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One pot Synthesis of Highly Substituted Quinolines in Aqueous Medium and its Application for the Synthesis of Azalignans

Amrendra Kumar,[a] Ramanand Prajapati,[a] Ruchir Kant[b] and Narender Tadigoppula*[a]

Abstract: A new one-pot method has been developed for the synthesis of highly substituted quinoline derivatives from α-amino ketone derivatives/glycine esters/glycine amide and aromatic/aliphatic alkynes/alkenyl esters using molecular I_2, K_2CO_3 and tetra butyl ammonium bromide (TBAB) and sodium dodecyl sulphate (SDS) surfactant combination in water at room temperature within 30-50 min. in moderate to good yields. This protocol has advantages like oxidant free, aqueous medium, simple operation, tolerance of various substrates and useful for the synthesis of bioactive aza-lignans.

Introduction

Quinoline subunits are widespread in natural products[1] and key structures of several pharmaceutical compounds[2] (Figure 1). These moieties have been reported to possess a diverse range of biological properties such as anti-inflammatory,[2b] anticancer,[3] antimicrobial,[4] and antipsychotics.[5] Mancheno and co-workers, in 2011, have synthesized various substituted quinolines from glycine derivatives using $FeCl_3$ by oxidative dehydrogenative coupling/aromatization tandem reaction for the first time (Scheme 1a).[6] In 2014, Huo and co-workers synthesized quinolines in presence of air as the oxidant by using an auto-oxidation coupling system and CBr_4.[7] Recently Liu and co-workers developed the Cu(II)-catalyzed aerobic oxidative C-H functionalization of glycine derivatives with olefins using N-hydroxy phthalimide (NHPI) as a co-catalyst and O_2 as the oxidant.[8] In all of the above transformations the iminium intermediates were generated by oxidation and subsequently captured by olefins and some of the reactions were carried out at high temperature, used toxic solvents, metal catalysts and additives, which are harmful for the environment and human health. Selective protocols for the synthesis of highly substituted quinoline derivatives with minimum number of steps and the reduced toxic waste materials are in great demand. In this direction very recently Yang and co-workers developed a direct photocatalytic aerobic oxidative dehydrogenative coupling-aromatization tandem reaction for the synthesis of substituted quinolines from glycine esters and unactivated alkenes under mild reaction conditions (Scheme 1b).[9]

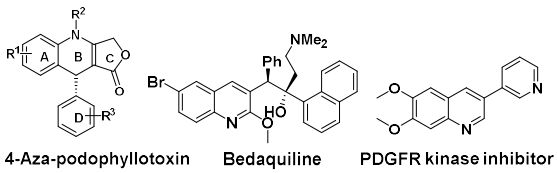
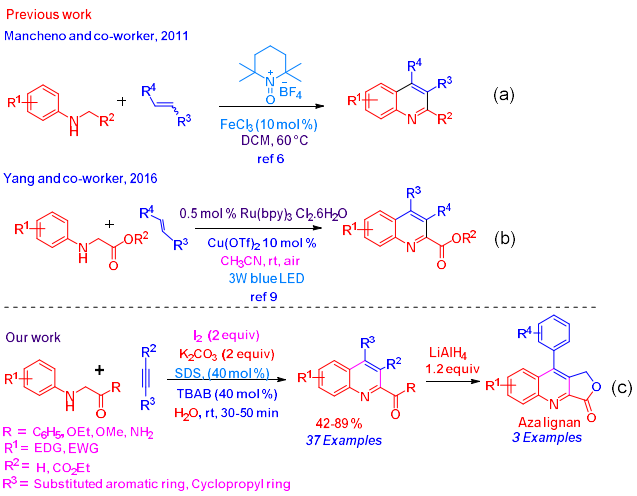


Figure 1. Bioactive molecules containing quinoline structures.



Scheme 1. Existing methods for the synthesis of highly substituted quinolines.

In continuation of our methodology development work, we discovered a new protocol for the synthesis of highly substituted quinolines from α-amino ketones and alkynes in the presence of molecular I_2 using K_2CO_3 as a base and surfactants tetrabutyl ammonium bromide (TBAB) and sodium dodecyl sulphate (SDS) combination and very mild reaction condition comparatively previous reports (Scheme 1c).

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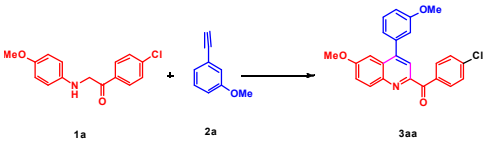
Table 1. Optimization of the reaction conditions between 1-(4-chloro phenyl)-2-((4-methoxy phenyl)amino)ethan-1-one (α-amino ketone) (**1a**) and 1-ethynyl-3-methoxy benzene (**2a**).



1a 2a 3aa

Entry	Base[a]	Surfactant (mole%)	Solvent	Time (min)	Yield[b] (%)
1	I_2/K_2CO_3	SDS (10)	Water	65	20
2	I_2/K_2CO_3	SDS (20)	Water	55	45
3	I_2/K_2CO_3	SDS (30)	Water	42	56
4	I_2/K_2CO_3	TBAB (40)	Water	44	51
5	I_2/K_2CO_3	TBAI (40)	Water	53	46
6	I_2/K_2CO_3	Tritonx-100 (40)	Water	120	NR
7	I_2/K_2CO_3	Tween 80 (40)	Water	140	NR
8	I_2/K_2CO_3	Pluronic F-127 (40)	Water	53	50
9	I_2/K_2CO_3	SDS (30) + TBAB (20)	Water	42	71
10	I_2/K_2CO_3	SDS (30) + TBAB (30)	Water	37	75
11	I_2/K_2CO_3	SDS (40) + TBAB (40)	Water	30	89
12	I_2/K_2CO_3	SDS (40) + TBAI (40)	Water	35	71
13	I_2/K_2CO_3	SDS (40) + Tritonx-100 (40)	Water	43	64
14	I_2/K_2CO_3	SDS (40) + Tween 80 (40)	Water	41	63
15	I_2/K_2CO_3	SDS (40) + Pluronic F-127 (40)	Water	23	73
16[c]	I_2/K_2CO_3	SDS (40) + TBAB (40)	Water	60	55
17	KI/K_2CO_3	SDS (40) + TBAB (40)	Water	60	NR
18	NIS/K_2CO_3	SDS (40) + TBAB (40)	Water	60	NR
19	ICl/K_2CO_3	SDS (40) + TBAB (40)	Water	60	NR
20	I_2/Cs_2CO_3	SDS (40) + TBAB (40)	Water	28	83
21	$I_2/NaHCO_3$	SDS (40) + TBAB (40)	Water	60	NR
22	I_2/K_2CO_3	None	DMF	105	59
23	I_2/K_2CO_3	None	1,4 Dioxane	90	45
24	I_2/K_2CO_3	None	DMSO	120	26
25	I_2/K_2CO_3	None	Toluene	70	38
26	I_2/K_2CO_3	None	Water	130	NR

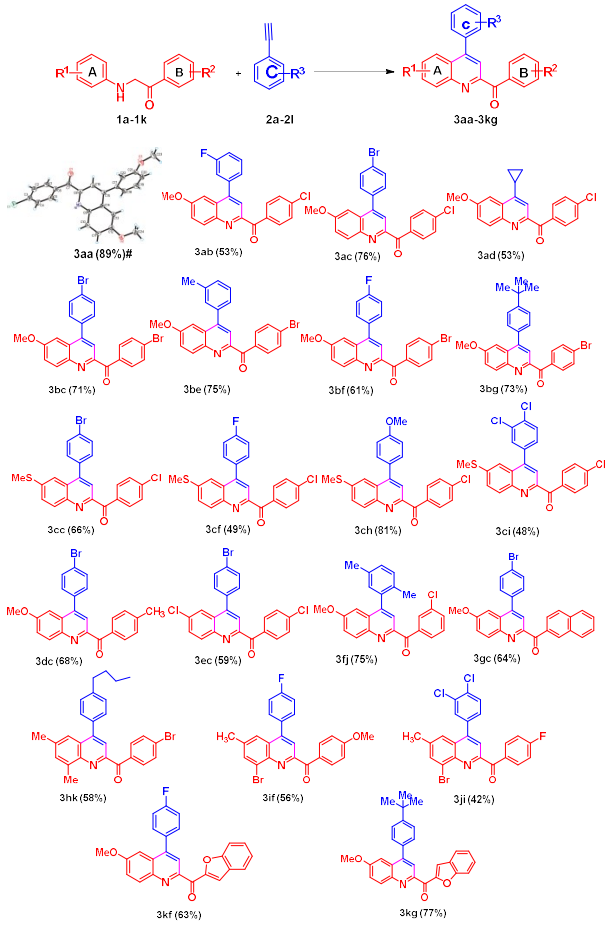
Reaction conditions. α-Amino ketone **1a** (1 equiv.), Alkyne **2a** (0.7 equiv.), I_2 (2.0 equiv.) in 1.5 ml of water at room temperature. NR = No reaction; [a]2 equivalents: [b]Isolated yields; [c]1 equivalent of I_2

We initiated the test reaction between 1-(4-chlorophenyl)-2-(4-methoxyphenyl)amino ketone **1a** and alkyne **2a** as model substrates to explore the reaction conditions using anionic surfactant SDS (Table 1). To our delight, the desired product **3aa** was obtained in 20% yield within 65 min using (2 equiv.) of iodine, (2 equiv.) of K_2CO_3 in combination with (10 mol %) SDS as a surfactant in water at room temperature (Table 1, entry 1). The chemical structure of **3aa** has been confirmed by spectral data and single crystal X-ray crystal data (CCDS No. 1845131). The low yield of the product **3aa** was attributed to insufficient quantity of surfactant in aqueous medium. Increasing the SDS loading from 10 to 30% mole was helpful to further improve the yield of the desired product **3aa** to 56% with reduced reaction time from 65 min to 42 min (Table 1, entry 2-3).The cationic surfactants such as tetra butyl ammonium iodide (TABI) and tetra butyl ammonium bromide (TBAB) (Table-1, entries 4-5) and non-ionic surfactants such as triton X-100, tween 80 and pluronic F-127 (Table 1, entries 6-8) were screened, however, none of them were efficient. We then moved on to test the various surfactants combination to improve the reaction conditions. Pleasingly, the SDS (40%) and TBAB (40%) combination was the most effective (Table 1, entry 11), affording **3aa** in 89% yield after 30 min at room temperature. Other combinations such as SDS (40 mole %) and TBAI (40 mole %), SDS (40%) and tritonx-100 (40 mole %), SDS (40 mole %) and tween-80 (40 mole %), SDS (40 mole %) and pluronic F-127 (40 mole %) gave **3aa** in yield of 71%, 64%, 63% and 73% respectively (Table 1, entries 12-15). Decreasing the quantity of iodine from 2 equiv. to 1 equiv. and base K_2CO_3 2 equiv. to 1 equiv. gave low yield of **3aa** (Table 1, entry 16). Reaction with iodine agents such as KI, NIS (N-iodo succinamide) and ICl failed to provide the desired quinolines (Table 1, entries 17-19). We also investigated the same reaction in the presence of few organic polar solvents at room temperature, however, relatively low yields were observed, when compared with aqueous conditions (Table 1, entries 22-25). Cs_2CO_3 is as good as K_2CO_3, however $NaHCO_3$ failed to give desired product may be due to weak basicity (Table 1, entries 20-21). In the absence of surfactants, the reaction did not give product in the aqueous medium (Table 1, entry 26).

With optimized conditions in our hand, we explored the substrate scope of our protocol in order to show the generality of the reaction (Table 2). A variety of substituted α-amino ketones **1a-1l** were investigated with substituted aryl alkynes **2a-2l** and synthesized respective quinolines **3aa-3kg** with the yield ranging from 42 to 89%. The compounds, which have electron donating-groups on the phenyl group (ring-A) of α-amino ketone gave good yields in comparison to electron withdrawing groups, which is evident from the yields of **3ac** (76%), **3cc** (66%) and **3ec** (59%). On the other hand electron withdrawing groups on ring B of α-amino ketone improves the yields of the products **3ac** (76%), **3bc** (71%) and **3dc** (68%). Substitution pattern on phenyl group (ring-C) of alkyne also influence on the yields of product. The electron withdrawing groups such as fluoro and bromo on phenyl (ring-C) of alkyne

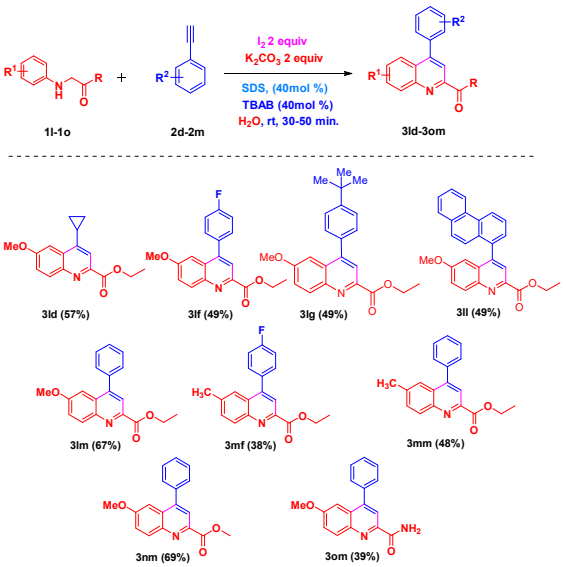
gave low yields. For example, the compound **3bc**, which has bromo substitution on *para* position of phenyl ring of alkyne gave 71% of yield, where as its fluoro substituted compound gave 61%. Similarly, the bromo substituted compound **3cc** was isolated in 66% of yields, where as fluoro substituted compound **3cf** was isolated in 49% only. Electron releasing groups at *para* position of phenyl group of alkyne improves the yields. This trend can be observed when we compare the yields of **3bg** (73%) vs **3bf** (61%) and **3ch** (81%) vs **3cf** (49%). It is also noteworthy to mention here that reaction with aliphatic alkyne also led to respective quinoline derivative **3ad**.

Table 2. Substrate scope of the α-amino ketones **1a-1k** and substituted phenyl acetylenes **2a-2l** and isolated yields of substituted quinolines**.**



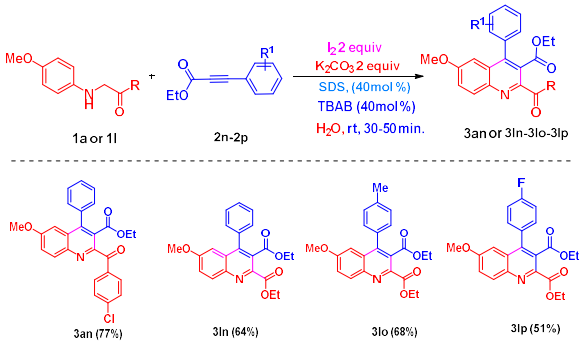
#- ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of the crystal structure of compound **3aa** determined at **293 K**.

We next examined the glycine ester derivatives such as ethyl (4-methoxy phenyl)glycinate **1l**, ethyl p-tolyl glycinate **1m** and ethyl 4-methoxy phenyl glycinate **1n** and substituted phenyl alkynes **2d**, **2f**, **2g**, **2l** and **2m** which have successfully furnished the desired products **3ld-3om** (Scheme 2). Glycine esters which have stronger electron releasing groups on its phenyl ring gave better yields (**3lm** 67% vs **3mm** 48%; **3lf** 49% vs **3mf** 38%). In contrast, electron withdrawing nitro and halo-substituted glycine esters failed to give the desired quinoline derivatives. Phenyl acetylenes with electron withdrawing groups furnished low yields of **3lf** and **3mf**. The glycine amide derivative 2-(p-tolyl amino)acetamide (**1o**) also successfully furnished the desired quinoline product **3om**, however the yield was poor (Scheme 2), when compared with glycine esters **1l-1n**.



Scheme 2. Substrate scope of glycine derivatives for the synthesis of substituted quinolines

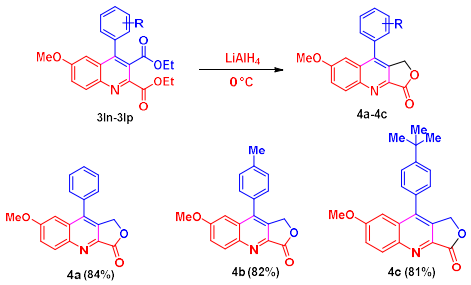
We then focused on to use activated phenyl alkynes, such as ethyl (E)-3-phenyl acrylate **2n**, ethyl (E)-3-(p-tolyl)acrylate **2o**, ethyl (E)-3-(4-fluoro phenyl)acrylate **2p** instead of phenyl alkynes. Delightedly, the reaction between α-amino ketone **1a** and **2n** proceeded smoothly and furnished the highly functionalized quinoline **3an** with 77% yield (Scheme 3). With this success, we further reacted **2n** with ethyl (4-methoxy phenyl)glycinate **1l**, which also gave quinoline **3ln** in 64% yield. Interestingly, the quinoline derivative **3ln** has two ester functionalities adjacent to each other, which are useful functionalities for converting them in to azalignan class of compounds. We therefore reacted **1l** with few more activated alkynes such as **2n-2p** and prepared respective quinolone derivatives **3ln-3lp**, which have di-ester functionality. Here also, the alkynes, which have electron donating groups gave better yields than electron withdrawing groups **3lo** vs **3lp**.



Scheme 3. Substrate scope of ethyl 3-phenyl propiolates for the synthesis of highly substituted quinoline derivatives.

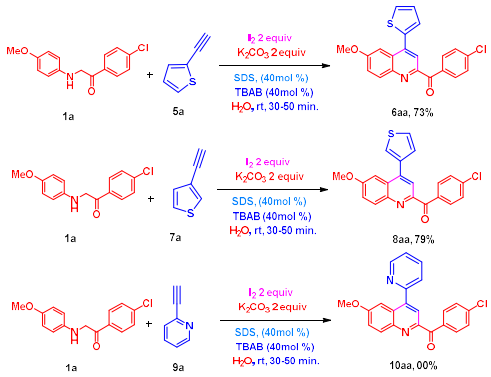
To demonstrate further application of this protocol for the synthesis nitrogen containing lignan type of natural products, we carried out a reductive cyclization reaction on quinolines containing di-ester functionality such as **3ln-3p** using $LiAlH_4$

(1.2 equiv.) in dry THF at 0°C for 25 min to produce the desired lignans **4a-4c** in good yields (Scheme 4).[10]



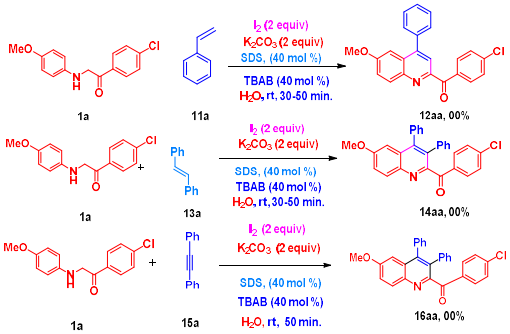
Scheme 4. Synthesis of aza-lignans.

Next, we investigated a few hetero aromatic acetylenes such as 2-ethynyl thiophene **5a** and 3-ethynyl thiophene **7a** (Scheme 5). Both compounds (**5a** and **7a**) were reacted with α-amino ketone **1a** under optimised conditions to affords the respective substituted quinolines **6aa** (73%) and **8aa** (79%). However, the reaction between α-amino ketones **1a** and nitrogen containing hetero aromatic acetylene 2-ethynyl pyridine **9a** did not give the desired product **10aa** under the standard reaction conditions (Scheme 5).



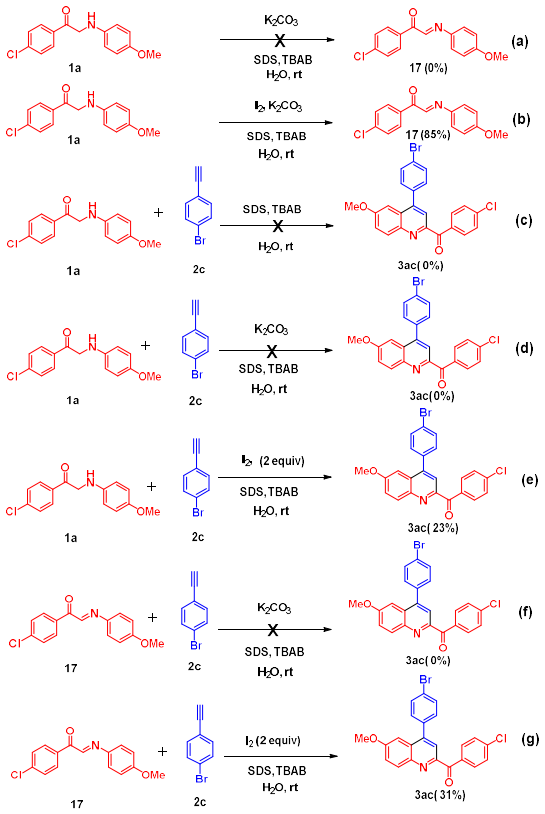
Scheme 5. Synthesis of hetero aryl containing quinolines.

Further, the reaction between α-amino ketone **1a** and styrene **11a**/1,2-diphenyl ethene **13a**/1,2-diphenyl acetylene **15a** failed to produce the desired product **12aa/14aa/16aa** under similar reaction conditions (Scheme 6).



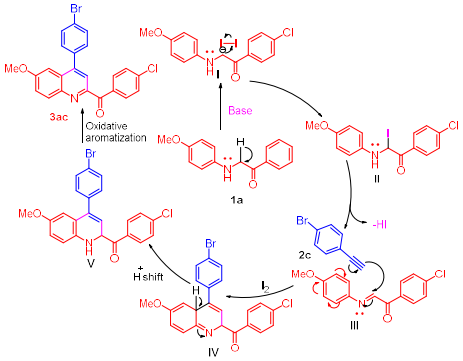
Scheme 6. Exploration of quinoline synthesis with styrene (**11a**)/1,2-diphenyl ethene (**13a**)/ diphenyl acetylene (**15a**).

To understand the mechanism of reaction, few control experiments were carried out as shown in (Scheme 7). None of the control experiments without iodine produced desired product **3ac** (Scheme 7 c, d and f). However, in the absence of **2c** with standard reaction conditions iminium intermediate **17** was obtained from **1a** (Scheme 7 b). We were fortunate to isolate and characterize the iminium intermediate **17** (Scheme 7, b)/**III** (Scheme 8) and use it for onward reaction with **2c** to give highly substituted quinoline **3ac**. It is also interesting to report here that the molecular iodine alone can also produce the desired product from α-amino ketones **1a** and its imine (**III/17**), however the yield was very poor (Scheme 7, e and g). The base K_2CO_3 is playing a key role to increase the reaction rate to improve the yields. The HI generated in the reaction mixture might have reconverted into iodine by aerobic oxidation in water.[11]



Scheme 7. Control experiments.

The possible reaction mechanism for the formation of highly substituted quinolines appears to be in the presence of the micellar system of SDS and TBAB the solubility of reactants improved in water (Scheme 8). The proton abstraction by K_2CO_3 in **1a**, might led to carbanion species **I**, which might have attacked on I_2 to give iodinated species **II**. Elimination of HI from **II** might have led to generation of imine intermediate **III**. Phenyl alkyne **2c** might have reacted in the presence of Iodine with intermediate **III** followed by inter molecular cyclization to give tetra hydro quinoline species **IV**. To increase the stability, hydrogen ion might have shifted as in **V** followed by aerobic oxidation to give highly substituted quinoline derivative **3ac.**



Scheme 8. Possible reaction mechanism.

In conclusion, we have developed a new approach for the synthesis of highly substituted quinolines, which involves the C(sp^3)-H functionalization of amino-ketones/glycine esters/glycine amide by molecular iodine followed by elimination of HI to generate imine and attack of aromatic/aliphatic, alkynes/alkenyl ester on imine and subsequent aerobic oxidative aromatization in tandem using K_2CO_3 and surfactants combination (SDS and TBAB) in water. Our protocol is operationally simple and avoids use of any oxidant, toxic metal or organic solvents. We have also demonstrated broad scope of the reaction for the synthesis of substituted quinolines and bioactive aza-lignans.

General procedure for synthesis of poly substituted quinolines

In an oven dried 50 ml R.B flask charged with stir bar, α-keto-amine (0.02 g, 0.94 mmol, 1.0 equiv.), alkyne (0.067 g, 0.66 mmol, 0.7 equiv.), Iodine (0.720 g, 2.84 mmol, 2.0 equiv.), K_2CO_3 (0.392 g, 2.84 mmol, 2.0 equiv.), sodium dodocyl sulphate (SDS), (0.327 g, 0.37 mmol, 0.4 equiv), tetrabutyl ammonium bromide (TBAB) (0.366 g, 0.37 mmol, 0.4 equiv) and water (5.0 mL), resulting mixture was stirred at rt for 30-50 min. After completion of reaction monitored by TLC (1:7 ethyl acetate and hexane) was cooled down to room temperature and diluted with 10 mL of H_2O. The resultant mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (100-200 mesh) by using hexane/ethylacetate solvent system to give desired poly substituted quinoline compounds.

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Keywords: α-Amino ketone • Phenyl acetylene • TBAB, SDS• C(sp^3)-H functionalization • Iodine • quinolines

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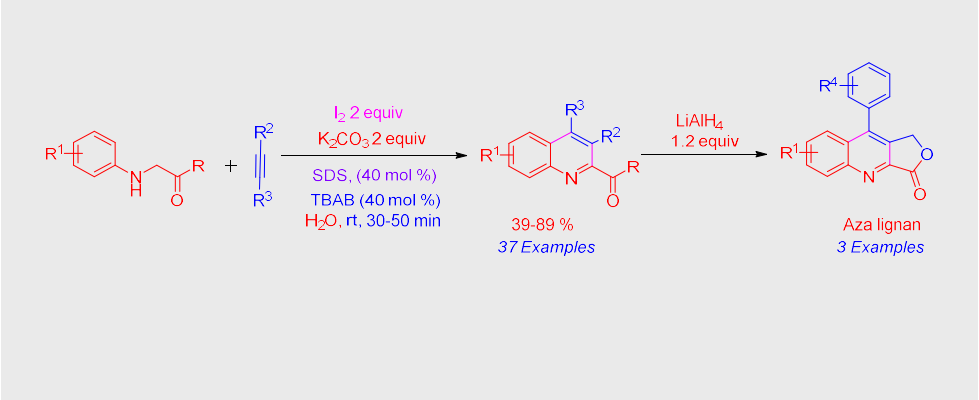

A one-pot method has been developed for the synthesis of highly substituted quinoline derivatives through C(sp^3)-H functionalization of α-amino ketone derivatives/glycine esters/glycine amide by iodine, nucleophelic substitution by aromatic/aliphatic alkynes/alkenyl esters and aerobic oxidative aromatization in tandem using K_2CO_3 and tetrabutyl ammonium bromide (TBAB) and sodium dodecyl sulphate (SDS) surfactant combination in water at room temperature within 30-50 min. in moderate to good yields.

Key topic: C(sp^3)-H functionalization

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