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Base-Promoted Synthesis of Polysubstituted 4-Aminoquinolines from Ynones and 2-Aminobenzonitriles under Transition-Metal-Free Conditions

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Dedication (optional)

Abstract: A transition-metal-free and base-promoted one-pot reaction of ynones with 2-aminobenzonitriles is described. The reaction was initiated through sequential aza-Michael addition/intramolecular annulation to afford various multisubstituted 4-aminoquinolines and 4-amino-1,8-naphthyridines in good to excellent yields. Operational simplicity, high atom-economy with broad substrate scope makes this protocol more attractive. Also, the gram-scale synthesis and further transformation of the product were studied. Additionally, 2-haloarylyones as substrate provide N-arylquinolones as the sole product via the S_NAr mechanism.

Keywords: Aminoquinolines • S_NAr • 2-Aminobenzonitrile • Ynones • Aza-Michael addition

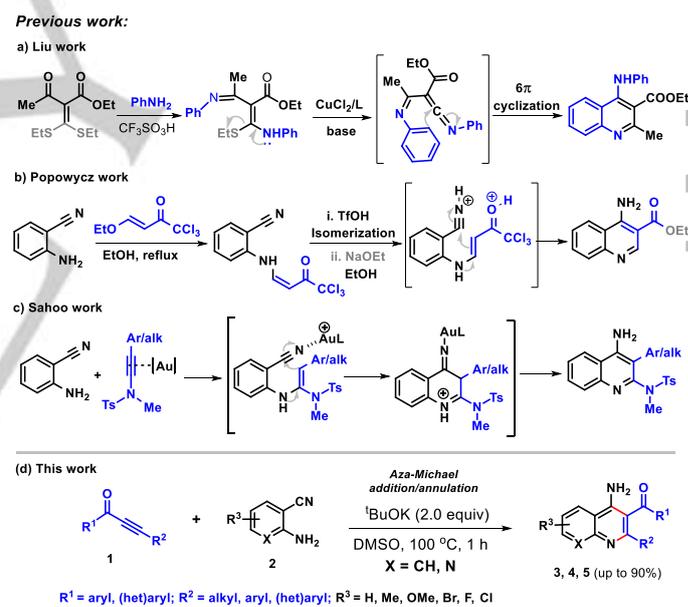
Malaria is a serious infectious disease caused by Plasmodium species, still, become a major global health problem in the world.^[1] Quinoline nucleus-containing drugs have been attracted due to their extensive application in medicinal chemistry.^[2] Among them, 4-aminoquinolines are potential drugs candidate for the treatment of malaria (Figure 1, A–C).^[3–5] For instance, chloroquine and hydroxychloroquine (HCQ) used as antimalarial drugs long ago. Recently, it emerged as a promising drug for the treatment of SARS-CoV-2 disease.^[6] Additionally, some analog of 4-aminoquinolines used analgesics or acetylcholinesterase inhibitors.^[7] However, chloroquine has been restricted due to resistant strains of *P. falciparum* and toxicity problems.^[8] Therefore; syntheses of new analog of 4-aminoquinolines are of continuous interest to discover the antimalarial activity.^[9]



Figure 1. Representative 4-aminoquinolines drugs

Several synthetic approaches have been reported for 4-aminoquinoline, which include the Friedlander reaction^[10], reduction of 4-azidoquinoline^[11], Buchwald–Hartwig amination.^[12] Other alternative

routes for access of 4-aminoquinolines were multi-component reaction^[13], metal-catalyzed cascade reaction,^[14] and cyclization with ynamides.^[15] In a similar context, Liu et al., developed Cu(II)-catalyzed desulfurative 6π electro-cyclization reaction for the synthesis of 4-aminoquinolines (Scheme 1a).^[16] In 2017, Popowycz and co-workers have demonstrated a multi-step synthesis of 4-aminoquinoline under super acidic conditions (Scheme 1b).^[17] Recently, Sahoo et al., developed the synthesis of 4-aminoquinoline from ynamides with 2-aminobenzonitriles via Au(I)-catalyzed nitrile activation (Scheme 1c).^[18]



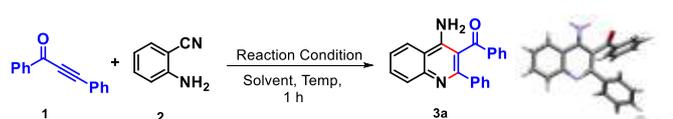
Scheme 1. Synthesis of Polysubstituted 4-Aminoquinolines

However, use of expensive catalyst, additive, limitation to the sensitive substrate and harsh reaction condition makes these methods less fruitful. These limitations encourage us to develop a novel practical approach to prepare highly substituted 4-aminoquinolines in one-step with a high atom-economy. In our continuing interest on base-mediated heterocyclic synthesis^[19] herein, we report base-promoted subsequently aza-Michael addition/cascade annulation of 2-amino benzonitriles with ynones for the synthesis of

highly substituted 4-aminoquinoline under transition-metal-free conditions (Scheme 1d).

We began our investigation employing 1,3-diphenylprop-2-yn-1-one **1a** and 2-aminobenzonitrile **2a** as model substrates. When the reaction of **1a** (0.50 mmol) and **2a** (0.60 mmol) was carried out in presence of K^tOBu (2.0 equiv) in dimethylsulfoxide solvent at 25 °C, the desired product substituted 4-aminoquinoline **3a** was obtained in 20% yield (Table 1, entry 1). To our delight, the desired product **3a** was obtained in high yield when the temperature of the reaction was increased from 25 °C to 100 °C (Table 1, entries 2–4). At 120 °C, the yield of **3a** was significantly dropped which possibly due to hydrolysis of **2a** (Table 1, entry 5).^[20] Increase of K^tOBu to 3.0 equiv did not significantly affect the yield of **3a** (Table 1, entry 6). Additionally, no desired product was formed in absence of a base (Table 1, entry 7). After screening other solvents, DMSO was proved to be the best choice (Table 1, entries 8–13).

Table 1. Optimization of Reaction Conditions^[a]



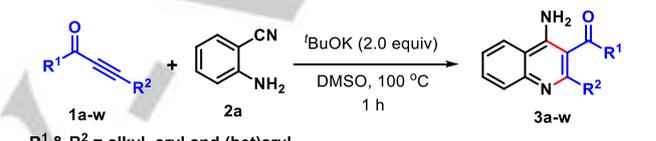
Entry	Base (equiv)	Solvent	Temp. (°C)	Yield of 3a (%) ^[b]
1	K ^t OBu (2.0)	DMSO	25	20
2	K ^t OBu (2.0)	DMSO	60	45
3	K ^t OBu (2.0)	DMSO	80	70
4	K ^t OBu (2.0)	DMSO	100	85
5	K ^t OBu (2.0)	DMSO	120	65
6	K ^t OBu (3.0)	DMSO	100	84
7	–	DMSO	100	0
8	K ^t OBu (2.0)	DMF	100	71
9	K ^t OBu (2.0)	DMA	100	58
10	K ^t OBu (2.0)	NMP	100	50
11	K ^t OBu (2.0)	dioxane	100	45
12	K ^t OBu (2.0)	toluene	100	0
13	K ^t OBu (2.0)	EtOH	100	0
14	Li ^t OBu (2.0)	DMSO	100	68
15	Cs ₂ CO ₃ (2.0)	DMSO	100	73
16	KOH (2.0)	DMSO	100	60
17	NaOH (2.0)	DMSO	100	25
18	K ₃ PO ₄ (2.0)	DMSO	100	45
19	DBU (2.0)	DMSO	100	40
20	DABCO (2.0)	DMSO	100	0

^[a] Reactions were performed using **1a** (0.5 mmol, 1.0 equiv), **2a** (0.6 mmol) and base (2.0 equiv) in 2.0 mL of solvent. ^[b] Isolated yield. DMF = dimethylformamide, DMA = Dimethylacetamide; CCDC No. (2027873)

The effect of other bases was also investigated. For example, Inorganic bases such as Li^tOBu, Cs₂CO₃, KOH, K₃PO₄ make possible the desired product **3a** in relatively lower yields (Table 1, entries 14–18). Furthermore, when organic base such as DBU and DABCO was employed in the reaction, only DBU was found effective to deliver the desired product in acceptable yield (Table 1 entries 19–20). The product **3a** was further characterized by single X-Ray crystallography.^[21]

With these optimized conditions in hand, we then examine the scope and generality of this reaction by employing various ynones and 2-aminobenzonitrile substrates (Table 2). Firstly, R² substituents on the terminal alkynes of ynones were investigated. A variety of ynones substrates (**1b–1g**) with electron-donating substituents on aryl groups could react with 2-aminobenzonitrile **2a**, providing the corresponding product **3b–3g** in excellent yields.

Table 2. Substrate Scope of Ynones^{[a], [b]}



R¹ & R² = alkyl, aryl and (het)aryl.

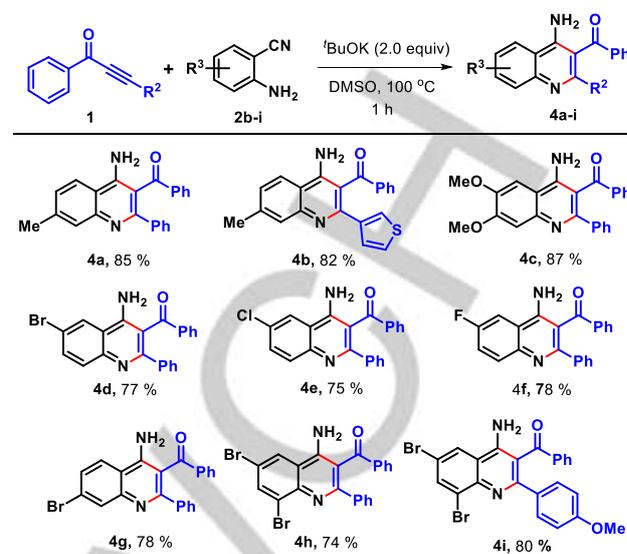
3a , R ² = H, 85% (80%) ^[c]	3h , R ² = 4- ^t Bu, 82%; 3i , R ² = 4- ^t Bu, 84%; 3j , R ² = 4-F, 65%; 3k , R ² = 4-CF ₃ , 60%
3b , R ² = 2-Me, 84%	3l , R ² = 2-Me, 84%
3c , R ² = 3-Me, 86%	3m , R ² = 3-Me, 85%
3d , R ² = 4-Me, 88%	3n , R ² = 4-Me, 80%
3e , R ² = 4-Et, 89%	3o , R ² = 4-Et, 75%
3f , R ² = 4-OMe, 90%	3p , R ² = 4-Et, 72%
3g , R ² = 3-OMe, 87%	3q , R ² = 4-OMe, 86%; 3r , R ² = 4-Me, 90%
3s , R ² = 4-OMe, 83%	3t , R ² = 4-OMe, 82%
3v , R ² = 4-OMe, 88%	3u , R ² = 4-Me, 85%
3w , R ² = 4-OMe, 45%	3x , R ² = 4-Me, 0%

^[a] Reactions condition: **1a–w** (0.5 mmol, 1.0 equiv), **2a** (0.6 mmol) and K^tOBu (2.0 equiv) in DMSO (2.0 mL) for 1h at 100 °C. ^[b] Isolated yield. ^[c] Gram scale

Interestingly, the presence of bulky substituents on the aryl group did not influence this transformation and afforded the desired product **3h–i** in 82% and 84% yields respectively. However, electron-withdrawing group (F–, CF₃–) substituted ynones (**1j–1k**) were provided corresponding products **3j–k** in moderate yields. When R² as fused aryl and heteroaryl group in ynones were used as starting substrates, the corresponding products **3l–3m** were furnished in excellent yields. Notably, ynones with the R² as aliphatic groups such as cyclohexenyl (**1n**), cyclohexyl (**1o**), and cyclopropyl (**1p**) were viable substrates and afforded desired products **3n–3p** in good yields. No desired product was observed when R² was a 2-pyridyl group. Next, the influence of R¹ groups in ynones was also screened. The substrates having electron-releasing substituents such as –OMe and –Me at 4-position afforded desired products **3q–r** in 86% and 90% yields respectively. Ynones containing a heterocyclic structural skeleton, thienyl, and furyl, for example, were reacted well under the standard reaction condition to deliver the corresponding 4-aminoquinolines **3s–3t** in good yields respectively. The ynones with the electron-donating group as R² and the heteroaryl group as R¹ provided the desired product **3u** and **3v** in 85 and 88% yield, respectively. The substrate having sulfonyl group is also provides a successfully desired product **3w** in 45% yield. The corresponding product **3x** was not formed when R¹ group is methyl in ynone substrate probably due to the self-condensation reaction in presence of acidic methyl group. It is noteworthy that a gram-scale reaction was performed under the standard condition that provides product **3a** in 80% yield.

To understand the generality and practicability of this reaction, we tested a range of 2-aminobenzonitriles **2** with various ynones (Table 3). 2-Aminobenzonitriles (**2b–c**) having electron-donating substituents such as 4-methyl and 4,5-dimethoxy group on reacting with ynones **1a**, **1m**, furnished the desired products **4a–c** in excellent yield. Notably, halogen (5-Cl, 5-Br, 5-F) substituted 2-aminobenzonitriles (**2d–f**) were also compatible with the reaction and provided the corresponding product **4d–f** in good yields. The reaction of 2-amino-4-bromobenzonitrile (**2g**) and 2-amino-3,5-dibromobenzonitrile (**2h**) with **1a**, afforded the corresponding product **4g** and **4h** in 78% and 74% yields respectively. Highly substituted 4-aminoquinoline **4i** was obtained in 80% yield when substrate **1f** reacted with **2h** under standard conditions. Unfortunately, the reaction of 2-amino-5-nitro-benzonitrile containing a strong electron-withdrawing nitro group, failed to produce the desired product, probably due to the lower nucleophilicity of the amine moiety.

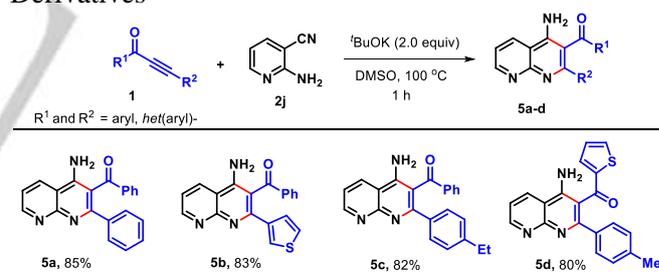
Table 3. Scope of Substituted 2-Aminobenzonitriles^[a].
[b]



[a] Reactions condition: **1** (0.5 mmol, 1.0 equiv), **2b–i** (0.6 mmol) and K^tOBu (2.0 equiv) in DMSO (2.0 mL) for 1 h at 100 °C. [b] Isolated yield.

Gratifyingly, the scope of this protocol was further extended towards the synthesis of biologically important amino-1,8-naphthyridine derivatives **5a–d** which are still not much explored.^[22] To our delight, the reaction of 2-aminonicotinonitrile **2j** with various ynones **1** proceeded smoothly to afford the corresponding products **5a–d** in good yields (Table 4).

Table 4. Synthesis of 4-Amino-1,8-naphthyridine Derivatives^[a]. [b]

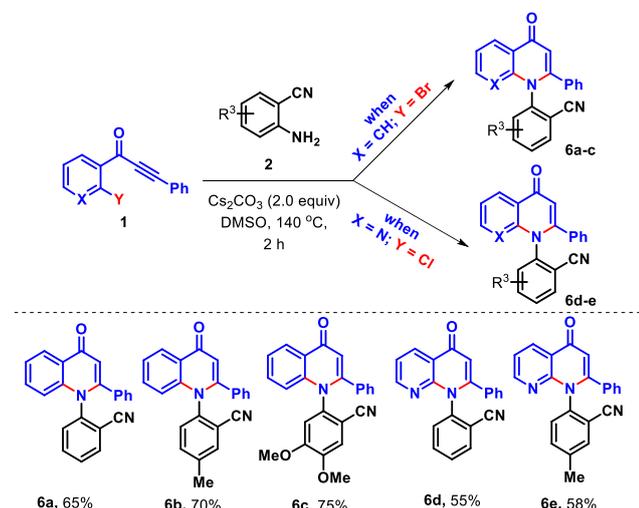


[a] Reactions condition: **1** (0.5 mmol, 1.0 equiv), **2j** (0.6 mmol) and K^tOBu (2.0 equiv) in DMSO (2.0 mL) for 1 h at 100 °C. [b] Isolated yield.

Surprisingly, the desired 4-aminoquinoline as a product was not obtained when reaction performed between *ortho*-haloaryl ynones with various substituted 2-aminobenzonitriles under optimized protocols. After switching base to Cs₂CO₃ and increase the temperature up to 140 °C, the *N*-arylquinolones **6a–c** was formed as a solo product when 2-bromophenylynone **1x** react with substituted 2-aminobenzonitriles *via* tandem aza-Michael addition followed by aromatic nucleophilic substitution reaction in good yields. Additionally, 1,8-naphtharidone **6d** and **6e** were also obtained in 55% and 58% yields

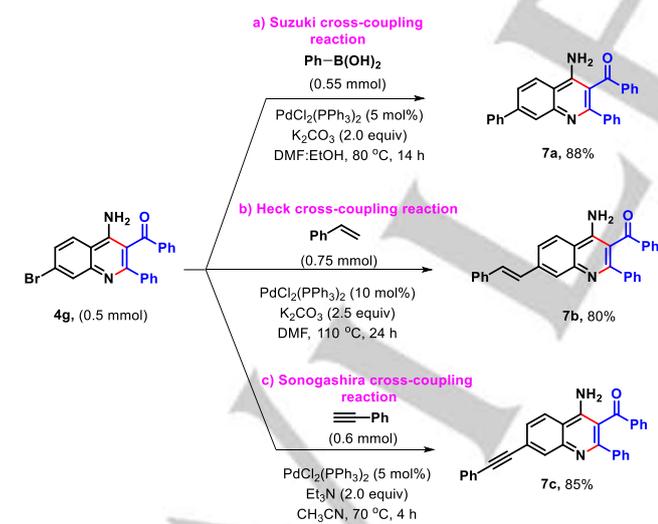
respectively when 2-chloropyridyl ynone **1y** was used as starting substrate. The formation of the N-arylquinolones suggests that after aza-Michael addition, nucleophilic substitution on halogen is more favorable than a nucleophilic attack on cyano group of 2-aminobenzonitriles (Table 5).^[23]

Table 5. Substrate Scope of *o*-Haloarylylones^{[a], [b]}



^[a] Reactions condition: **1** (0.5 mmol, 1.0 equiv), **2** (0.6 mmol) and Cs₂CO₃ (2.0 equiv) in DMSO (2.0 mL) for 2 h at 140 °C. ^[b] Isolated yield.

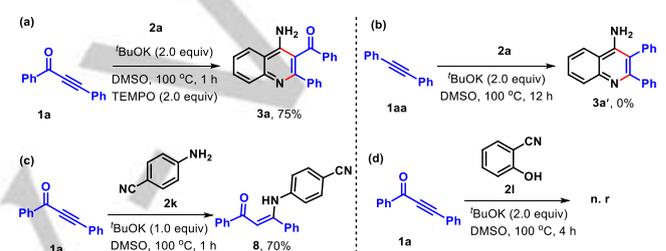
The synthetic utility of the product was further demonstrated. The product **4g** underwent various palladium-catalyzed synthetic transformations such as Suzuki, Heck, and Sonogashira coupling to furnished the diversified products **7a-c** in good yields (Scheme 2).



Scheme 2. Synthetic Transformation of 4-Aminoquinoline

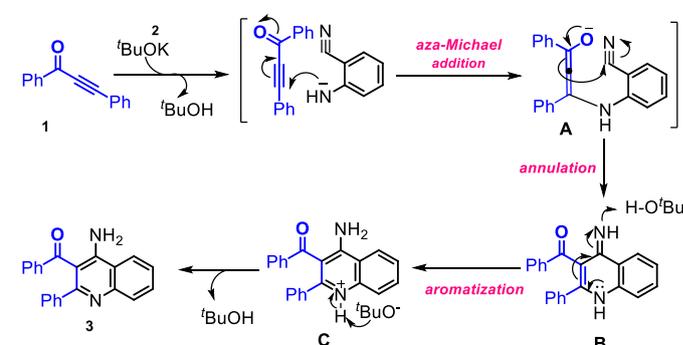
To gain mechanistic insights into the current protocol, several control experiments were performed (Scheme 3). To find the reaction pathway whether ionic or radical in a basic medium, we have used 2.0 equiv. of TEMPO as a radical scavenger in the reaction

of **1a** and **2a**. The formation of product **3a** in 75% yield confirmed that the reaction did not proceed via the radical pathway (Scheme 3a). No desired product was formed when diphenylacetylene **1aa** react with 2-aminobenzonitrile under standard reaction conditions. This observation ruled out the possibility of [4+2] cycloaddition reaction (Scheme 3b). When reaction performed between 4-aminobenzonitrile **2k** with **1a**, resulted in the product **8** that confirmed the aza-Michael addition first then cyclization will happen (Scheme 3c). No product was formed when **2a** was replaced by 2-hydroxy benzonitrile **2l** under optimized conditions. The reason might be the low nucleophilicity of hydroxyl group in the basic medium due to generation of phenoxide ion or instability of intermediate **B** which underwent retro-cyclization (ring-opening) and retro-aza-Michael addition (Scheme 3d).



Scheme 3. Control Experiments

Based on the above observation and previous report,^{24]} we proposed a mechanistic pathway for the synthesis of polysubstituted 4-aminoquinolines as described in Scheme 4. The mechanism initially leads through the deprotonation of amine moiety of **2** which facilitates nucleophilic attack on ynone via aza-Michael pathway to generate reactive species enolic-allene **A**. The species **A** underwent C-cyclization to produce unstable intermediate quinoline-4(1H)-imines **B**. Subsequently aromatization of species **B** to give species **C** that undergoes proton abstraction to provide the desired product **3**.



Scheme 4. Proposed Reaction Mechanism

In conclusion, we have developed an efficient base-promoted annulation of ynone with 2-

aminobenzonitrile to prepare multisubstituted 4- aminoquinolines and 4-amino-1,8-naphthyridines in good to excellent yields. The reaction proceeds *via* aza-Michael addition/intramolecular annulation. The present strategy is novel, inexpensive, and highly atom-economical with broad substrate scope. Additionally, *N*-arylquinolones were obtained when *o*-haloarylynones were used as substrate. Further investigation of the scope and synthetic applications of the present strategy is currently underway and will be reported in due course

Experimental Section

General Procedure for the Synthesis of products 3, 4, 5.

In an oven-dried 15 mL reaction vial, a solution of ynone **1** (0.5 mmol), 2-aminobenzonitrile **2** (0.6 mmol) and 2.0 equiv. of anhydrous KO^tBu in 2.0 mL of DMSO were added. The resulting reaction mixture was stirred at 100°C for 1 h. Progress of the reaction was monitored by TLC analysis, after completion of starting materials; the reaction mixture was poured in water and extracted by ethyl acetate (3X10 mL). The organic layer was washed with saturated brine solution and dried over Na₂SO₄. The crude material was purified by column chromatography on silica gel (100–200 mesh) (hexane-ethylacetate, 8:2) to give the desired products **3**, **4**, **5**.

General Procedure for the Synthesis of Product 6.

In an oven dried 15 mL reaction vial, a solution of *o*-haloarylynone **1** (0.5 mmol), 2-aminobenzonitrile **2** (0.6 mmol) and 2.0 equiv. of Cs₂CO₃ in 2.0 mL of DMSO were added. The resulting reaction mixture was stirred at 140°C for 2 h. Progress of the reaction was monitored by TLC analysis, after completion of starting materials; the reaction was poured in water and extracted by ethyl acetate (10 mL). The organic layer was washed with aqueous saturated brine solution and dried over Na₂SO₄. The crude material was purified by column chromatography on silica gel (100–200) (hexane-ethylacetate, 70/30) to give the desired products **6**.

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