maintaining 1.2 equiv of base (entries

1-4). All entries yielded good results, highlighting triflate 72% (entry 2) and nitrate 69% (entry 4) as the best anions.

Table 3. Optimization of the direct C_{sp}^2-O bond formation in the metal-free one-pot synthesis of 4-aryloxiquinolines.

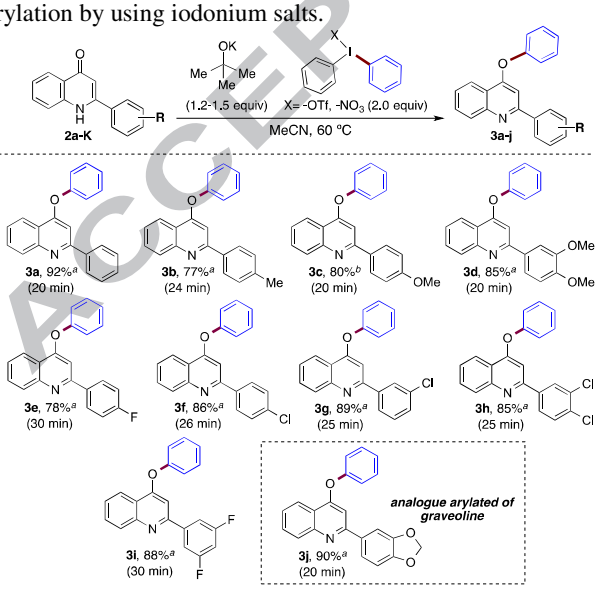


Entry	^{t}BuOK Equiv	X^{Θ} (Equiv)	Yield %[a]
1	1.2	PF_6 (1.2)	60
2	1.2	OTf (1.2)	72
3	1.2	Cl (1.2)	65
4	1.2	NO_3 (1.2)	69
5	1.2	OTf (1.5)	77
6	*1.2*	*OTf (2.0)*	*80*
7	1.2	NO_3 (1.5)	72
8	1.2	NO_3 (1.8)	76
9	1.2	NO_3 (2.0)	78
10	*1.5*	*NO_3 (2.0)*	*85*[b]

[a] Isolated yields. [b] Complicate chromatographic purification.

Then, we focused our attention to optimize the reaction using these two salts. On the treatment with 1.2-1.5 equiv of triflate salt the yield increases from 77% until 80% (entries 5 and 6). Regarding to the nitrate, a slightly bigger amount of salt (1.5-2 equiv) was necessary. Thus with 1.5 equiv, 72% of yield was observed (entry 7), and with 1.8 and 2.0 equiv (entries 8 and 9) 76% and 78%, respectively, were obtained. Finally, in the increase to 1.5 equiv of base, we found an excellent 85% of yield. In this way, the entries 6 and 10 were the best conditions and they validated our hypothesis. With optimal conditions for the direct C_{sp}^2-O bond formation, the scope in the 1,4-quinolone was explored with **2a-k** as starting materials (**Scheme 2**).

Scheme 2. Scope at the 2-arylquinolone for the direct C-O arylation by using iodonium salts.

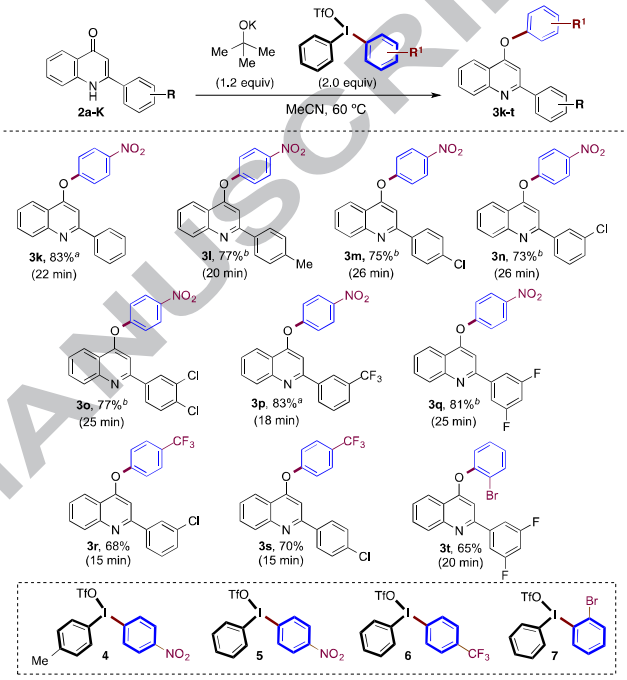


[a] Ph_2INO_3 (2 equiv), ^{t}BuOK (1.5 equiv). [b] Ph_2IOTf (2 equiv), ^{t}BuOK (1.2 equiv). Reaction times in brackets.

All of the reactions were carried out by using conventional heating under very mild temperature conditions. Also very short reaction times (*20-30 min*) were observed to complete the starting material. Additionally good to excellent yields (77-92%) were obtained after chromatography purification. This procedure tolerates electron-neutral (**3a**), electron-rich (**3b-d, 3j**) and electron-poor (**3e**-i) functional groups at the 2-aryl fragment of the quinolone.

To complete the scope of the developed procedure, we decided to test different iodonium salts[25] with the 2-arylquinolones **2a-k** (**Scheme 3**).

Scheme 3. Scope at the iodonium salt for the direct C-O arylation in 2-arylquinolones **2a-k**.



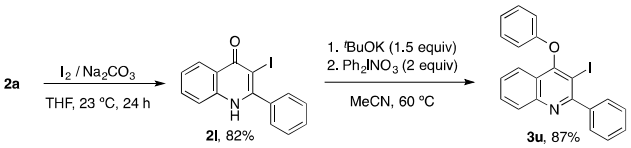
[a] Iodonium salt **4** was used. [b] Iodonium salt **5** was used. Reaction times in brackets.

Iodonium salts **4**-**7** were synthesized and used. As shown for the phenyl group (**Scheme 2**), *p*-nitrophenyl, *p*-trifluorophenyl and 2-bromophenyl groups were transfered directly to electron-neutral (**3k,** 83%), electron-rich (**3l**, 77%) and electron-poor (**3m-3l**, 65-83%) 2-aryl-4-quinolones (**Scheme 3**). The yields of the 4-aryloxyquinolines obtained were moderate to good. In this part, it is of crucial importance to mention three points: 1) The procedure in general is totally regioselective, since only *O*-arylation was observed at least by the NMR detection limit. 2) The protocol is totally chemoselective the electron-poor aryl is exclusively transfered. This result was in the same for all of the examples (**Scheme 3**) and is in agreement with the DiMagno[26,27] observation. Additionally, our procedure avoids the use of symmetrical iodonium salts, which is an strong limitation in previous reports.[22] This implies the use of pre-functionalized substrates to access into this class of symmetric salts and is wasted the half of such functionalized molecule in the reaction process. 3) The procedure tolerates important substituents like chlorine, fluorine or trifluoromethyl which are relevant in medicinal chemistry. In fact, we focused on the application of the developed procedure to the synthesis of these potentially biological active of derivatives.

In order to test the application of the synthesized compounds by our procedure, we decide to carry out the following short

sequence of reactions to prepare the iodinated quinoline **3l** as potential starting building block in different organic reactions (**Scheme 4**).

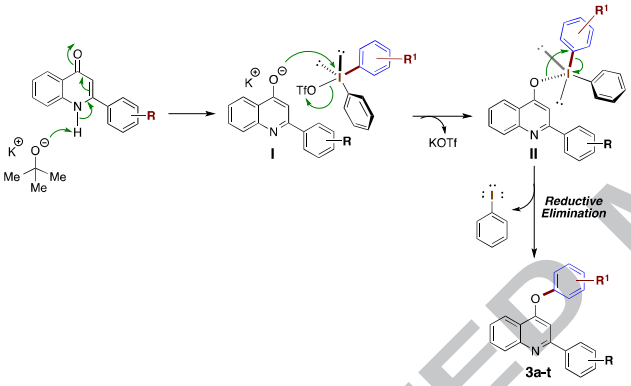
Scheme 4. Application of the developed procedure to the synthesis of quinoline **3u**.



The quinolone **2a** was iodinated to yield **2l**[28] in good 82% of yield. This compound was arylated under our optimized conditions giving rise to the quinoline **3u** in excellent 87% of yield. The presence of a bulky iodine close to the arylation center did not affect the reaction.

Finally according to the precedents of the iodonium salts chemistry,[19,29-30] it is plausible to propose the following mechanism of reaction (**Scheme 5**).

Scheme 5. Proposed mechanism of reaction for the direct C-O arylation of 2-aryl-4-quinolones by using iodonium salts.



The mechanism starts with the deprotonation of quinolone by potassium t*ert*-butoxide to generate **I**. This bidentade anion regioselectively attacks at the electrophilic iodine center in the salt giving rise to **II**. The evolution of this intermediate via reductive elimination yields compounds **3a-t** with a concomitant releasing of iodobenzene.

In summary we developed a mild, efficient and operationally simple procedure for the direct arylation of 2-aryl-4-quinolones, to produce in one-pot a new C_{sp}^{2}-O bond under metal- and ligand-free conditions. To the best of our knowledge, this is the first work with a wide application totally directed to the synthesis of functionalized bioactive 2-aryl-4-aryloxyquinoline core, containing groups like -Cl, -F or $-CF_3$ relevant in medicinal chemistry. The procedure was carried out with the use of conventional heating. Additionally, it shows totally regio- and chemoselectivity allowing for synthesizing exclusively *O*-arylquinolines by using simple non-symmetrical iodonium salts. This represents a more atom-economical protocol regarding to those previously described,[22] which use symmetrical salts. The procedure has a broad scope and tolerates different functional groups nature.

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Supplementary Material

Full details about experimental procedures, optimization protocols as well as copies of ^{1}H and ^{13}C NMR, for unknown compounds are available.

HIGHLIGHTS

- The first genral method for synthesizing in one pot 2-aryl-4-aryloxyquinolines, which is a tremendous important pharmacophore.

- A metal- and ligand-free procedure for the direct formation of a C-O bond giving rise to functionalized quinolines.

- A totally, regio- and chemioselective *O*-arylation procedure for the functionalization of quinolines.

- The use of non symetrical bisaryliodonium salts expending only PhI as organic byproduct of the reaction.