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Transition metal-free one-pot double C-H functionalization of quinolines by disubstituted electron-deficient acetylenes

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Transition metal-free one-pot reaction of quinolines with acylarylacetylenes and water proceeds in the presence of KOH (55-60 °C, MeCN, 48 h) to afford 2-aryl-3-acylquinolines in up to 66% yield. Here, a formal replacement of acetylene moiety by the aryl and acyl substituents in the quinoline scaffold takes place. In fact, it has been proved experimentally that the reaction involves the ring cleavage, accompanied by the rearrangement and insertion of the electron-deficient acetylene moiety to form the dihydroquinoline intermediate with aldehyde function in the position 4. This intermediate an aldehyde to give the corresponding doubly functionalized quinolines.

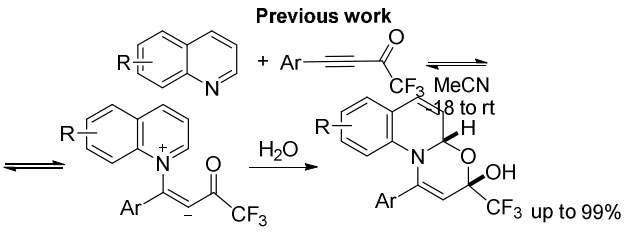
Functionalized quinolines are now extensively studied and applied as drugs,[1] their precursors[2] and privileged building blocks[3] in heterocyclic chemistry. Consequently, the search for their expedient concise syntheses from available starting materials remains a standing challenge in this field.

Now a particular attention is paid to the transition metal-free protocols because contamination with heavy metals often presents problems for using the synthesized compounds as drugs and their precursors.

Commonly, the doubly functionalized quinolines are synthesized from acyclic precursors, *e.g.*[4] 3-Acyl-2-arylquinolines are usually assembled from *o*-aminobenzaldehyde[4a,b] or its precursors (*o*-nitro-[4d,g] or *o*-bromobenzaldehyde[4j]) and 1,3-dicarbonyl compounds or electron-deficient acetylenes[4e] and also by oxidative cyclization of *N*-(2-alkenylaryl)enamines under the action of $Mn(OAc)_3$[4g] or $CuCl_2$[4h] in the oxygen atmosphere. In spite of numerous data on the C-H functionalization of azines using the transition metal catalysis,[5] the information on the synthesis of 2-aryl-3-aroylquinolines *via* this approach is lacking in the literature.

Meanwhile, 2 and 3 aryl and aroyl substituted quinolines are potential inhibitors of Tubulin polymerization[6] and display activity against Dengue virus.[7] Diverse 2-arylquinolines exhibit excellent fluorescent properties,[8] and are employed as precursors in the synthesis of photolabile compounds.[9] Therefore, the atom-economic transition metal-free short-cut to such quinolines based on the double C-H functionalization of the quinoline ring with such accessible starting materials as substituted acetylenes looks desirable.

During our systematic study[10] of the azine functionalization with electron-deficient acetylenes *via* 1,3-dipole (zwitterion) intermediates we have found that quinolines, upon treatment with aryltrifluoroacetylacetylenes, undergo an efficient 1,2-double substitution to diastereoselectively deliver hydroxyl trifluoromethyl oxazinoquinolines in a one synthetic operation (Scheme 1).[10d]



Scheme 1 Synthesis of hydroxyl trifluoromethyl oxazinoquinolines from quinolines, aryltrifluoroacetylacetylenes and water

As it is experimentally established, this assembly tolerates aryltrifluoroacetylacetylenes only, while their non-fluorinated analogues do not undergo this reaction.[10b] However, to our delight, when the reaction of quinolines **1a** with benzoylphenylacetylene **2a** was carried out in the presence of KOH, the formation of 3-benzoyl-2-phenylquinolines **3a**, though in low yield (26%), was observed (Scheme 2).

A.

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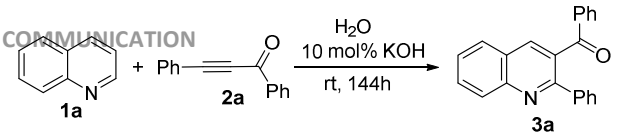

Scheme 2 Reaction of quinoline **1a** and benzoylphenylacetylene **2a**, catalyzed by KOH

In this communication, this unexpected double 2,3-C-H functionalization of quinolines, some regularities and key features of this peculiar assembly are briefly described. For optimization of the reaction conditions to increase the yield of the target product **3a** and to shorten the reaction time as well as to get a better understanding of the effects, governing the reaction as a whole, we have chosen the same the reactant pair as shown in Scheme 2, *i.e*. quinoline **1a** and acetylene **2a**. For the further analyses, the selected experimental results are shown in the Table 1.

Table 1 Effect of the reaction condition on the yield of 3-benzoyl-2-phenylquinoline **3a** obtained from quinoline **1a** and benzoylphenylacetylene **2a**

Entry	Molar ratio **1a**:**2a**[a]	H_2O (equiv)[b]	KOH (mol%)[b]	Solvent	Temp. (°C)	Time (h)	Yield of **3a** (%)
1	1.5:1	5	0	none	rt	144	-
2	1.5:1	5	5	none	rt	144	23
3	1.5:1	5	10	none	rt	144	26
4	1.5:1	5[c]	10	none	rt	144	19
5	1.5:1	0	10	none	rt	144	-
6	1.5:1	5	10	none	50-55	54	20
7	1.5:1	5	10	none	75-80	39	1
8	1.5:1	5	20	none	rt	144	34
9	1:1	5	20	none	rt	144	29
10	1:1	5	20	MeCN	rt	144	6
11	1:1	5	20 (Pd)[d]	MeCN	rt	144	9
12	1:1	5	20 (Cu)[e]	MeCN	rt	144	6
13	1:1	5	20 (Zn)[f]	MeCN	rt	144	5
14	1:1	5	20	MeCN	55[g]	21	3
15	1:1	55	20	none	55-60	24	26
16	1:1	55	20	MeCN	55-60	24	36
17	1:1	55	20	MeCN	55-60	48	45
18	1:1	55	20	none	55-60	48	48
19	1:1	55	20	none[h]	55-60	48	50
20	1:1	5	20	DMSO	rt	144	-

[a] 0.5 mmol of **2a**; [b] relative to acetylene **2a**; [c] with D_2O; [d] 10 mol% $PdCl_2$ was added; [e] 10 mol% CuI was added; [f] 10 mol% $Zn(OAc)_2$ was added; [g] under MWI activation; [h] 10 mol% TEBAC.

The reaction was monitored by the IR spectroscopy following the drop of intensity of acetylene **2a** C≡C bond at 2198 cm^{-1} until it stopped changing.

As seen from Table 1, one of the major factors influencing the yield of product **3a** is the water content: without water the reaction does not take place (entry 5), whereas with 5 equivalent of water the yields range 1-34% (depending on other reaction conditions, entries 1-14). A much better yield of **3a** (45%) is reached with 55 equivalent of water in MeCN (entry 17). Importantly, in neat water (without MeCN), the reaction also takes place (entry 15) to give 26% yield of product **3a** for 24 h, while at a longer time (48 h), the yield increases up to 48% (entry 18). In this case, contrary to expectations, the phase-transfer catalyst (TEBAC, 10 mol%) does not improve the yield noticeably (50%, entry 19). These results imply that water may take part in a key step of the reaction, though no extra oxygen atom is introduced into the product molecule, *i.e*. formally no molecule of water is incorporated in the product. Another major factor controlling the reaction (its product yield and duration) is the KOH concentration. In fact, the reaction does not occur when it is performed without KOH (entry 1). When KOH loading increases (0-20 mol% KOH), the yield of **3a** is augmented from zero to 34% (other conditions being the same, entries 1-3, 8). This indicates that some important steps of the assembly are the based-catalyzed ones. A particularly peculiar feature of this double C-H functionalization is its long time (mainly 24-144 h), which cannot be shorten by the temperature increase without loss of the yield (entries 6 and 7). It is curious that it was impossible to increase the yields by the microwave assistance: the process is not facilitated, but almost inhibited (entry 14). Another surprising fact is that transition-metal salts often used as catalysts in the reactions with acetylenes[11] like $PdCl_2$, CuI, $Zn(OAc)_2$ did not show any catalytic effect in this case (entries 11-13). The "lethargic" character of the whole process can be understood as a clue to a narrow channel (bottle neck) in the rate-determining step of reaction, involving the initial reactive species formed in a small concentration. This preliminary analysis of the experimental background proved to be helpful for the below mechanistic rationalization.

Also, in some cases, the reaction can be implemented without a solvent because the reactants themselves play a role of a dissolving medium. Acetonitrile was found to be a solvent of choice, whereas other solvents such as DMSO were much more inferior (entry 18).

The provisionally optimum conditions of Table 1 (the reactant **1a**:**2a** molar ratio = 1:1, 20 mol% KOH, 55 equiv. H_2O, 1 mL MeCN, temperature 55-60 °C, time 48 h), which provide for the maximal yield of **3a** (45%) have been further employed to check the substrate scope of the synthesis (Scheme 3).

As Scheme 3 shows, the discovered functionalization of quinolines can be extended over quinolines functionalized in the benzene ring with such substituents as halogens, alkoxy, and alkylsulfanyl groups. Also, the reaction tolerates different aryl, aroyl and heteroaroyl electron-deficient acetylenes. The yields are mostly moderate (38-66%). The best yields (59-66%) are observed for quinoline **1a**, 3-methyl and 6-methoxy substituted quinolines **1b**,**d** in combination with benzoyl-, furoyl- and thenoylphenylacetylenes **2a**,**e**,**f**. The yields drop significantly (20-31%) in the case of 6-chloroquinoline **1c**, when it reacts with the same acetylenes **2a**,**e**,**f**. The lowest yield 19% is reached with the pair quinoline **1a** and 4-nitrobenzoylphenylacetylene **2d**. In this case, the side (*Z*)-hydroxy-enone has been isolated (11% yield, see SI).
Oddly, in the pure water (without MeCN), the yield of quinoline **3d** increases (24%) likely because the reaction proceeds in organic phase of the heterogenic reaction mixture.

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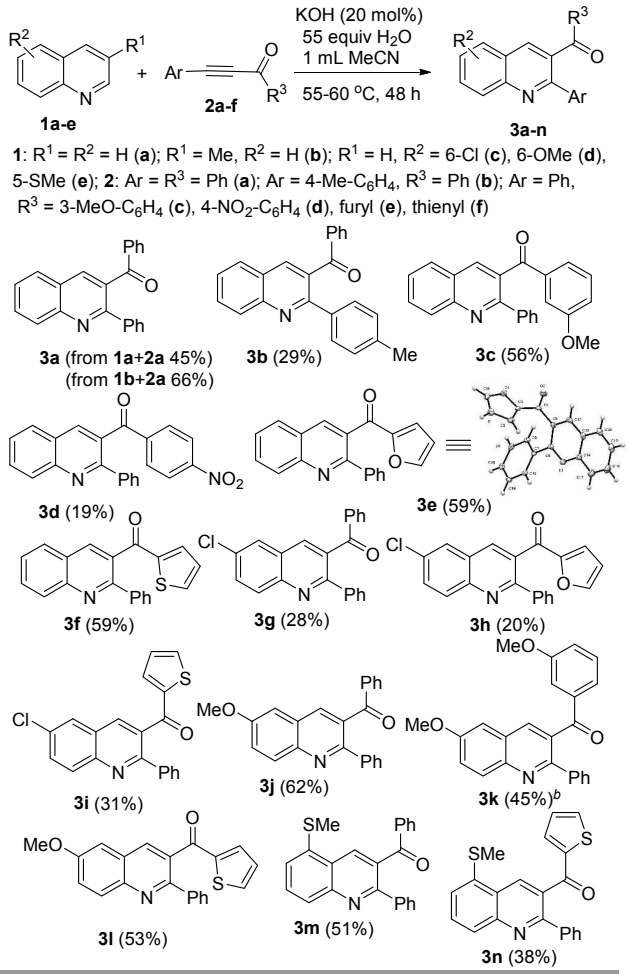
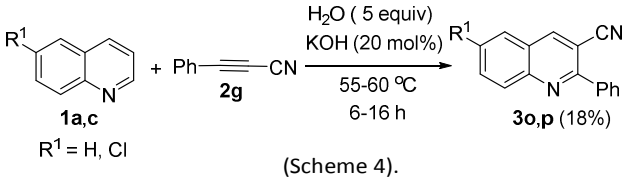


Scheme 3 Scope of acylacetylenes **2** and X-ray structure of **3e**.[a] [a] *Conditions*: quinoline **1** (0.5 mmol), acetylene **2** (0.5 mmol), KOH (20 mol%), H_2O (55 equiv), MeCN (1 mL); [b] reaction time was 24 h.

The series of electron-withdrawing acetylenes capable of functionalizing the quinoline moiety is not limited to acylacetylenes, For instance, cyanophenylacetylene **2g** under the elaborated conditions was found to doubly functionalize quinolines **1a**,**c** to give 3-cyano-2-phenylquinolines **3o**,**p** (9%). When the reaction was carried out with 5 equivalents of water, the yields of functionalized quinolines **3o**,**p** became twice as much (18%), seemingly for the same reason as with acetylene **2d**



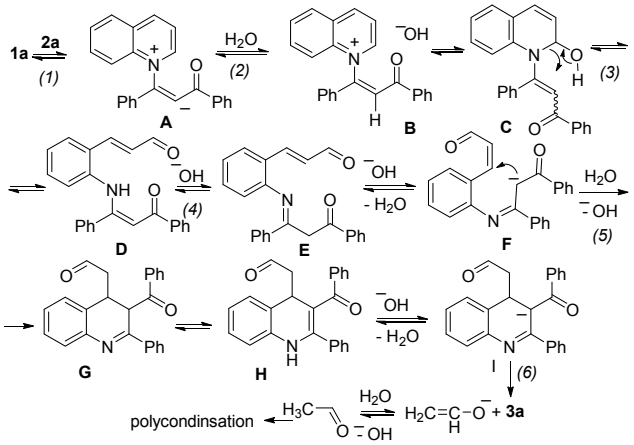
(Scheme 4).

Scheme 4 2,3-C-H Functionalization of quinolines **1a**,**c** with cyanophenylacetylene **2g**

Such fluctuation of yields and their responsiveness to the substrate structure and the reaction conditions definitely show that for each separate reactant pair (**1**/**2**), a special optimization of the experimental procedure is required.

The structures of the synthesized compounds were unequivocally proved by ^1H, ^{13}C and ^{15}N NMR techniques and a signal crystal X-ray analysis (for the compounds **3e,l** see Scheme 3 and SI).

In light of the above experimental results (Table 1 and Scheme 3) and the accompanied comments, the plausible mechanism of the functionalization studied can be schematically represented by the following stepwise sequence (Scheme 5). Step 1. The reversible nucleophilic addition of quinolines **1** by their basic nitrogen to the triple bond of acetylenes **2** to generate 1,3-dipole (zwitterion) having the vinyl carboanionic site (intermediate **A**). Step 2. Neutralization of the negative charge in intermediate **A** by a proton of water to produce ammonium hydroxide intermediate species **B** existing in equilibrium with its covalent form, *N*-ethenyl-2-hydroxyquinoline (intermediate **C**). Step 3. Rearrangement of the intermediate **C** with the ring opening to deliver *o*-(*N*-ethenyl)amino cinnamon aldehyde **D**. Step 4. The KOH-catalyzed 1,3-prototropic shift in the amino-ethenyl group leading to imine **E**. Step 5. The carbanion **F** (deprotonated form of the intermediate **E**) attacks the electrophilic double bond of the cinnamon moiety with the ring closure to afford the dihydroquinoline carbaldehyde **G**, in equilibrium with its NH-



isomer **H**. Step 6. The aromatization of dihydroquinoline carbaldehyde **G** *via* carbanion **I** and the elimination of enolate anion, as good leaving group, to deliver acetaldehyde (or propionic aldehyde in case of quinoline **1b**), which further undergoes the KOH-catalyzed polycondensation.

Scheme 5 Plausible mechanism of the product **3** formation

The above mechanism (Scheme 5) got a robust support by isolation of the dihydroquinoline intermediate **H** (**5g**) in 12% yield along with quinoline **3g** (11%) when the reaction was conducted under mild conditions (**1c**:**2a**:H_2O = 1:1:5, 10 mol% KOH, rt, 336 h) (Scheme 6).

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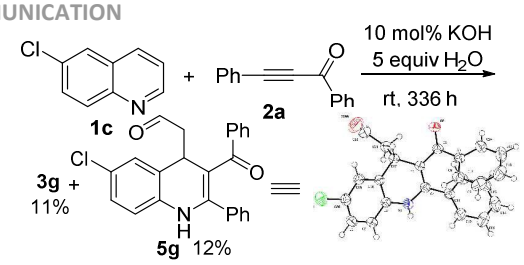

Scheme 6 Formation of the dihydroquinoline **5g** in the reaction between quinoline **1c** and acetylene **2a**

The structure of dihydroquinoline intermediate **5** has been unambiguously established by the ^{1}H, ^{13}C NMR technique and single crystal X-ray analysis.

Other evidence in favour of the proposed mechanism is the result obtained using D_2O. As follows from Scheme 5, no isotope label should be introduced into the final product that indeed is observed experimentally (see SI). Accordingly, the yield of product **3a** with D_2O is considerably lower than with H_2O (19% *vs* 26%, entries 3 and 4, Table 1) that is the expected synthetic consequence of the deuterium isotopic effects.[12] The role of water as a necessary mediator without incorporation into the product molecule also well follows from the mechanistic scheme. The same is true for the understanding the role of KOH as a necessary basic catalyst securing steps 4 and 5. In keeping with the above mechanism is also a "lethargic" character of the mechanism suggesting the reversible formation of the initial 1,3-dipole **A** that triggers the reaction in small concentration (bottle neck) thus slowing down the whole process.

According to the proposed mechanism, the second product of the reaction is an aldehyde. Its formation (on the example of **1a**+**2a** reaction) has been detected by mass-spectrometry (see SI). The absence of deuterium in the acetaldehyde molecule is predictable basing on much faster (up to 10 times)[12] hydrogen transfer compared to that of deuterium (kinetic deuterium isotopic effect).

Additionally, the proposed mechanism implies facilitation of the reaction by the donor substituents in the quinoline ring and acceptor substituents in the acetylenes (and vice versa) that is the case (Scheme 3).

In conclusion, we have elaborated the transition metal-free one-pot double C-H functionalization of quinolines with electron-deficient acetylenes in the KOH/H_2O (MeCN) system under mild conditions. The yields of 2,3-difunctionalized quinolines reach 66%. This unprecedented disassembling / assembling / difunctionalization of the quinoline scaffold unveils a novel facet of the azine / acetylene reactivity and opens acetylene-based short-cuts to the controlled molecular diversity and complexity.

The main results were obtained with Baikal analytical centre of collective using SB RAS.

Conflicts of interest

"There are no conflicts to declare".

Notes and references

‡ Solution of KOH (0.006 g, 20 mol%) in H_2O (0.5 mmol) was added to solution of quinoline **1** (0.5 mmol) and acetylene **2** (0.5 mmol) in MeCN (1 mL). The reaction mixture was stirred 55-60 ^{o}C for 48 h. The solvents were removed under reduced pressure, the residue was purified by column chromatography (SiO_2, $CHCl_3$/toluene/EtOH 20/4/1).

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