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Synthesis of Substituted Quinazolin-4(3*H*)-imines From Aryldiazonium Salts, Nitriles and 2-Cyanoanilines via A Metal-Free Tandem Approach

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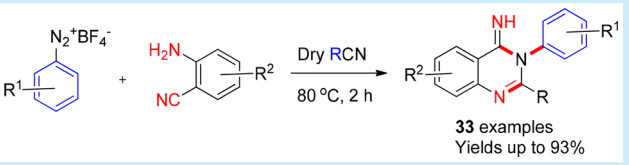
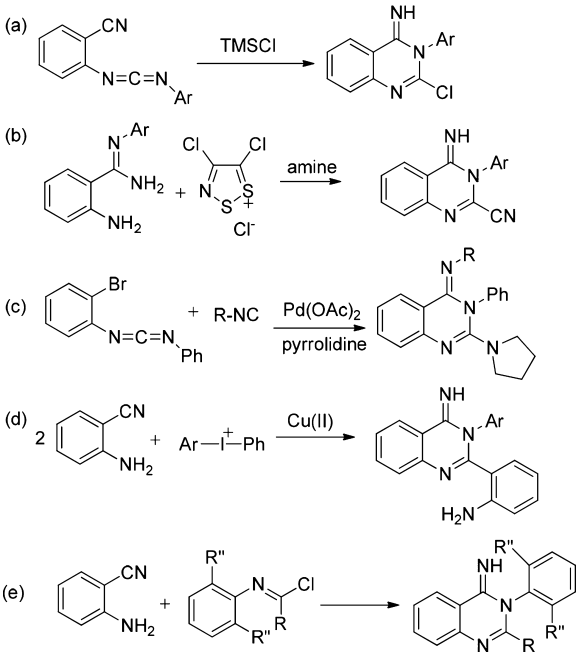
Supporting Information

ABSTRACT: A transition metal-free synthesis of multisubstituted quinazolin-4(3*H*)-imines has been realized by the direct reaction of aryldiazonium salts, nitriles, and 2-cyanoanilines in a one-pot fashion. This strategy utilizes the *in situ* formation of reactive *N*-arylnitrilium intermediate, which undergoes further tandem cyclization with consecutive formation of N−C bonds. Broad functional group compatibility, mild conditions, shorter time, and operational simplicity are the notable features of this report.



Quinazolin-4(3*H*)-imines represent a privileged class of annulated six-membered aza-heterocycles with diverse biological activities such as antimicrobial,[1] antihypertensive,[2] antiproliferative,[3] cholinesterase,[4] and cMET kinase inhibitory properties.[5] Furthermore, these molecules could serve as precursors for quinazolin-4(3*H*)-one derivatives.[6] Because of their biological portfolio, several appealing synthetic approaches were reported in recent years and are summarized in Scheme 1.[7] Rayat et al. demonstrated a Lewis acid mediated three-step synthesis of 3-aryl-2-halo-4(3*H*)-quinazoliniminium halides from heteroenyne-allenes (Scheme 1a).[7a] A base promoted one-step synthesis of 3-aryl-4-imino-3,4-dihydroquinazolin-2-carbonitriles from 2-amino-*N*′-arylbenzamidines and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) was achieved by Koutentis' group (Scheme 1b).[7b] A multicomponent synthesis of quinazolin-4(3*H*)-imines via Pd-catalyzed reaction of isocyanide, carbodiimide in the presence of a cyclic amine or alcohol was developed by Wu's group, in which the insertion of isocyanide was illustrated to be the key step (Scheme 1c).[7c] Recently, Chen and co-workers described an efficient synthesis of 2-aminoaryl substituted quinazolin-4(3*H*)-imines via Cu-$(OTf)_2$ catalyzing the tandem reaction of diaryliodonium salts with 2 equiv of *o*-cyanoanilines at an elevated temperature (Scheme 1d).[7d] In addition, Rojas and co-workers reported that quinazolin-4(3*H*)-imines could be also prepared by reaction of phenylchloroimines with 2-aminobenzonitrile (Scheme 1e).[7e] Finally, Szczepankiewicz's group reported the preparation of desired imines from from 2-amino-*N*′-arylbenzamidines and triethyl orthoformate.[7h]

Scheme 1. Recent Works in Preparation of Quinazolin-4(3*H*)-imines



Despite the proven advancements, there are limitations due to the complicated prefunctionalized sites, multistep procedures, metal catalysts, harsh conditions, and the formation of waste byproduct. Thus, development of a convenient and atom-economical synthetic route from easily available precursors under mild conditions is highly desirable.

Aryldiazonium salts, an important class of readily available and inexpensive precursors, have been used in various organic reactions.[8] In continuation of our recent studies on the use of aryldiazonium salt as the precursor for the preparation of various heterocycles,[9] herein, we report a general, mild, and transition metal-free synthesis of quinazolin-4(3*H*)-imines (Scheme 2). We envision that the reactive *N*-arylnitrilium

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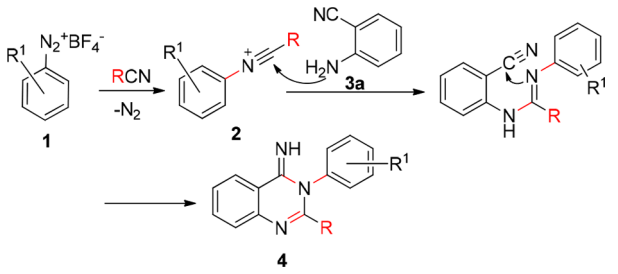
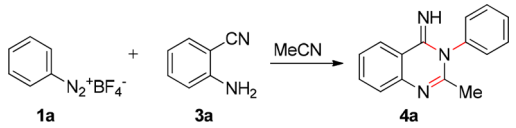
Scheme 2. Our Proposed Synthetic Approach



intermediate (**2**), generated *in situ* from the reaction of the arenediazonium salt with a nitrile molecule,[9,10] could further react with *o*-cyanoanilines via amination/tandem cyclization to afford quinazolin-4(3*H*)-imines directly.

To probe our hypothesis, the reaction of phenyldiazonium tetrafluoroborate (**1a**) with anthralonitrile (**3a**) in anhydrous MeCN was carried out at room temperature for 12 h. To our delight, the expected 2-methyl-3-phenylquinazolin-4(3*H*)-imine was obtained in 78% isolated yield. When the reaction was carried out at 80 °C for 2 h, the desired compound **4a** was isolated in 92% yield as a sole product. Lowering or raising the reaction temperature resulted in diminished yields (Table 1, entries 3−4). Performing the reaction in the presence of base or in organic solvents, such as toluene, THF, DMSO, and DCE, led to inferior results (Table 1, entries 5−9).

Table 1. Reaction Optimization[a]

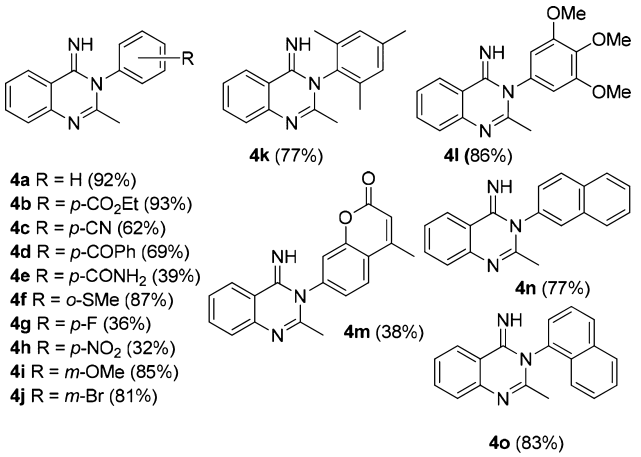


entry	solvent	temp	*t* (h)	yield (%)[b]
1	MeCN	rt	12	78
2	MeCN	80 °C	2	92(95)
3	MeCN	60 °C	2	(88)
4	MeCN	110 °C	1	(79)
5[c]	MeCN	80 °C	2	trace
6	MeCN/toluene[d]	reflux	12	ND[e]
7	MeCN/THF[d]	reflux	12	ND[e]
8	MeCN/dmso[d]	100 °C	12	ND[e]
9	MeCN/$ClCH_2CH_2Cl$[d]	reflux	12	trace

[a]Reaction conditions: a mixture of **1a** (0.52 mmol), **3a** (0.52 mmol), and acetonitrile (2 mL) in a reaction tube. [b]Yields given in parentheses were determined by ^1H NMR; others refer to isolated yields. [c]K_2CO_3 (1 equiv) was added in the reaction mixture. [d]MeCN (2.6 mmol) in solvent (2 mL). [e]ND = not detected.

With the optimized conditions in hand, the scope of the aryldiazonium salts for this reaction was studied, and the results are summarized in Scheme 3. The reaction tolerated a variety of electronically distinct substituents on the aryl ring (Scheme 3, **4b−4j**). All desired products were isolated with moderate to excellent yields. To our delight, varieties of functional groups such as ester, nitrile, arylketone, amide, bromo, ether, and thioether were compatible under the reaction conditions and furnished the expected compounds in synthetically useful yields. However, it was noticed that aryldiazonium salts bearing *p*-F and *p*- NO_2 substituents furnished the desired products **4g** and **4h**, respectively, in acceptable yields. Preparation of such functionalized quinazolin-4(3*H*)-imines through other existing

Scheme 3. Reactions of Various Aryldiazonium Salts with 3a in MeCN[a]

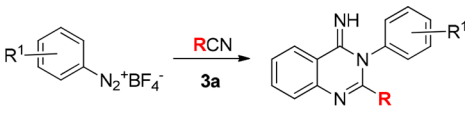


[a]Reaction conditions: $ArN_2^+BF_4^-$ (0.52 mmol) and **3a** (0.52 mmol) in MeCN (2 mL) were heated at 80 °C for 2 h; isolated yields.

methods would be challenging and may demand multistep synthesis. Multiple substituted and fused aryldiazonium salts were also viable and provided the desired compounds in excellent yields (Scheme 3, **4k−4m**). Notably, 2,4,6-trimethyl phenyldiazonium salt with distinct steric substituents afforded **4k** in good yield. Pleasingly, the use of 1-naphthyl and 2-naphthyl diazonium salts also produced the corresponding naphthyl bound quinazolin-4(3*H*)-imines in excellent yields (Scheme 3, **4n**,**4o**). To further demonstrate the practicality and efficiency of the developed method, a gram-scale synthesis of quinazolin-4(3*H*)-imine **4a** was performed. Typically, reaction of **1a** (1.1 g) with **3a** (0.68 g) in acetonitrile (20 mL) delivered **4a** (1.16 g, 87%) [***Caution:*** *The aryldiazonium tetrafluoroborates are potentially explosive upon heating and* reactions *should be performed using appropriate precautions.*]

Next, the limitation of this method with various nitriles was investigated (Scheme 4). A series of differently substituted benzonitriles was successfully used in this tandem reaction to furnish *N*-aryl substituted quinazolin-4(3*H*)-imines in yields ranging from 48−79% (Scheme 4, **5a−5e**). The use of 1°, 2°, 3° aliphatic nitriles gave the desired products in reasonable

Scheme 4. Reaction Scope of Various Nitriles[a]



5a R = C_6H_5-, R^1 = H (79%)
5b R = C_6H_5-, R^1 = *o*-SMe (54%)
5c R = *o*-MeC_6H_4-, R^1 = H (72%)
5d R = *p*-MeC_6H_4-, R^1 = H (76%)
5e R = *m*-BrC_6H_4-, R^1 = H (62%)
5f R = $CH_3CH_2CH_2$-, R^1 = H (81%)
5g R = i-Pr, R^1 = H (72%)
5h R = *t*-Bu, R^1 = H (66%)
5i R = $ClCH_2$-, R^1 = H (76%)
5j R = $PhCH_2$-, R^1 = H (83%)
5k R = thiaphen-2-yl-, R^1 = H (87%)
5l R = naphth-2-yl-, R^1 = H (48%)

[a]Reaction conditions: diazonium salt (0.52 mmol) and **3a** (0.52 mmol) in RCN (2 mL) were heated at 80 °C for 2 h; isolated yields.

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yields (Scheme 4, **5f**–**5h**). Notably, α-chloroacetonitrile was also applicable for this reaction to provide the desired compound **5i** in 76% yield (Scheme 4, **5i**). The chloro group remains intact on the aliphatic side chain, providing a potential handle for further transformation. Other nitriles such as benzyl, naphthyl, and heteroaryl nitriles also led to the products in moderate to excellent yields (Scheme 4, **5j**–**5l**). X-ray crystallography of **5k** was determined to support the structure of the compound (Figure 1). Malonic mononitrile, with an

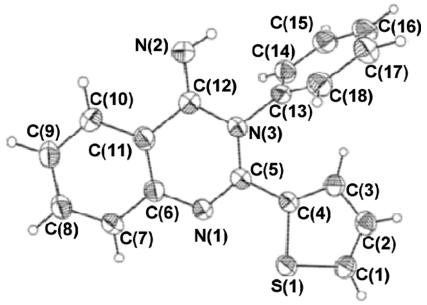
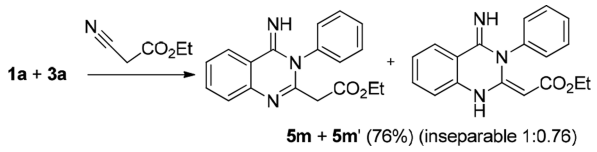


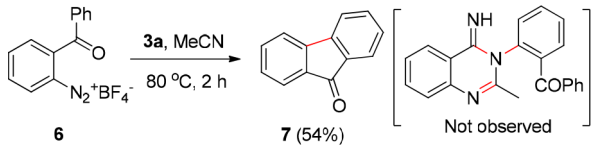
Figure 1. ORTEP Plot of **5k** (30% probability ellipsoids).

active methylene unit in the molecule, reacted with **1a** and **3a** smoothly to render a mixture of tautomers (**5m** and **5m′**) as an inseparable mixture (eq 1):



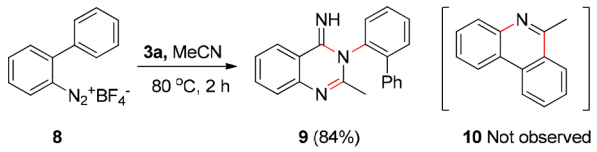
5m + **5m′** (76%) (inseparable 1:0.76)

Intriguingly, when aryldiazonium salt **6** bearing an adjacent benzoyl group was employed in this reaction, an intramolecular arylation took place to yield 9*H*-fluoren-9-one as the sole product (eq 2). In contrast to our previous observations,[9a,b,d]



6 **7** (54%)

aryldiazonium salt **8** reacted with **3a** in acetonitrile to give **9** in excellent yield instead of the formation of 6-methylphenanthridine (**10**) (eq 3). Evidently, the rate of intermolecular

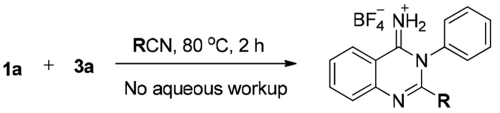


8 **9** (84%) **10** Not observed

amination/tandem cyclization appears to be faster than that of intramolecular arylation of *N*-arylnitrilium ion. Moreover, stable quinazolin-4(3*H*)-iminium salts could be conveniently obtained by simple trituration of crude reaction residue with ether, thus making the overall procedure more sustainable (Scheme 5):

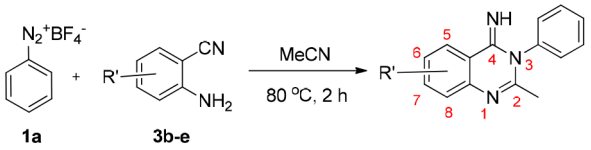
The scope of this method was further applied to various substituted 2-cyanoanilines (**3b**–**3e**). As shown in Scheme 6, *o*-cyanoanilines with bromo and chloro substitutents at different positions were smoothly reacted with **1a** and produced the corresponding quinazolin-4(3*H*)-imines in good yields

Scheme 5. Isolation of Quinazolin-4(3*H*)-iminium Salts



11, **R** = Me (97%)
12, **R** = Ph (74%)

Scheme 6. Reaction Scope of Various 2-Cyanoanilines[a]



1a 3b-e

13a R′ = 6-Br (68%)
13b R′ = 6-Cl (83%)
13c R′ = 8-Cl (88%)
13d R′ = 6-(2-MeC$_6$H$_4$) (79%)

[a]Reaction conditions: **1a** (0.52 mmol) and **3** (0.52 mmol) in MeCN (2 mL) were heated at 80 °C for 2 h; isolated yields.

(Scheme 6, entries **13a**–**13c**). The use of 5-aryl-2-aminobenzonitrile delivered the desired product **13d** in 79% isolated yield. However, reaction of **1a** with 2-amino-1*H*-indene-3-carbonitrile in MeCN led to a mixture of unidentified products with no formation of the expected product.

In summary, we have reported a facile and sustainable method for the preparation of quinazolin-4-(3*H*)-imines via an intermolecular amination/tandem cyclization from readily available aryldiazonium salts, nitriles, and 2-cyanoanilines. A wide range of typical functional groups are tolerated, and the corresponding products are isolated in high yields under transition-metal free conditions. Experimental simplicity and mild reaction conditions are the advantage of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02822.

Experimental procedures; details of characterization of all new compounds; complete bond distances and bond angles of **5k** (PDF)
Crystal data (CIF)

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Notes

The authors declare no competing financial interest.

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