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Synthesis of polysubstituted quinolines *via* copper(II)-catalyzed annulation of 2-aminoaryl ketones with alkynoates†

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Copper triflate catalyzed annulation of 2-aminoaryl ketones with internal alkynes has been developed for the synthesis of polysubstituted quinolines in high yields under solvent-free conditions. Phenyl propiolic acid afforded the 3-unsubstituted quinolines *via* decarboxylation. The protocol is compatible with various internal alkynes and is expected to find wide applications due to its operational simplicity.

Quinolines represent a major class of nitrogen-containing heterocyclic compounds which are found to be the key structural unit in many natural products (Fig. 1).[1] Quinoline derivatives show a wide range of biological activities such as anti-malarial,[2a] anti-microbial,[2b] anti-bacterial,[2c] anti-inflammatory,[2d] anti-diabetic,[2e] anti-alzheimer,[2f] tyrosine kinase inhibitor,[2g] anti-platelet activity,[2h] and anti-hypertensive.[2i] Quinolines, in particular, constitute the core structure of many currently marketed drugs such as Singulair, Tafenoquine, and Hydroxychloroquine *etc.*[3] In addition, quinoline based polymers have applications in the field of electronics, optoelectronics and nonlinear optics. Furthermore, quinoline derivatives have been used as organocatalysts and are well known as useful tools for asymmetric synthesis.[4] Among various quinoline derivatives, 2-arylquinoline scaffolds are associated with a wide range of biological properties, such as P-selectin antagonism, antimalarial, and antitumor activities.[5]

Due to their wide range of bioactivities, synthesis of 2-arylquinoline derivatives has gained special attention. Established strategies for assembling quinoline rings are the classic annulation reactions like Friedlander,[6] Combes,[7] Povarov,[8] Doebner-von Miller[9] and Skraup[10] syntheses *etc.* Among these reported methods, Friedlander reaction is one of the simple methods involving condensation between 2-aminoaryl ketone/aldehyde and carbonyl compound bearing a reactive α-methylene group. However, strong acid or base and high reaction temperature are required for this transformation. Synthesis of diversified quinolines is more challenging to meet up the need of medicinal and material chemists. So the development of new approaches to synthesize quinolines from common building blocks other than carbonyl compounds is attractive. In this context, only a few methods have been developed to construct the quinoline moieties using alkynes as the precursor.[11] However, these methods are focused on the use of terminal alkynes, which is a notable limitation in terms of substrates applicability. Internal alkynes have rarely been used as the starting materials to construct these scaffolds directly. Recently a one-step $InCl_3$ catalyzed procedure has been reported; however this is not very satisfactory with regards to yield and substrates scope.[11d] Liu and co-workers also developed a method to synthesize 2-arylquinolines in presence of a combination of Au and Ag.[12] However, the use of highly expensive metal catalyst makes this method less feasible in common laboratory as well as industry. In addition, variation of alkynes is necessary to afford the diverse substituents in these scaffolds. So there is a requirement for simple, versatile and effective method to construct

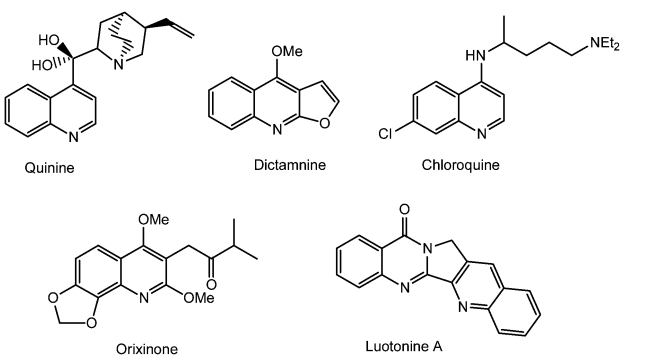

Fig. 1 Some biologically active compounds containing quinoline moiety.

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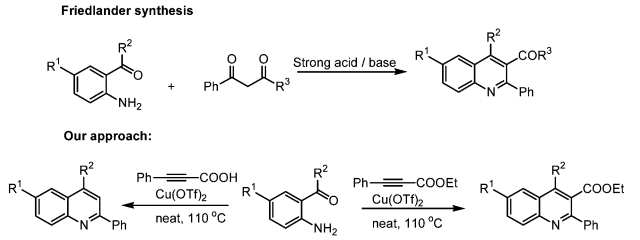


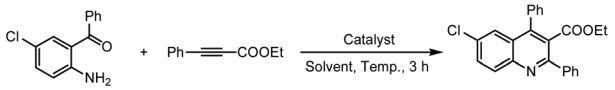
Scheme 1 Synthesis of polysubstituted quinolines.

polysubstituted quinolines with selective control of substitution patterns from easily available basic chemical materials.

During the last few years, significant interest has been focused on the development of new protocols for environmentally benign processes those are both economically and technologically feasible. Especially nonhazardous and less expensive metals as well as solvent-free reactions have gained much interest in organic synthesis. In this context, we are actively engaged for the development of newer methodologies under solvent-free conditions.[13] Due to their unique catalytic properties, copper triflate have been widely used for a variety of organic transformations.[14] Based on our continuing efforts to achieve copper-catalyzed C–C and C-heteroatom bond formations,[15] we envisaged another application of copper triflate for the synthesis of 2-arylquinoline derivatives by the annulation of 2-aminoaryl ketones with internal alkynes under solvent-free conditions (Scheme 1).

We commenced our study taking 2-amino-5-chlorobenzophenone (**1a**) and ethyl phenylpropiolate (**2a**) as the model substrates using copper triflate (10 mol%) as catalyst in DMF solvent at 110 °C (Table 1, Entry 1). To our delight, desired quinoline derivative was obtained in 66% yield after 3 hours and no further improvement was noticed by increasing reaction time. Encouraged by this initial result, we proceeded to optimize the reaction conditions which are summarized in Table 1. Other common solvents such as toluene, CH_3CN, dichloroethane, ethanol, DMSO did not improve the yields (Table 1, Entries 2–6). These poor results prompted us to investigate the reaction under solvent-free conditions. Gratifyingly, the desired product was obtained in 90% yield under neat conditions at 110 °C (Table 1, Entry 7). Yield of the reaction was reduced at lower temperature (80 °C, Table 1, Entry 8). Finally, the optimized reaction conditions were set at 110 °C. The variation of the amount of the copper salt from 5 mol% to 15 mol% gave 81%, 90% and 92% yields respectively (Table 1, Entries 9, 7, 10). Thus it was cleared that decreasing the catalyst loading gave lower yield whereas increasing the amount did not improve the yield so much. Among the readily available copper salts; copper triflate was proven to be the most efficient catalyst for this reaction in terms of yields (Table 1, Entries 11–14). Other metal triflates such as $Zn(OTf)_2$, $In(OTf)_3$, $La(OTf)_3$ were also surveyed and found to be less effective for this transformation. However no desired product was detected without the catalyst (Table 1, Entry 15). Triflic acid is not also effective, producing only 20% desired product (Table 1, Entry 16).

Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

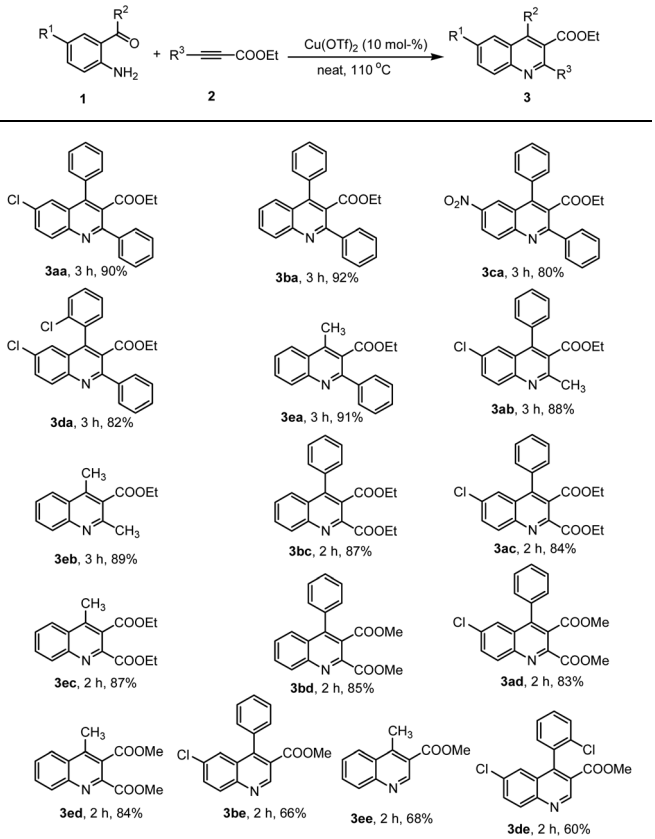
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield[b] (%)
1	$Cu(OTf)_2$ (10)	DMF	110	66
2	$Cu(OTf)_2$ (10)	Toluene	Reflux	64
3	$Cu(OTf)_2$ (10)	CH_3CN	Reflux	52
4	$Cu(OTf)_2$ (10)	DCE	Reflux	60
5	$Cu(OTf)_2$ (10)	EtOH	Reflux	48
6	$Cu(OTf)_2$ (10)	DMSO	110	30
7	$Cu(OTf)_2$ (10)	Neat	110	90
8	$Cu(OTf)_2$ (10)	Neat	80	70
9	$Cu(OTf)_2$ (5)	Neat	110	81
10	$Cu(OTf)_2$ (15)	Neat	110	92
11	$Cu(OAc)_2$ (10)	Neat	110	40
12	$CuCl_2$ (10)	Neat	110	41
13	$CuBr_2$ (10)	Neat	110	43
14	CuI (10)	Neat	110	<10
15	—	Neat	110	—
16	TfOH (10)	Neat	110	20

[a] Carried out with 1 mmol of **1a** and 1 mmol of **2a** in solvent (2 mL) for 3 h. [b] Isolated yields.

After optimizing the reaction conditions, we turned our attention to the substrate scope of the reaction which is summarized in Table 2. Ethyl phenylpropiolate was reacted with various 2-aminoaryl ketones and in all cases the desired products were obtained in high to excellent yields (**3aa**, **3ba**, **3ca**, **3da**). It is noteworthy to mention that the reaction of 2-amino-5-nitrobenzophenone with ethyl phenylpropiolate also gave the corresponding annulated product with high yield (**3ca**). The reaction proceeded smoothly in case of 2-aminoacetophenone also (**3ea**). Ethyl methyl propiolate reacted efficiently with 2-aminoaryl ketones to afford the products (**3ab**, **3eb**). Other internal alkynes such as dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate reacted well with 2-aminoaryl ketones under the present reaction conditions to afford various quinoline derivatives in high yields (**3bc**, **3ac**, **3ec**, **3bd**, **3ad**, **3ed**). Although a method reported by Taylor and Hiendel[11i] described the preparation of a few phenyl substituted quinoline derivatives such as **3ac** and **3bc** by the reaction of dimethyl acetylenedicarboxylate with 2-aminobenzophenones in benzene under reflux in absence of any catalyst, it required much more longer reaction times (24 h) compare to our present solvent-free method. Additionally, it was unsuccessful to other alkynes and 2-aminoaryl ketones. Our present protocol is also effective for the synthesis of 2-unsubstituted derivatives. Methyl propiolate regioselectively produced the corresponding 2-unsubstituted quinolines when it was reacted with various 2-aminoaryl ketones (**3be**, **3de**, **3ee**).

To extend our methodology, phenyl propiolic acid was used as an internal alkyne. Interestingly the reaction proceeded very well and 3-unsubstituted quinolines were obtained in high yields. Decarboxylation was occurred during the course of the reaction (Scheme 2). So it could be used as an alternative source of phenylacetylene. However, direct use of phenylacetylene

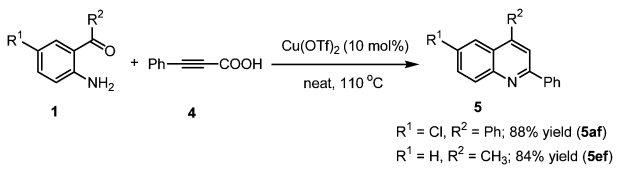
Table 2 Substrate scope[a]



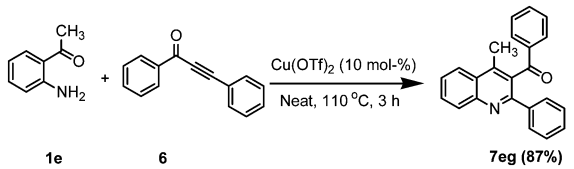
[a] *Reaction conditions*: 1 mmol of **1** and 1 mmol of **2** in the presence of $Cu(OTf)_2$ (10 mol%) at 110 °C; Isolated yields.

produced a mixture of product including dimerization of phenylacetylene. 2-Amino-5-chlorobenzophenone and 2-aminoacetophenone both gave the corresponding decarboxylative products under the present reaction conditions (**5af**, **5ef**).

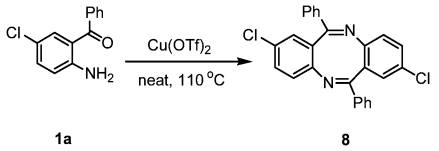
In addition to phenyl propiolic acid and different alkynoates, conjugated ynone such as diphenylpropynone (**6**) was also



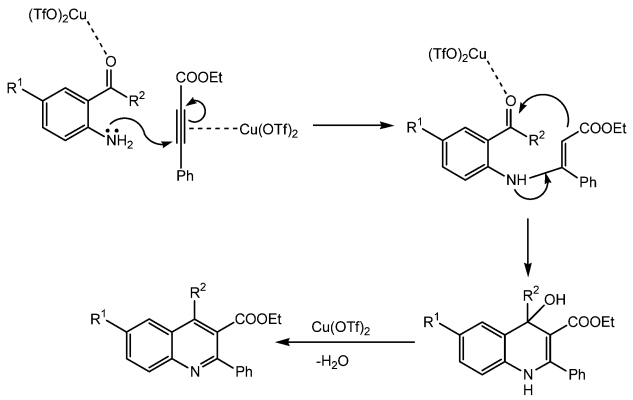
Scheme 2 Synthesis of quinolines *via* decarboxylation of phenyl propiolic acid.



Scheme 3 Synthesis of quinoline from ynone.



Scheme 4 Self condensation of 2-aminoaryl ketone.



Scheme 5 Probable mechanism.

examined. Reaction between ynone (**6**) and 2-aminoaryl ketone (**1e**) successfully produced the corresponding quinoline (**7eg**) in high yield (Scheme 3).

Other kind of internal alkynes such as diphenylacetylene, 4-octyne and alkynylphosphonate were also tested, but they did not afford the desired products. In these cases self condensation of 2-aminobenzophenone was occurred under the present reaction conditions (Scheme 4).

Based on the literature the probable mechanism for this cyclization reaction is outlined in Scheme 5. Presumably, the process proceeds through Michael addition of 2-aminoaryl ketones to alkynes followed by intramolecular condensation and dehydration. However, we are unable to isolate the Michael adduct under the present reaction conditions. Probably, after forming the Michael adduct, it transformed to the final product quickly. In case of phenyl propiolic acid, decarboxylation might occur after cyclization.

Conclusions

In conclusion, we have developed a sustainable method for the synthesis of densely functionalized quinolines *via* copper triflate catalyzed annulation of 2-aminoaryl ketones with various internal alkynes. To the best of our knowledge this is the first report for the use of phenyl propiolic acid as an alternative of terminal alkyne for the synthesis of quinolines. Various types of substituted quinolines could be synthesized by choosing proper alkynes employing this methodology. Furthermore, H_2O as the only byproduct makes this transformation atom efficient. In nutshell, simple reaction procedure, environmentally friendly reaction conditions avoiding toxic organic solvent, cheap catalyst and aerobic reaction conditions make this procedure

convenient and useful for the synthesis of diversified quinolines. Further study to broaden the scope of this methodology towards pharmaceuticals and biologically active compounds are under investigation.

Acknowledgements

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