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IODINE CATALYSEDSYNTHESISOF QUINOLINE FRAMEWORKS*VIA* TANDEM CYCLIZATION

R. L. Satyanarayana[a], N. PrudhviRaju[a*], K. PavanKrishna[a], KiranManda[b], B.Jagan Mohan Reddy[c], G.RamaSwamy[d]

[a]*DepartmentofChemistry,B.V. RAJUCollege, Bhimavaram,AP-534202,India.*
[b]*DepartmentofChemistry,Shri Vishnu College of PharmacyCollege, Bhimavaram,AP-534202,India.*
[c]*DepartmentofChemistry,AdikaviNannaya University,Rajamahendravaram,AP-533296, India.*
[d]*Department of Basic Sciences,Vishnu Institute of Technology, Bhimavaram,AP-534202, India.*
**CorrespondingAuthor E-mail: prudhvi115@gmail.com*

ABSTRACT: Iodine-catalyzed threecomponent tandem cyclization reactions of aldehydes, terminal alkynes, and primary amines have been developed. The processes can provide adiverse range of quinoline derivatives in good yields from simple starting materials.

KEYWORDS:Phenyl Acetylene, Aldehydes, Anilines,QuinolineDerivatives, Iodine,Tandem Cyclization,

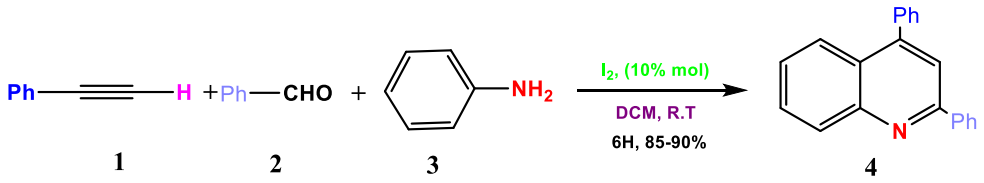
INTRODUCTION:

Iodine is effective, alternative, and promising non metal catalysts have received much more attention in recent years because of their less expensive, readily available, and environmentally benign properties. During the last half decade, Iodine catalyzed oxidation [i],hydrosilylation [ii-iii],andcarbon-carbon bond forming reactions have been intensively investigated [iv–vi]. Most recently, Iodine catalyzed *S*-arylation of thiols [vii], *N*-arylation of nitrogen nucleophiles [viii], and*O*-arylation of phenols [ix] with aryl halides, and A^3-coupling reaction of aldehyde, alkyne, and amine have been developed [x]. Because of interest for both the academic and the industrial community, it is desirable to expand the application scope of Iodine catalysts in organic transformations due to their unique and significant advantages.

One current important area of modern synthetic chemistry is the development of efficient practical methodsthat minimize the requisite time, cost, labour, resource management, and waste generation (atom economy) for the desired transformation [xi]. Tandem reaction (several transformations in one synthetic operation)approach isrecognizedasapowerfulmethodtowardthisgoal, andonlyasingle reactionsolvent,workupprocedure, and purification step may be required to provide a

productthatwouldotherwisehavetobemadeoverthe course of several individual steps [xii].
The quinoline nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important pharmacological and biological activities [xiii–xv], and thus the development of efficient syntheses of highly functionalized quinoline derivatives has been the focus of most researches for many decades andcontinuestobeanactiveandrewardingresearch area [xvi]. However, most of the existing methods suffer from the limited availability of substrates or require multistep procedures. During the course of our efforts directed toward the development of Iodine-catalyzed organic transformations, we found that treatment of aldehydes, primary amines, with terminal alkynes in the presence of I_2(10% mol) without any ligand and additive gave 2,4-disubstituted quinoline derivatives in good yields with high atom economy [xvii]. This reaction would proceed presumably through a tandem cyclization /oxidation reaction with only water as the waste product (Scheme 1).

RESULT AND DISCUSSION:



Scheme 1

Table 1:*Effectofsolventintandem cyclization*

Entry	Solvent	Yield(%)
a	Toluene	70
b	Dioxane	55
c	CH_3NO_2	60
d	1,2-Dichloromethane	90
e	1,2-Dichloroethane	85
f	Ethyleneglycol	25

Phenylacetylene (112 mg, 1.10 mmol), benzaldehyde (106 mg, 1.00mmol),aniline(91mg,1.00mmol), I_2(0.01mmol), solvent(2.0 mL) at 25°C for 6 h under an air atmosphere

Our initial investigation focused on the effect of solvent on the three-component tandem reactions of aldehydes,terminalalkynes,andprimaryamines. Several solventswerescreenedinamodelreactionofphenylacetylene, benzaldehyde, and aniline, and a significant solvent effect was observed (Table 1). When the reactions were conducted in 1,2-dichloromethane and dichloroethane under an air atmosphere, excellent yields ofproducts(90%,85%)wereobtained.Useoftoluene,nitromethane(CH_3NO_2),anddioxaneassolvents ledtolower yields of isolated products, and only 25% yield of the desired product was obtained while the reaction was performed in ethylene glycol.

Table 2: ***Synthesisofquinolinederivativesby Iodine-catalyzedtandemcyclization***[a]

Entry	R^1	R^2	R^3	Yield(%)
a	Ph	Ph	H	90
b	Ph	*p*-CH_3Ph	H	85
c	Ph	*p*-CH_3OPh	H	88
d	Ph	*p*-ClPh	H	87
e	Ph	*p*-BrPh	H	89
f	Ph	*m*-ClPh	H	85
g	Ph	*o*-ClPh	H	84
h	Ph	Ph	*p*-CH_3	91
i	Ph	Ph	*p*-CH_3O	83
j	Ph	Ph	*p*-Cl	92
k	Ph	Ph	*o*-CH_3	81
l	*p*-CH_3Ph	Ph	H	84
m	*p*-FPh	Ph	H	88
n	*p*-ClPh	Ph	H	89
o	*p*-PhPh	Ph	H	92

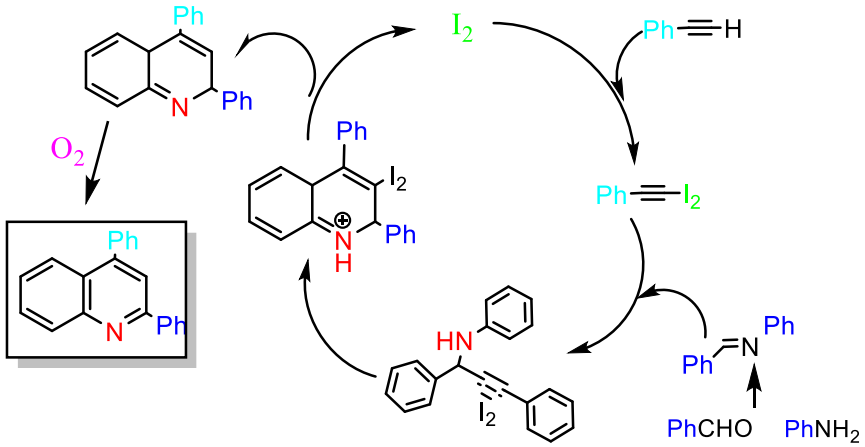
[a]Alkyne(1.10mmol),aldehyde(1.00mmol),amine(1.00mmol),I_2(0.01mmol),1,2-dichloromethane(DCM,2.0mL)at25°Cfor6hunder an air atmosphere.

With respect to the catalyst loading, 10 mol% of I_2 was found to be optimal. When only 5 mol% of $I_2$was used, the desired product was isolated in 65% yield, and no significant improvement was observed with 20 mol% of I_2. During the course ofourfurtheroptimizationofthereactionconditions,thereaction was generally completed within 6h when itwas performed at 25°C by using 10 mol% of I_2 inthe absence of any ligand and additive.

Under the optimized conditions, we extended our studies to different combinations of aldehydes, primary amines, and terminal alkynes, and the results are summarized in Table 2. Phenylacetylene and aniline were initially used as model substrates for exploring the aldehyde substrate scope. Ascan be seen from Table 2, benzaldehyde and substituted benzaldehydes with both electron-donating and electron-withdrawing functionalities, such as methoxy, methyl, bromo, and chlorogroups,affordedthecorrespondingquinolinederivativesin good yields (Table 2, entries a—g). It seems that this reactionwasnotsensitivetostericeffects(suchas,2-chlorobenzaldehyde giving the desired product in 84% yield), nor was it to electronic effects (Table 2, entries c*vs* d). However, when an aliphatic aldehyde (isobutyraldehyde)wassubjectedtothereaction,only26%yield of the desired product was obtained. Then, we examined the scope of primary amine substrates, a combination of phenylacetylene-benzaldehyde-amine was chosen and various amines were surveyed. The results listed in Table 2 indicated that *p*-toluidine, *o*-toluidine, *p*-anisidine, and *p*-chloroaniline were good substrates for this tandem transformation, and high yields of the corresponding products were isolated under the optimized reaction conditions (Table 2, entries h–k. Subsequently, the scope of alkynes in this reaction was also investigated, and it was found that substituted phenylacetylenes, including *p*-methylphenylacetylene, *p*-chlorophenylacetylene, *p*-fluorophenylacetylene, and diphenylacetylene, were suitable

substrates for this transformation,andthedesiredproductswereobtained in good yields (Table 2, entries l–p). Unfortunately, aliphatic alkynes were aborted in this process.

A possible mechanism of the I_2-catalyzed one-pot tandem three-component reaction of aldehyde, alkyne,andaminewasproposedinScheme2.



Scheme 2. Possible mechanism of Iodine-catalyzed tandem reaction ofaldehyde, alkyne, and amine.

The formed alkynylate complex underwent nucleophilic addition to imine formed *in situ* from aldehyde and primary amine to generate propargylamine. The triple bond of propargylamine could be activated by I_2 as Lewis acid to promote an intramolecular nucleophilic attack by the *N*-substituted phenyl ring attached to the nitrogen.The resulting complex subsequently underwent decomposition to give the dihydroquinoline intermediate and regenerate I_2catalyst for further reactions. In the presence of air oxygen, the generated dihydroquinoline could be further oxidized by O_2 to afford quinoline product. Comparing with the similar Au^{III}-catalyzed tandem transformation, the stronger Lewis acidity ofI_2than $AuCl_3$ appears to be the main reason for the higher efficiency of this catalytic system.

GENERAL PROCEDURE:

All ^{1}H NMR spectra were recorded at 400 MHz by BrukerFT-NMRspectrometers.Chemicalshiftisgivenasdvaluewith reference to tetramethylsilane (TMS) as internal standard. The CHN analysis was performed on a Vario El III elementar. Products were purified by flash chromatography on 200–400 mesh silica gel, SiO_2. The chemicals were purchased from commercial suppliersAldrich Chemical Company and were used without purification prior to use.

Generalexperimentalprocedureforthetandem reaction. Under an air atmosphere, a 10 mL of round bottom flaskequippedwithamagneticstirbarwaschargedwith an aldehyde (1.00 mmol), amine (1.00 mmol), and the mixture washeatedandstirredat0°Cfor30 minute. Then I_2 (16.2 mg, 0.10 mmol), alkyne (1.10 mmol) were added. The reaction mixture was then stirred at 25°C untilthe substrateswereconsumed completely (about 6h), andthenthe residue was purified by flash chromatography (hexane/AcOEt15:1) to afford the desired product.

2,4-Diphenylquinoline(4a)^{1}HNMR(400MHz, $CDCl_3$):8.26(d,1H),8.21–8.18(m,2H),7.93–7.90 (m, 1H), 7.82 (s, 1H), 7.76–7.72 (m, 1H), 7.57–7.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 156.7, 149.1, 148.2,139.7,138.4,130.5,129.3,129.4,128.4,128.7,128.1,127.5,126.2,125.5,125.4,119.7.

2-(4-Methylphenyl)-4-phenylquinoline(4b)].^{1}HNMR(400MHz,$CDCl_3$):8.23(d,1H),8.08(d,2H),7.86(d,1H),7.77(s,1H)

,7.71–7.67(m,1H),7.53–7.45(m,5H),7.45–7.40(m,1H),7.30 (d, 1H), 2.40 (s, 3H); ^{13}C NMR (100MHz,$CDCl_3$):156.5,148.6,148.1,139.4,138.6,136.1,129.3,129.6,129.8,128.1,128.7,127.8, 126.6,125.1,125.4,119.9,21.7.

2-(4-Methoxylphenyl)-4-phenylquinoline(4c).^{1}H NMR(400MHz,$CDCl_3$):8.21(d,1H),8.17–8.15(m,2H),7.87(d,1H),7.76(s,1H),7.72–7.68(m,1H),7.55–7.49(m,5H),7.45–7.41(m,1H),7.40–7.22(m,1H),3.86(s,3H);^{13}CNMR(100MHz, $CDCl_3$)160.5,156.7,148.8,148.6,138.5,132.8,129.1,129.2,129.3,128.7,128.5,128.3,125.3,125.8 ,125.5,118.6,114.6,55.4.

2-(4-Chlorophenyl)-4-phenylquinoline(4d). ^{1}H NMR(400 MHz, $CDCl_3$): 8.21 (d, 1H), 8.13–8.11 (m,2H),7.89–7.87(m,1H),7.74(s,1H),7.73–7.69(m,1H),7.53–7.49 (m, 5H), 7.47–7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):155.8,149.1,148.5,138.5,137.8,135.6,129.8,129.5,129.6,128.3,128.5,128.7,128.5,126. 8,125.2,125.1,118.2.

2-(3-Chlorophenyl)-4-phenylquinoline(4f). ^{1}H NMR (400 MHz,$CDCl_3$):8.25(d,1H),7.98–7.96(m,1H),7.76–7.71(m,2H),7.70(s,1H),7.57–7.47(m,7H),7.42–7.33(m,2H);^{13}CNMR(100MHz,$CDCl_3$):156.6,148.3,147.6,139.9,137.2,132.4,131.5,130.1,129. 8,129.6,129.6,129.3,128.6,128.2,127.0,126.5,125.6,125.7,122.5.Anal.Calcd.for$C_{21}H_{14}ClN$:C,7 9.87;H,4.4;N,4.44.Found:C,79.81;H,4.51;N,4.52.

6-Methyl-2,4-diphenylquinoline(4h).^{1}HNMR(400 MHz,$CDCl_3$):8.18–8.13(m,3H),7.77(s,1H),7.65(s,1H),7.58–7.49(m, 8H),7.46–7.43(m, 1H),2.47(s,3H); ^{13}C NMR(100MHz,$CDCl_3$):155.9,148.4,147.1,139.9,138.8,136.7,131.5,129.8,129.3,129.5,128.7,1 28.6,128.8,127.4,125.5,124.6,119.3,21.2.

6-Methoxyl-2,4-diphenylquinoline(4i)[23].^{1}HNMR(400 MHz,$CDCl_3$):8.16–8.13(m,3H),7.76(s,1H),7.58–7.48(m,7H),7.44–7.37(m,2H),7.19(d,,1H),3.78(s,3H);^{13}CNMR (100MHz,$CDCl_3$):157.1,154.7, 147.2,144.1,139.5, 131.3,129.1, 128.2, 128.3, 128.6,128.1, 127.4,126.6, 121.8, 119.4.103.5, 55.7

6-Chloro-2,4-diphenylquinoline(4j).^{1}HNMR(400 MHz,$CDCl_3$):8.18–8.15(m,3H),7.86(d,1H),7.82(s,1H),7.66–7.64(m,1H),7.58–7.50(m,7H),7.48–7.44(m,1H);^{13}CNMR(100MHz,$CDCl_3$):157.1, 148.8, 147.4, 139.2, 137.7,132.5, 131.6, 130.1, 129.4,129.8, 128.4, 28.6,128.8, 127.9, 126.2, 124.4,120.1

2-Phenyl-4-p-tolylquinoline(4l) .^{1}H NMR (400 MHz, $CDCl_3$):8.26–8.24(d,1H),8.19–8.18(m,2H),7.94(q1.2Hz,1H),7.81(s,1H),7.74–7.71(m,1H),7.54–7.51(m,2H),7.47–7.45(m,4H), 7.36(d,1H),2.48(s,3H);^{13}CNMR(100MHz,$CDCl_3$): 156.8,149.7,148.8,139.1,138.2,135.7,130.1,129.7,129.9,128.2,127.7,126.2,125.5,125.8,119.4, 21.2.

4-(4-Chlorophenyl)-2-phenylquinoline(4m).^{1}HNMR (400MHz,$CDCl_3$):8.25–8.23(m,1H), 8.23–8.16(m,2H),7.84–7.81(m,1H),7.76(s,1H),7.74–7.70(m,1H),7.54–7.43(m,8H);^{13}CNMR(100MHz,$CDCl_3$):156.9, 148.0, 147.7,139.6,136.8,134.4,130.9, 130.6, 129.5, 129.2, 128.1, 128.2,127.1, 125.3, 125.2,119.1.

4-(Biphenyl-4-yl)-2-phenylquinoline(4n).^{1}HNMR(400 MHz,$CDCl_3$):8.26(d,1H),8.19(d,2H),7.95(d,1H),7.82(s,1H),7.74–7.65(m,5H),7.59(s,1H),7.57(s,1H),7.52–7.41(m,6H),7.39–7.35(t,,1H);^{13}CNMR(100MHz,$CDCl_3$):156.2,148.8,148.8,141.2,140.4,139.2,137.8, 130.9,129.7,129.4,129.1,128.8,128.7,127.5, 127.1, 127.3, 127.0, 126.3, 125.4, 125.5, 119.3. Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C,90.81; H, 5.38; N, 3.81.

CONCLUSION:

In summary, we have developed an efficientand economic method for the synthesis of quinoline derivatives through a I_2catalyzed threecomponent tandem cyclization reactions with

only water as the waste product. These processes can provide a diverse range of quinoline derivatives in good yields from simple starting materials. The method has advantages of broad substrate scope, simple operation, mild reaction conditions, and high effectiveness. Further studies on the synthetic application of Iodineas catalyst in organic synthesis are currently ongoing in our group.

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