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One-pot synthesis of quinazoline derivatives *via* [2+2+2] cascade annulation of diaryliodonium salts and two nitriles†

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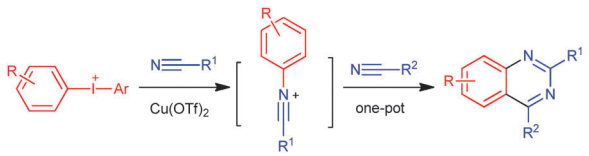
An efficient one-pot approach to multiple substituted quinazolines with diaryliodonium salt 1, and two nitriles 2 has been presented. The reaction enables great flexibility of the substitution patterns on quinazolines and is applicable to two different nitriles to give a regio-selective product.

Quinazolines are one of the most important nitrogen hetero-arenes commonly found in lots of natural products, pharmaceutical molecules, pesticides and functional organic materials. As main building blocks, quinazolines widely occur in many natural alkaloids isolated from plants, animals and various microorganisms.[1] Quinazoline derivatives have also shown diverse biological and therapeutic properties such as anticancer, antitubercular, antibacterial, and antiviral agents.[2] The approval of quinazoline-based drugs – gefitinib (Iressa) and erlotinib hydrochloride (Tarceva) for the treatment of non-small-cell lung cancer,[3] has renewed the passion of developing new synthetic strategies to prepare quinazolines.[4] Traditionally, numerous named reactions, including Niementowski synthesis, Bischler synthesis, Riedel synthesis and modified Duff synthesis,[5] are known for the synthesis of quinazolines. These methods generally proceed *via* classic condensation, addition and substitution reactions, often suffering from a limited source of starting materials and low tolerance of functional groups. Recently, the synthesis of quinazoline derivatives based on C–H-bond activation has been realized and received much attention due to step-economy and a lower requirement of functionality.[6] However, the new synthesis requires much work on the optimization of catalysts, ligands, oxidants and other reaction conditions and is still at the infant stage of being well understood. To meet the high demand of the efficient synthesis of quinazolines (especially those with poly-substituents), it is highly desired to develop synthetic methods with a new strategy. Herein, we would like to report a novel one-pot synthesis of quinazoline derivatives through cascade annulation of diaryliodonium salts and two nitriles. The reactions are catalyzed by $Cu(OTf)_2$ in the [2+2+2] cyclization mode with three molecules, in which the diaryliodoniums provide aryl groups serving as the C2-building block (Scheme 1).



Scheme 1 One-pot synthesis of quinazoline derivatives through cascade annulation of diaryliodonium salts and two nitriles.

As part of our ongoing project of efficiently and ecologically synthesizing nitrogeneous hetero-arenes with diaryliodonium salts, we recently reported a novel method to prepare quinolines with diaryliodonium salts, nitriles and alkynes catalyzed by $Cu(OTf)_2$.[7] The reaction proceeded *via* a series of electrophilic reactions and a key intermediate was the *N*-aryl nitrilium cation generated *in situ* by the reaction of nitrile and iodonium salt in the presence of $Cu(OTf)_2$. So we envisioned that if the alkyne molecule is replaced by a second molecule of nitrile, a quinazoline product would be obtained alternatively. Thus, we examined a simple [A + 2B] annulation: the reaction of diphenyliodonium **1a** with 2 eq. of benzonitriles **2a** at the same condition as used in the previous study. To our delight, the expected 2,4-diphenyl quinazoline **3a** was isolated in 64% yield. When 3 eq. of benzonitrile were used, the yield was increased to 84% (Table 1, entry 1).

Next, a range of aromatic nitriles, including 1-naphthyl and 2-thienyl nitriles were examined and in all cases 2,4-diaryl quinazolines were obtained in good isolated yields (Table 1, entries 2–8). Aliphatic nitriles were also fit for the reaction to give 2,4-dialkyl quinazolines, albeit in lower yields (entries 9 and 10). However, ethyl cyanoformate ($NCCO_2Et$) and diethyl cyanphosphate ($NCPO(OEt)_2$) didn't undergo the quinazoline annulation presumably because of their electron-deficiency (entries 11 and 12).

The above results have shown the facile construction of quinazolines with substituents on the pyrimidine ring. Encouraged by this,

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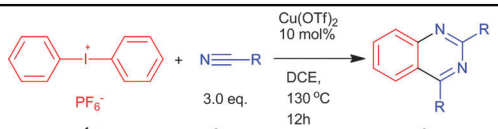
† Electronic supplementary information (ESI) available: Experimental procedures, full characterization including ^1H NMR, ^{13}C NMR, ESI-MS and HRMS data for all new compounds and X-ray crystal structure of **4f**, and X-ray data for **5a**. CCDC 934862 and 935164. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43216e

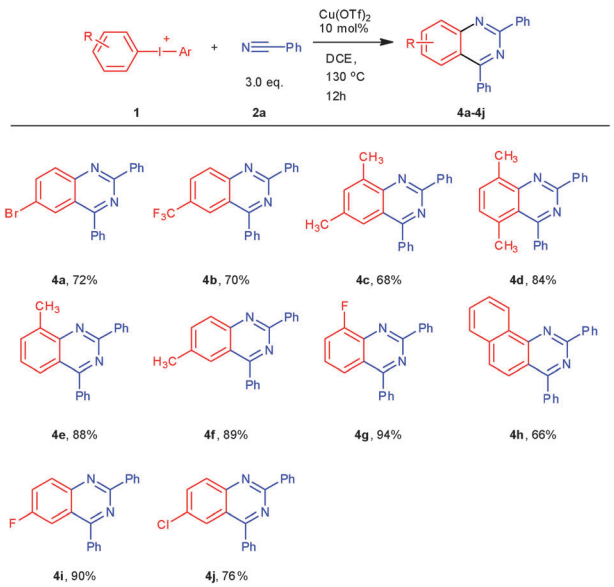
Table 1 Quinazoline **3** formed from the reaction of diphenyliodonium **1a** with various nitriles **2**



Entry	R	Product, isolated yield
1	Ph	**3a**, 84%
2	4-Br-Ph	**3b**, 59%
3	4-CF_3-Ph	**3c**, 66%
4	4-MeO-Ph	**3d**, 90%
5	4-CH_3-Ph	**3e**, 88%
6	2-CH_3-Ph	**3f**, 82%
7	1-Naphthyl	**3g**, 71%
8	2-Thienyl	**3h**, 80%
9	Bn	**3i**, 52%
10	Bu	**3j**, 54%
11	CO_2Et	NP
12	$PO(OEt)_2$	NP

we introduced substituents on the phenyl ring, by the use of functionalized diaryliodonium salts. Various diaryliodonium triflates were readily prepared by known methods.[8,9] Diaryliodoniums with a range of substituents involving 4-bromo, 4-trifluoromethyl, 2,4- and 2,5-dimethyl, 2- and 4-methyl, 2- and 4-fluoro, 4-chloro and benzo groups all worked well with 3.0 eq. of benzonitrile **2a** to give the desired products **4** (Scheme 2). The structure of **4f** was further confirmed by XRD of its single crystal (Fig. 1, CCDC 934862).

These successful examples are actually realized with two components *via* the [A + 2B] cyclization mode and provide quinazolines with identical substituents at the 2- and 4-positions. Consequently, we attempted to prepare quinazolines by the use of two different nitriles, which are obviously more useful but challenging due to the close reactivity. To avoid the formation of regio-isomers, the diaryliodonium salt and the first nitrile (1.1 : 1) were allowed to react for a while converting all of the first nitrile into the *N*-aryl nitrilium salt discretely before the second nitrile was added. With the first nitrile



Scheme 2 The synthesis of quinazolines **4** from various diaryliodonium triflates **1** with benzonitrile **2a**.

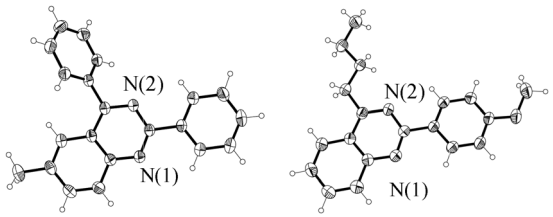
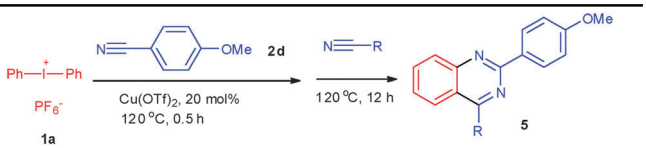


Fig. 1 Crystal structure of **4f** (left) and **5a** (right).

Table 2 Quinazoline **5** formed from the reaction of **1a** and **2d** with various second nitriles **2**

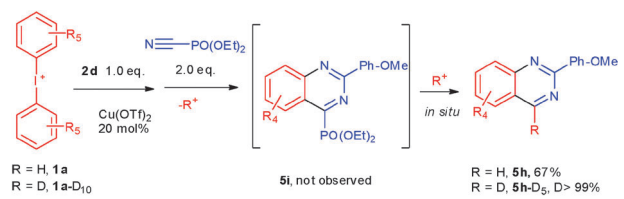


Entry	R	Product, isolated yield
1	Bu	**5a**, 69%
2	Bn	**5b**, 50%
3	4-CF_3-Ph (1 eq. 100 °C)	**5c**, 72%
4	$BrCH_2$	**5d**, 55%
5	Br	**5e**, 65%
6	$ClCH_2$	**5f**, 57%
7	CO_2Et	**5g**, 60%

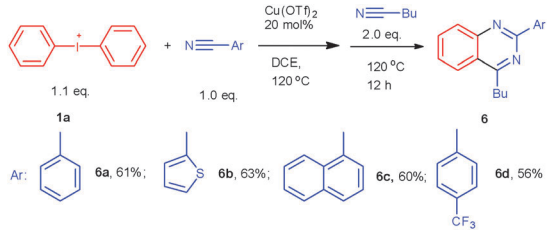
exemplified as 4-methoxy benzonitrile **2d**, the optimized procedure was: diphenyliodonium **1a** (1.1 eq.) and 4-methoxybenzonitrile **2d** (1.0 eq.) were reacted at 120 °C for 0.5 h and then a second nitrile was added to continue reacting for 12 h to produce quinazoline **5** respectively (Table 2). The second nitriles with Bu, Bn or 4-trifluoromethyl phenyl groups gave the desired product in synthetically useful yields. The structure of **5a** was unequivocally confirmed by XRD analysis (Fig. 1, CCDC 935164).

To our delight, the second nitriles with bromo, bromomethyl, chloromethyl, or ester groups also worked well to give functionalized quinazolines which were not readily accessible *via* traditional quinazoline synthesis methods. The reaction of **1a** and **2d** with diethyl cyanophosphate ($NCPO(OEt)_2$) afforded protonated product **5h** instead of **5i** (Scheme 3). The protonated product was already formed before the reaction was quenched. The deuteration reaction proved the H-atom at the 4-position came from diphenyliodonium **1a** and the mechanism for this specific reaction is not clear at present.

In this [A + B + C] cyclization, the first nitrile is possibly alternated to other aromatic nitriles under re-optimized conditions and selected examples with isolated yield are shown in Scheme 4 (the second nitrile was exemplified as valeronitrile **2j**). Unfortunately, the use of alkyl nitrile as the first nitrile was unsuccessful (around 10% yield whatever the second nitrile was).

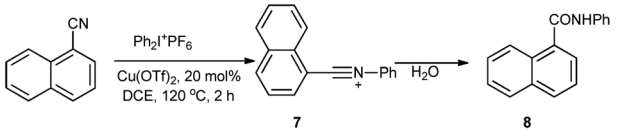


Scheme 3 The investigation of **5h** formed in the reaction of **1**, **2d** and diethyl cyanophosphate ($NCPO(OEt)_2$).



Scheme 4 Quinazoline **6** formed from the reaction of **1a** and aromatic nitrile with valeronitrile **2j** as the second nitrile (see ESI† for details).

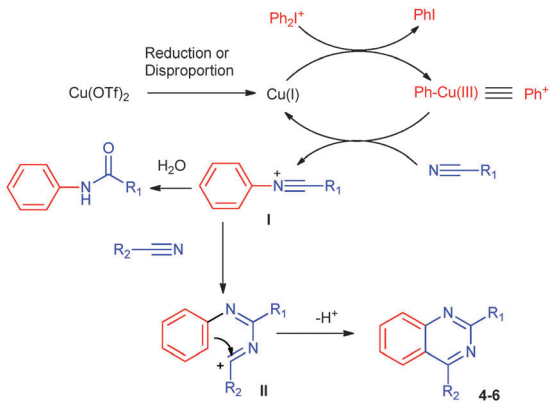
In the preparation of these quinazolines, we often observed *N*-aryl amide as a byproduct by GC-MS (around 10% yield). This phenomena was attributed to the hydrolysis of the *N*-aryl nitrilium salt formed during the reaction.[7,10] Actually, Ph_2IPF_6 **1a** and 1-naphthonitrile (1 eq.) were heated with $Cu(OTf)_2$ (0.2 eq.) at 120 °C for 2 h to give *N*-phenyl 1-naphthonitrilium **7**, which was identified by HRMS. The hydrolysis of **7** gave *N*-phenyl-1-naphthamide **8** in isolated 88% yield (eqn (1), see also ESI†).



(1)

Based on the above findings and previous report, we proposed a mechanism for this reaction with an Ar–Cu(III) species involved shown in Scheme 5. At the beginning, $Cu(OTf)_2$ is converted to Cu(I) *via* reduction or disproportion and then oxidative addition to the Cu(I) species by the diaryliodonium salt (exemplified as Ph_2I^+) gives a Ph–Cu(III) species,[11] which transfers the phenyl group to the nitrile to give *N*-phenylnitrilium intermediate **I**. Intermediate **I** would produce the anilide by hydrolysis. *N*-phenylnitrilium species **I** is quickly attacked by the second nitrile to give intermediate **II**, which undergoes an electrophilic substitution on the aryl ring to give the quinazoline product.

In summary, an efficient one-pot approach to multiple substituted quinazolines with diaryliodonium salts **1**, and two nitriles **2** has been presented. The reactions are applicable to two different nitriles to give a regio-selective product. This strategy of electrophilic annulations enables great flexibility of the substitution patterns on quinazolines and marks a significant departure from known methods based on traditional carbonyl condensation,



Scheme 5 Proposed mechanism.

and elimination chemistry. The facile construction of the quinazoline skeleton and simple manipulation might be useful for the design and generation of a quinazolines' library.

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