Organic LETTERS

Letter

pubs.acs.org/OrgLett

Metal- and Protection-Free [4 + 2] Cycloadditions of Alkynes with Azadienes: Assembly of Functionalized Quinolines

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Supporting Information

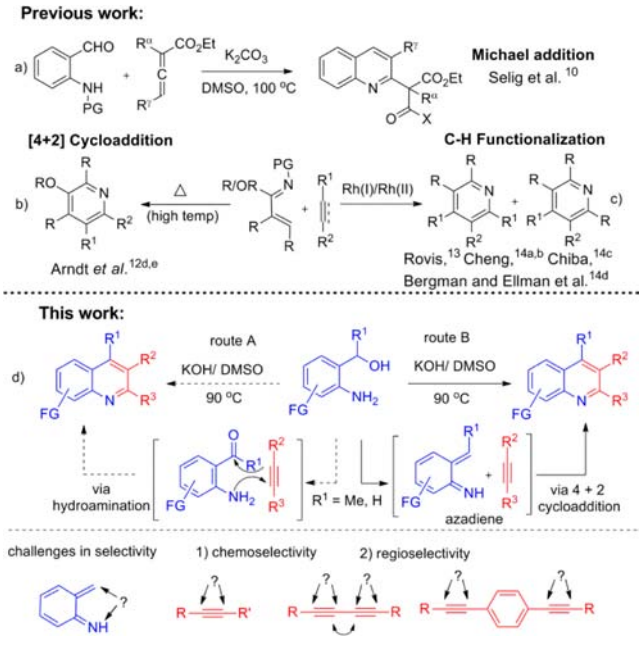
ABSTRACT: A base promoted, protection-free, and regioselective synthesis of highly functionalized quinolines via [4 + 2] cycloaddition of azadienes (generated in situ from *o*-aminobenzyl alcohol) with internal alkynes has been discovered. The reaction tolerates a wide variety of functional groups which has been successfully extended with diynes, (2-aminopyridin-3-yl)methanol, and 1,4-bis(phenylethynyl)benzene to afford (*Z*)-phenyl-2-styrylquinolines, phenylnaphthyridine, and alkyne-substituted quinolines, respectively. The proposed mechanism and significant role of the solvent were well supported by isolating the azadiene intermediate and deuterium-labeling studies.

Owing to their diverse pharmaceutical and biological activities,[1] quinoline nuclei are common templates for steroids that are used as antimalarial, schistosomiasis, and antifungal drugs.[2] The construction of suitably functionalized quinoline frameworks plays a vital role in many natural product syntheses.[3]

A number of traditional approaches for synthesizing quinolines have arisen from many renowned reactions, such as the Skraup,[4] Friedlaender,[5] Combes,[6] and Larock quinoline syntheses[7] and many others.[8] The DeShong,[9a] Wang,[9b] and Liang[9c] groups have demonstrated a facile route for the synthesis of substituted quinolines. Recently, Ghorai,[9d] Reddy,[9e] and co-workers reported the synthesis of quinolines via oxidative cycloisomerization and via hydroamination, respectively. In 2014, Selig et al. explored the base-mediated, three-step cascade synthesis of quinolines using protecting amino aldehyde via Michael addition[10] (Scheme 1a); however, a base-promoted regioselective synthesis of quinolines by intermolecular [4 + 2] cycloaddition has not been well explored.

The [4 + 2] cycloaddition reaction is among the most powerful tool for generating carbocycles[11] and *N*-heterocycles,[12] which is often difficult to form systems that are highly congested or possess substituent arrays that are incompatible with the reaction. An elegant work on [4 + 2] cycloaddition for the synthesis of pyridines using a dienimine (azadiene)-type motif was reported by Arndt et al.[12d,e] in 2008 (Scheme 1b). Recently, the Rovis,[13] Cheng,[14a,b] Chiba,[14c] and Bergman and Ellman[14d] groups have demonstrated the *N*-protected azadiene core moiety and alkynes for the synthesis of pyridines via rhodium-catalyzed C−H functionalization (Scheme 1c). A literature survey revealed that metal- and protection-free, base-promoted intermolecular [4 + 2] cycloaddition for the synthesis of quinoline remains elusive.

Scheme 1. Synthesis of Functionalized *N*-Heterocycles



In continuation of our ongoing research on base-mediated reactions[15] and *N*-heterocyclic synthesis,[16] we hypothesized that the direct synthesis of quinoline could occur via KOH−DMSO-promoted oxidation of benzyl alcohol to benzaldehyde followed by the hydroamination though the reaction of 2-aminobenzaldehyde with alkyne was unsuccessful (Scheme 1d, route A, and Scheme 7 (i). We also speculated a modular route

Received: March 21, 2016
Published: April 27, 2016

DOI: 10.1021/acs.orglett.6b00817
Org. Lett. 2016, 18, 2200−2203

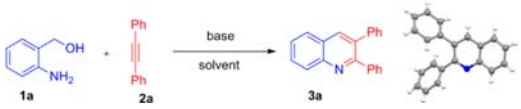
for the assembly of structurally diverse quinolines with excellent regioselectivity via KOH−DMSO-mediated [4 + 2] cycloaddition of azadiene (can be generated in situ from *o*-aminobenzyl alcohol) with internal alkyne (Scheme 1d, route B).

However, four major challenges have to be overcome:

(1) Intermolecular [4 + 2] cycloaddition of 2-aminobenzyl alcohol must occur in the presence of base without using any activation source/metal.
(2) Chemoselectivity: Aminobenzyl alcohol has two nucleophilic sites, and the in situ generated azadienes also have two nucleophilic sites. Thus, it is challenging to achieve high chemoselectivity.
(3) Protection-free: It is tedious to perform the selective quinoline synthesis without protection due to the presence of two labile sites in the substrate.
(4) Regioselectivity: Besides the chemoselectivity, cycloaddition of the C−C triple bond should be regioselective.

Our investigation to explore the base-assisted [4 + 2] cycloaddition began with the examination of a number of bases reported in the literature using 2-aminobenzyl alcohol **1a** and diphenylacetylene **2a** as a model substrates (Table 1). Inspired by Ghorai conditions,[9d] we carried out the reaction of **1a** with alkyne **2a** using K^{t}OBu in DMSO at 25 °C, but the desired product **3a** was obtained in only trace amounts (Table 1, entry 1). The promotional effect of temperature increases the yield of the product **3a** (Table 1, entries 2 and 3). On replacing K^{t}OBu with KOH, a slight improvement in the yield of the desired product was observed (Table 1, entry 4). The reaction of **1a** with internal alkyne **2a** at 90 °C fruitfully provided the quinoline **3a** in 75% yield (Table 1, entry 5). Further increasing the reaction temperature declines the yield of product **3a** (Table 1, entry 6). A number of bases such as NaOH and CsOH were examined, and it was found that the nature of bases, as well as their counterions, influenced the reactivity of cycloaddition reaction and provided the product **3a** in moderated yields (Table 1, entries 7 and 8), while no product was observed with K_2CO_3 and K_3PO_4 (Table 1, entries 9 and 10) (for detailed optimization, see the SI).

Table 1. Reaction Development[a]

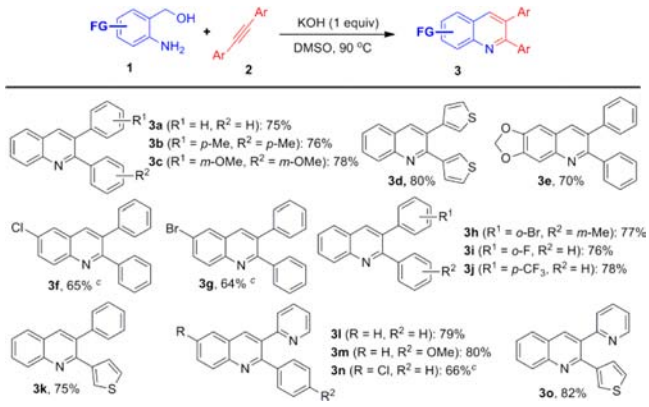


entry	base	solvent	time (h)	temp (°C)	yield[b] of **3a** (%)
1[9d]	K^{t}OBu	DMSO	24	25	trace
2	K^{t}OBu	DMSO	24	50	30
3	K^{t}OBu	DMSO	24	80	65
4	KOH	DMSO	24	80	67
5	KOH	DMSO	24	90	75
6	KOH	DMSO	24	100	68
7	NaOH	DMSO	24	90	65
8	CsOH	DMSO	24	90	63
9	K_2CO_3	DMSO	12	90	*c*
10	K_3PO_4	DMSO	12	90	*c*

[a]Reactions were performed using 0.5 mmol of **1a**, **2a** (0.4 mmol), and base (1.0 equiv) in 2.0 mL of solvent. [b]Isolated yield. [c]No reaction. CCDC no. for **3a** is 1435832.

With optimized reaction conditions in hand, we extended the scope of the developed protocol with various symmetrical and unsymmetrical aryl alkynes (Scheme 2). The reaction of substrate **1a** with electron-neutral **2a**, electron-releasing **2b**, and alkyne **2c** afforded the product **3a**−**c** in 75−78% yields. It is worth noting that reaction of **1a** with electron-rich thiophene-substituted alkyne **2d** provided the desired product **3d** in 80% yield. Reaction of substrate **1d** with alkyne **2a** provided the tricyclic product **3e** in 70% yield. Notably, the halogen-substituted (2-aminophenyl)methanol **1b,c** effectively gave the corresponding quinolines **3f** and **3g** in 65 and 64% yields, respectively. The unsymmetrical internal alkynes **2e**−**g** afforded the desired quinolines **3h**−**j** regioselectively in 76−78% yields. The reactions of unsymmetrical heteroalkynes **2h**−**k** were well implemented to form the intriguing fused products **3k**−**o** in 66−82% yields. The electronic bias of the ring/substituents on the C−C triple bond of the unsymmetrical alkynes plays an important role in the regioselective formation of quinolines **3h**−**o** (Scheme 2).[17]

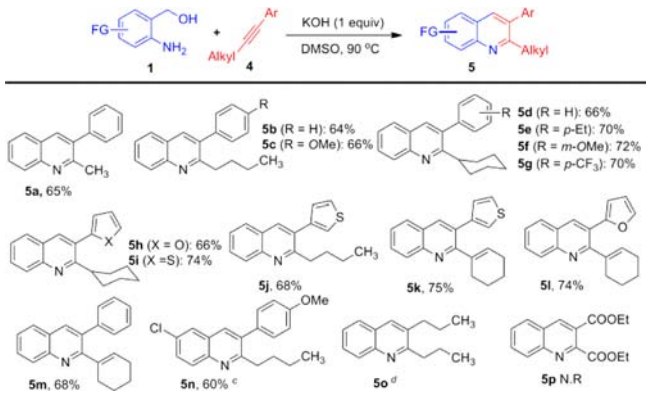
Scheme 2. Scope of Aryl Internal Alkynes[a,b]



[a]Using optimized conditions (entry 5, Table 1). [b]Isolated yield. [c]30 h.

Encouraged by the above results, the reaction of **1a** with aryl alkyl unsymmetrical internal alkynes was performed (Scheme 3). The reaction of aryl alkyl substituted alkynes **4a**−**c** provided the desired quinolines **5a**−**c** in 65, 64, and 66% yields, respectively, with excellent regioselectivity. When a combination of unsymmetrical internal alkynes **4d**−**g** containing a

Scheme 3. Scope of Aryl Alkyl Internal Alkynes[a,b]



[a]Using optimized conditions (entry 5, Table 1). [b]Isolated yield. [c]40 h. [d]Inseparable complex mixture. N.R. = no reaction.

DOI: 10.1021/acs.orglett.6b00817
Org. Lett. 2016, 18, 2200−2203

substituted aryl ring on one side and a cyclohexyl ring on the other side was used for the reaction, the functionalized quinolines **5d–g** were obtained in 66–74% yields. The reaction of heteroalkyl alkynes **4h–m** with substrate **1a** afforded the products **5j–m** in 66–75% yields. The cycloaddition of (2-amino-5-chlorophenyl)methanol **1b** with alkyne **4c** provided the desired product **5n** in 60% yield. Inferior results were obtained in the reaction of **1a** with oct-4-yne (**4n**) and diethyl but-2-ynedioate (**4o**) (Scheme 3).

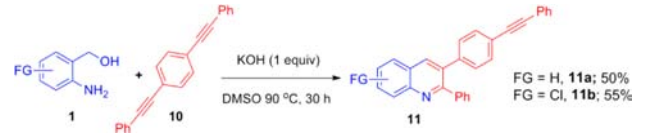
The scope of this base-assisted [4 + 2] cycloaddition was further investigated by using phenyldiynes **6a–d** (Scheme 4a).

Scheme 4. Scope of 1,3-Diyne and Pyridinyl Methanol

Electron-donating diynes were tolerated in this transformation, providing the (*Z*)-phenyl-2-styrylquinolines **7a–d** in 59–63% yields (see the SI for the mechanism). The regio- and stereochemistry of the reaction was established on the basis of chemical shifts, coupling constants (J_{H-H}), and NOESY studies. To our delight, the reaction of (2-aminopyridin-3-yl)methanol **8** with alkyne **2a** produced the biologically important naphthyridine **9** albeit in lower yield (Scheme 4b).

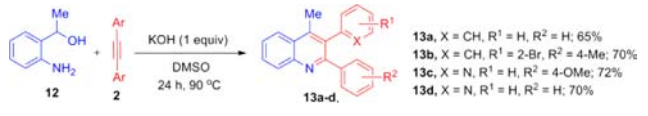
Achieving the selectivity in base-mediated annulations of 2-aminophenylmethanol **1** is a significant challenge with 1,4-bisalkyne **10**. When H and Cl groups were used as FG, the reactions were well implemented to form the cyclized products **11a–b** in 50–55% yields (Scheme 5).

Scheme 5. Scope of Bis-alkyne



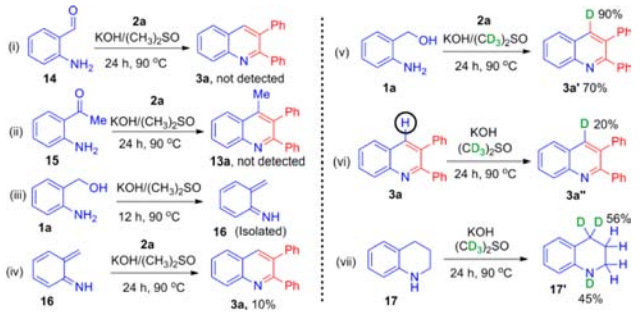
Reaction of secondary alcohol **12** with internal aryl alkynes **2a**, **2e**, and **2j** was successful and provided the highly functionalized quinolines **13a–d** in good to moderate yields (Scheme 6).

Scheme 6. Scope of Secondary Alcohol



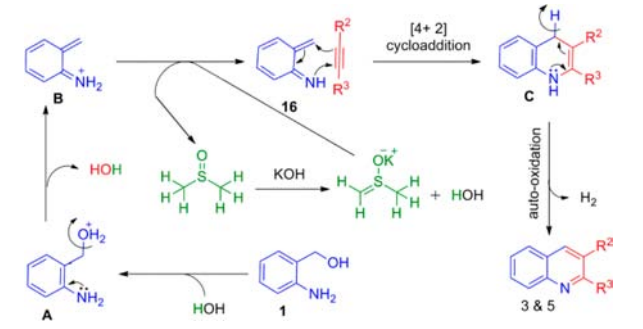
In order to support the proposed mechanistic pathway, various preliminary experiments were performed (Scheme 7). Initially, we thought the reaction was proceeding via aldehyde formation; for validation of the possible reaction intermediate, we performed the reaction of 2-aminobenzaldehyde **14** and 2-aminoacetophenone **15** with **2a**; however we failed to obtain the desired products **3a** and **13a** (eqs i and ii). The results of the above two control experiments rule out the formation of product via hydroamination (Scheme 1, route A). We further examined the reaction of **1a** with KOH–DMSO at 90 °C; the formation of the highly unstable azadiene intermediate **16**

Scheme 7. Mechanistic Control Experiments



(confirmed by ^{1}H, ^{13}C and HRMS; along with unidentified complex mixture) supports the formation of the desired products via [4 + 2] cycloaddition (eq iii). The reaction of azadiene intermediate **16** with alkyne **2a** provided the quinoline **3a** in 10% yield along with an unidentified complex mixture which further supports the proposed mechanistic pathway (eq iv). The deuterium-labeling experiment of 2-aminobenzylalcohol **1a** with **2a** in DMSO-d_6 provided the desired product **3a′** in 70% yield with 90% exchange of D at the C-4 position (eq v). In order to validate the exchange of deuterium with quinoline protons, we heated the quinoline **3a** with KOH–DMSO-d_6 at 90 °C for 24 h, and only 20% of H–D exchange was observed in product **3a″** (eq vi). The reaction of 1,2,3,4-tetrahydroquinoline **17** in the presence of deuterated DMSO provided the product **17′** with 56% incorporation of D at C-4 position (eq vii), which supports the formation of transition state **C** in the proposed mechanism (see Scheme 8).

Scheme 8. Proposed Mechanism



Based on the previous mechanistic studies, we put forward the following mechanistic hypothesis as described in Scheme 8. The mechanism is initiated by protonation[15e,f] of the 2-aminobenzyl alcohol **1** via KOH–DMSO suspension, which leads to the formation of imine type motif **B**. The anion of the DMSO abstracts the proton and forms an intermediate **16**.[18] The reaction of azadiene intermediate **16** with alkyne would form new N–C and C–C bonds (**C**) in a [4 + 2] cycloaddition manner, which upon autoxidation[12d] successfully provided the final quinoline product.

In conclusion, we have described an efficient base-promoted metal- and protection-free synthesis of highly functionalized quinolines from in situ generated azadiene and internal alkynes via a [4 + 2] cycloaddition process with excellent chemo- and regioselectivity. An electronic effect of the substrates plays a key role in controlling the chemo- and regioselectivity in the reaction. The three pairs for substrate scope, namely Ar–Ar, Ar–alkyl, and diynes with 2-amino benzyl alcohols, were

DOI: 10.1021/acs.orglett.6b00817
Org. Lett. 2016, 18, 2200–2203

established for the synthesis of biologically active quinolines. The preliminary control experiments succeeded in the isolation of the azadiene intermediate, which supports the proposed mechanistic pathway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00817.

X-ray crystallographic data for **3a** (CIF)

Experimental details, crystallographic information, and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by SERB (SB/EMEQ-098/2014) and (SB/S1/OC-84/2013). R.K.S and M.P. thank the UGC and SERB for fellowships.

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DOI: 10.1021/acs.orglett.6b00817
Org. Lett. 2016, 18, 2200−2203