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Advanced Synthesis & Catalysis

Iodine Catalyzed C2-H Formamidation of Quinoline *N*-Oxides using Isocyanides: A Metal-Free Approach

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Abstract: A molecular iodine catalyzed regioselective insertion of isocyanide into C2-H of quinoline *N*-oxides has been developed. The reaction proceeds through the nucleophilic addition of isocyanide on quinoline *N*-oxides followed by rearrangement in presence of iodine. This metal-free reaction affords rapid access to quinoline 2-formamides with exceptional functional group tolerance, broad substrate scope and 100% atom-economy. A library of 33 *N*-(2-quinolinyl)formamides are synthesized, which may find applications in pharmaceuticals and synthetic chemistry.

Keywords: Formamidation; Iodine; Isocyanides; *N*-oxides; *N*-(2- quinolinyl)formamides

Introduction

Among diverse classes of *N*-hetero-aryl compounds, quinoline containing compounds display significantly wide spectrum of interesting biological activities and physicochemical properties.[1] The quinoline ring is the core structure for several natural products, biologically active molecules and privileged synthon in medicinal chemistry for the discovery of new drug leads.[2] The exemplifications of quinolines and its derivatives are used for the treatment of malaria, and various functional groups have been introduced onto the quinolines to improve its therapeutic activities.[3] However, the quinoline core moiety is prone to detoxification in the human body by hydroxylation of its C2 position, resulting in a dramatic decrease in its therapeutic effects.[4] To address this problem, several modifications have been explored at the C2 position of quinolines including sulfonylation, amination and alkylation to prevent the hydroxylation.[5,6] Owing its biological importance, a multitude of methodologies have been researched by synthetic chemists to functionalize the C2 position in the quinolines. Among the C2 modifications the prominent ones being *N*-acylated 2-aminoquinolines, 2-carbamoyl quinolines and *N*-(2-quinolinyl)formamide motifs which are extensively used in many pharmaceutical molecules (Figure 1).[7] But the limitations to these existing methods include that only a few amination methods that are available for the synthesis of 2-aminoquinolines.[8] The traditional methods in this category of synthetic preparation of 2-aminoquinolines involves amination reaction with 2-chloroquinolines which further mandates taking up

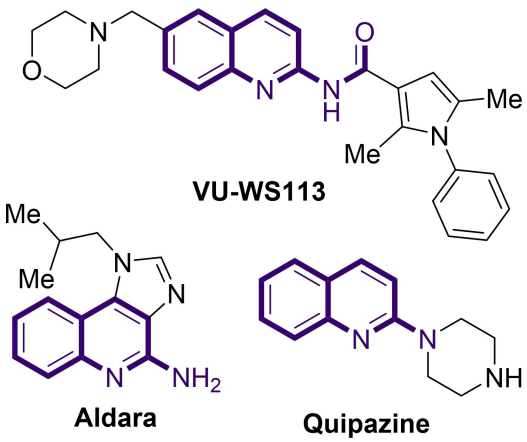

Figure 1. Some examples of functional 2-aminoquinolines.

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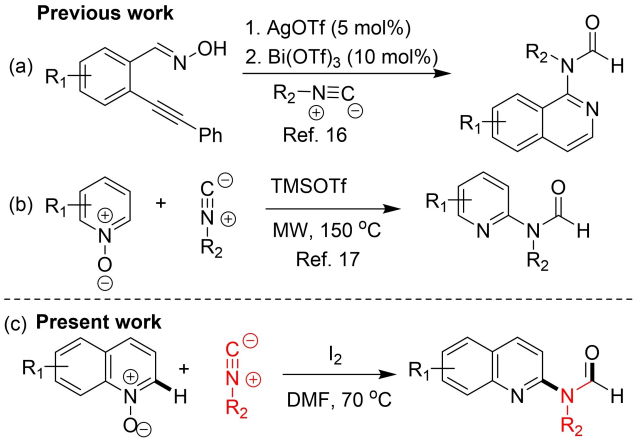
the cumbersome process of chlorination of quinoline *N*-oxides with poor 2,4-regioselectivity.[9]

Thus, activation of quinoline *N*-oxides with suitable activators remain challenging to functionalize the quinolines at C2 position. Although, there are various activators available which includes sulfonyl chlorides,[10] acyl chlorides,[11] anhydrides,[12] PyBroP[13] and boron reagents[14] to C2-H functionalization but have their own limitations such as stoichiometry, cost and toxicity. Among the C2 functional groups, the biologically important *N*-acylated 2-aminoquinolines are mainly synthesized from *N*-oxides with amide source via metal or radical initiators.[15]

Wu *et al.* reported Ag(I) and $Bi(OTf)_3$ mediated tandem reactions on 2-alkynylbenzaldoximes to obtain substituted isoquinolines (Scheme 1a).[16] However, the above mentioned method showed inferior results with quinoline *N*-oxides. In 2014, Vamos and co-worker were introduced activated isocyanides into the C2-H of pyridine *N*-oxides with the help of TMSOTf (Scheme 1b).[17] Recently, Sundararaju *et al.* have reported cobalt-catalyzed incorporation of *N*-*tert*-butyl-formyl functionality at C2 position as an application of their method on C-8 selective allylation of quinoline.[18]

To the best of our knowledge, there is no direct method available for the synthesis of *N*-(2-quinolinyl) formamides from quinoline *N*-oxides and isocyanides catalyzed by iodine. As part of our ongoing interest in the green chemistry,[19] we have proposed iodine catalysed C2-H functionalization of quinoline *N*-oxides with isocyanides to obtain *N*-(quinolin-2-yl) formamides. In this paper we tried to come up with a process which uses a metal-free molecular iodine catalyzed deoxygenative 2-amidation of quinoline *N*-oxides with isocyanides. Major advantages of this method not only include coming up with a mild, efficient and a novel approach to the synthesis of *N*-(2-quinolinyl)formamides, which itself is a structurally important compound but also comes as a handy method to complement the existing C2 aminoquinolines.



Scheme 1. Synthesis of 2-formamoyl pyridines and quinolines.

Results and Discussion

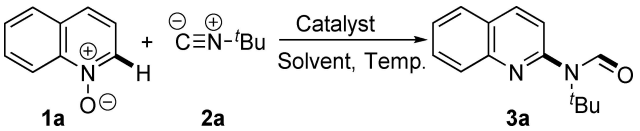
In our initial screening experiments, the reaction between quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine with suitable solvent and temperatures was investigated to optimize the reaction conditions, and only the key facts are reported in the Table 1. The reaction of quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine in CH_3CN at room temperature did not afford the desired product even after stirring for 24 h (Table 1, entry 1).

To our delight, the formation of *N*-*tert*-butyl-*N*-(quinolin-2-yl)formamide **3a** was observed with 50% in CH_3CN at elevated temperatures (Table 1, entry 2). These results motivated us to optimize the reaction conditions to improve the product yield. Next, we have carried out the reaction in various solvents to assess their effect on the reaction efficiency. Among all the solvents used, DMF was superior to the tested solvents, such as chlorinated solvents, THF, CH_3NO_2 ,Toluene and DMSO for this transformation (Table 1, entries 3–9). Further, change in the temperature did not improve the yield. (Table 1, entry 10–11).

Disappointingly, other promotor sources including *N*-iodosuccinimide, *N*-bromosuccinimide and NaI were investigated and found to have negative impact on reaction yields (Table 1, entries 12–14). Additionally, changing the loadings of catalyst had no positive effect on the transformation, only 65% and 30% yields are obtained when 5 mol% and 2 mol% of catalyst were used respectively (Table 1, entries 15–16). It is worth mentioning that our method proceeds with 100% atom-economy. Therefore, the optimized reaction conditions are 0.5 mmol of quinoline *N*-oxide, 0.5 mmol of isocyanide and 10 mol% of I_2 in 2 mL DMF at 70 °C for 6 h as shown in (Table 1, entry 8).

With the optimized conditions in hand, we commenced the evaluation of the scope of the reaction by examining diversely substituted quinoline *N*-oxides with *tert*-butyl isocyanide and results are showed in Scheme 2. In the beginning we have explored the effect of electron donating groups on quinoline *N*-oxides with *tert*-butyl isocyanide to obtain the corresponding quinoline 2-formamides and found to be well tolerated (Scheme 2, **3b**–**e**). Also, the electron withdrawing group on sixth position of quinoline gave the target product **3f** in 70% yield. Likewise, halogen substituted quinoline *N*-oxides were reacted smoothly with *tert*-butyl isocyanide to give the corresponding 2-formamide quinolines in good yields (Scheme 2, **3g**–**h**). Notably, substitution at C8 position such as benzyl, allyl, propargyl ethers, *N*-acetyl and *N*-tosyl of the

Table 1. Optimization of the Reaction Conditions.[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	I_2	CH_3CN	rt	0
2	I_2	CH_3CN	70	50
3	I_2	CH_2Cl_2	40	n.r
4	I_2	$ClCH_2CH_2Cl$	60	n.r
5	I_2	THF	70	10
6	I_2	CH_3NO_2	70	n.r
7	I_2	Toluene	70	n.r
8	**I_2**	**DMF**	**70**	**90**
9	I_2	DMSO	70	75
10	I_2	DMF	60	70
11	I_2	DMF	100	80
12	NIS	DMF	70	30
13	NBS	DMF	70	40
14	NaI	DMF	70	n.r
15	I_2	DMF	70	65[c]
16	I_2	DMF	70	30[d]
17	–	DMF	70	n.r

[a] Reaction conditions: Quinoline *N*-oxide **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.5 mmol), catalyst (10 mol%), solvent (2 mL), 6 h.
[b] Isolated yield.
[c] Iodine (5 mol%).
[d] Iodine (2 mol%) used.
n.r = No reaction.

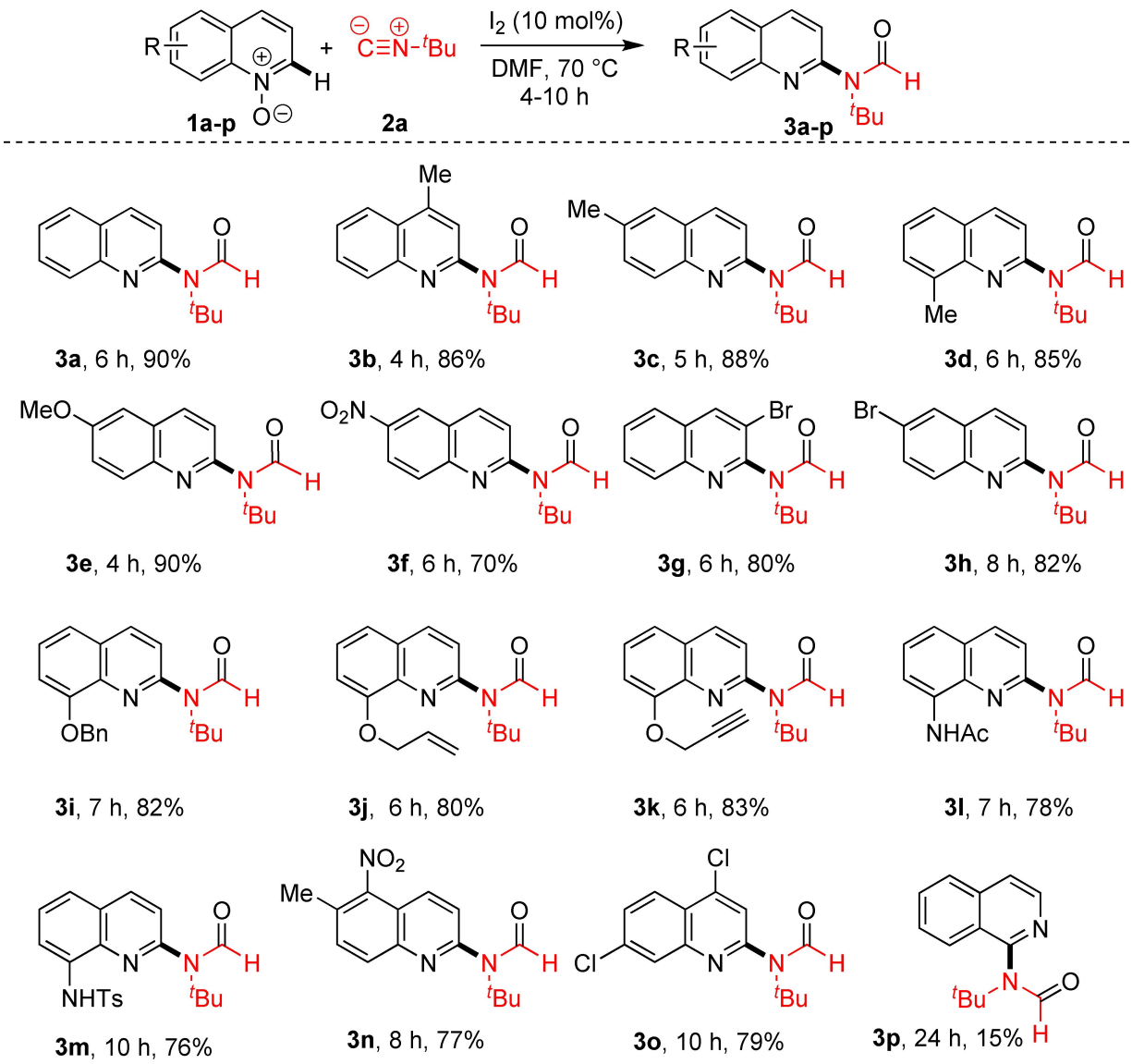
quoniline *N*-oxides are readily converted into the respective C2-formamides in 76–83% yields (Scheme 2, **3i–m**). It is worth noting that the quinoline *N*-oxides having disubstitutions also delivered the product **3n–o** in 77–79% yield. Indeed, C2 formamidation of pyridine *N*-oxide was not successful, but isoquinoline *N*-oxide gave poor yield (Scheme 2, **3p**).

Further, we have turned our attention to the scope of other isocyanides with different quinoline *N*-oxides and results are summarised in Scheme 3.The 1-pentyl isocyanide **4a** has effortlessly reacted with quinoline *N*-oxide **1a** and produced corresponding product **5a** in 80% yield. Besides, *p*-toluenesulfonylmethyl isocyanide (TosMIC) has been extensively preceded with diverse quinoline *N*-oxides to deliver corresponding formamide derivatives **5b–f** in 78–89% yields. Interestingly, ester attached isocyanides such as methyl isocyanoacetate **4c** and ethyl isocyanoacetate **4d** reacted with functional quinoline *N*-oxides to deliver target products **5g–k** in good to excellent yields (74–90%). In addition, the cyclohexyl isocyanide **4e** has been reacted smoothly with several quinoline *N*-oxides to furnish final products **5l–q** in 76–90% of yields.

Further, we investigated the efficiency of this protocol for gram scale reaction using quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine under the standard condition. The reaction afforded the final product **3a** in 85% of yield (Scheme 4).

Formamides are found to be a versatile substrate, and it can act as a hydrogen bonding acceptor.[20] However, it can be further deprotected selectively at later stage keeping the other substituents intact as described in Scheme 5. Selective aldehyde deformylation of **3a** mediated by aqueous NaOH has resulted in the formation of *N*-(*tert*-butyl)quinolin-2-amine **6** with 60% yield (Scheme 5).[21]

Apart from the traditional FT-IR, ^1H & ^{13}C NMR and mass spectral analysis, the formation of *N*-(quinolin-2-yl)formamide was also unambiguously verified by X-ray crystallography of compounds **3f** and **3o** (Figure 2). The crystallographic data and structure refinement parameters are given in the supporting information (Table S1). ^1H & ^{13}C NMR of compounds **3a–p** revealed that they exist as a mixture of two rotamers due to the different orientations of the C–N bond. It is well documented that *N*-formyl compounds exist in a solution as interconverting rotamers.[22] Hence, variable-temperature NMR experi-



Scheme 2. Generality in the synthesis of *N*-(quinolin-2-yl)formamide. Reactions were carried out using quinoline *N*-oxides **1a**–**p** (0.5 mmol), isocyanide **2a** (0.5 mmol), I_2 (10 mol%), DMF (2 mL), 70 °C and the yields are given for isolated products.

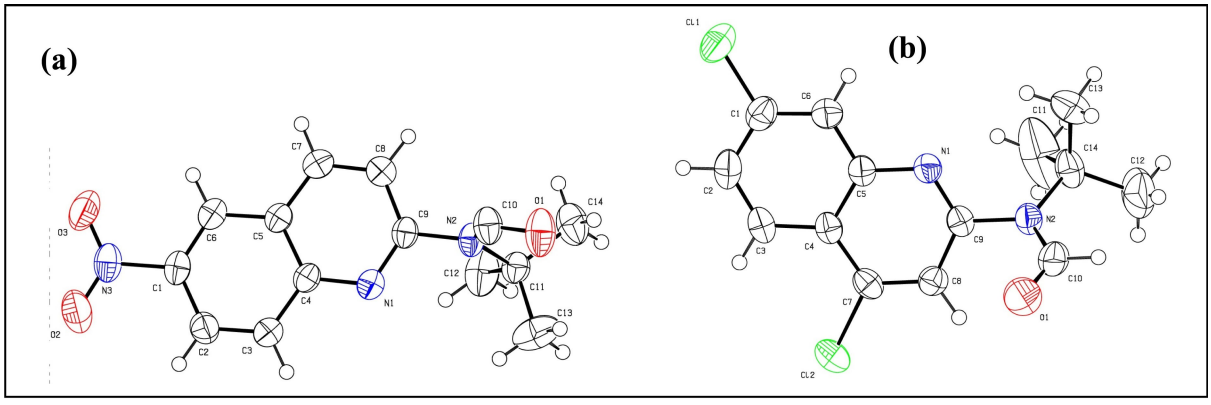
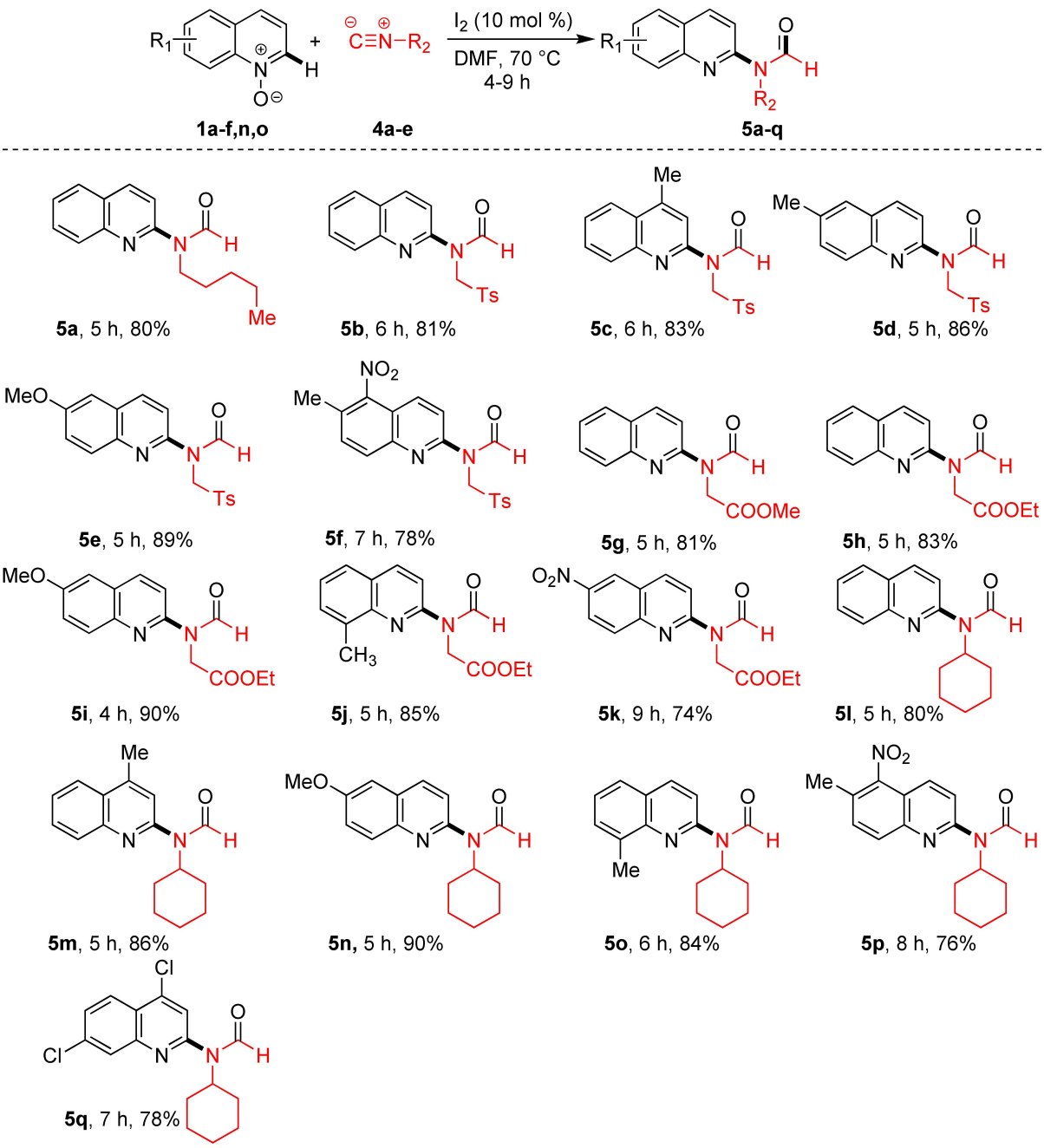
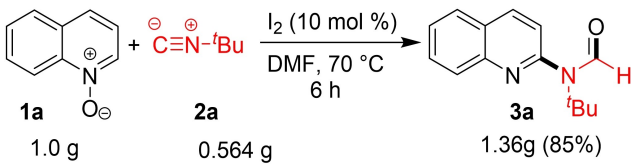


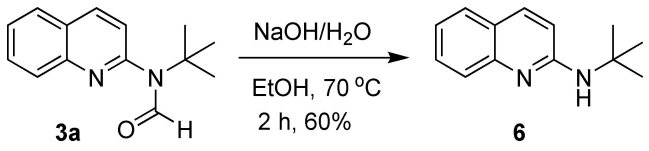
Figure 2. (a) X-ray ORTEP representations of (a) *N*-*tert*-Butyl-*N*-(6-nitroquinolin-2-yl)formamide **3f**; (b) *N*-*tert*-Butyl-*N*-(4,7-dichloroquinolin-2-yl)formamide **3o**. The thermal ellipsoids are drawn at 50% probability level.



Scheme 3. Generality in the synthesis of *N*-(quinolin-2-yl)formamide. Reactions were carried out using quinoline *N*-oxides **1a–f**, **n** and **o** (0.5 mmol), isocyanide **4a–e** (0.5 mmol), I_2 (10 mol%), DMF (2 mL), 70 °C and the yields are given for isolated products.



Scheme 4. Gram-Scale Reaction.



Scheme 5. Aldehyde deformylation of of *N*-*tert*-butyl-*N*-(quinolin-2-yl)formamide.

ments were performed to confirm the presence of rotamers in solution.

All the variable-temperature NMR experiments were carried out on model compound **3 a** in dimethyl sulfoxide (DMSO-d_6), which has a higher boiling point and results are showed in Figure 3. From the variable-temperature ^{1}H NMR experiments in DMSO-d_6, it was observed that three protons showed a broad singlet at δ 8.61–8.95, 8.52–8.32 and 7.53–7.25 at 25 °C, later the broad singlet at δ 8.61–8.95 was converted to sharp singlet at elevated temperatures. Similarly, the peaks at δ 8.52–8.32 and 7.53–7.25 were started splitting into doublets at high temperature and gave resolved peaks at 60 °C, which is due to the dynamic exchange between the two rotamers (Figure 3a–f).

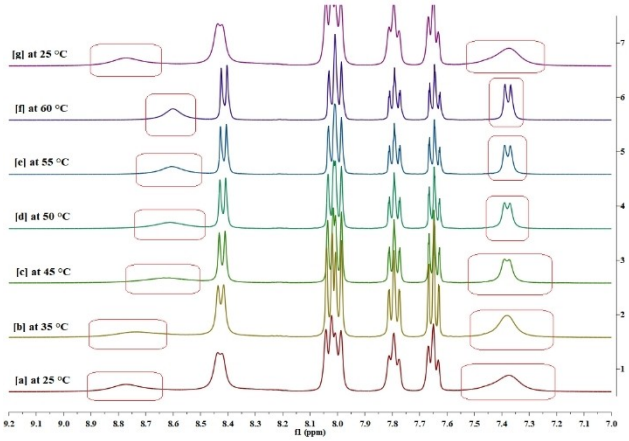


Figure 3. Variable-temperature ^{1}H NMR spectra of **3 a** in DMSO-d_6 from 25 °C to 60 °C demonstrating the presence of rotamers.

From the variable-temperature ^{13}C NMR experiments in DMSO-d_6, it was observed that broadening for a subset of ^{13}C NMR peaks at higher temperatures, which is due to the dynamic exchange between the two rotamers (Figure 4a–g). The complete resolved ^{13}C NMR signals were achieved at 60 °C, where the conformation interconversion is fast on the NMR time scale. The reversibility of these changes were verified when the experimental temperature was returned to 25 °C (Figure 4a–i).

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 6). Initially, quinoline **7** was treated with *tert*-butyl isocyanide **2 a**

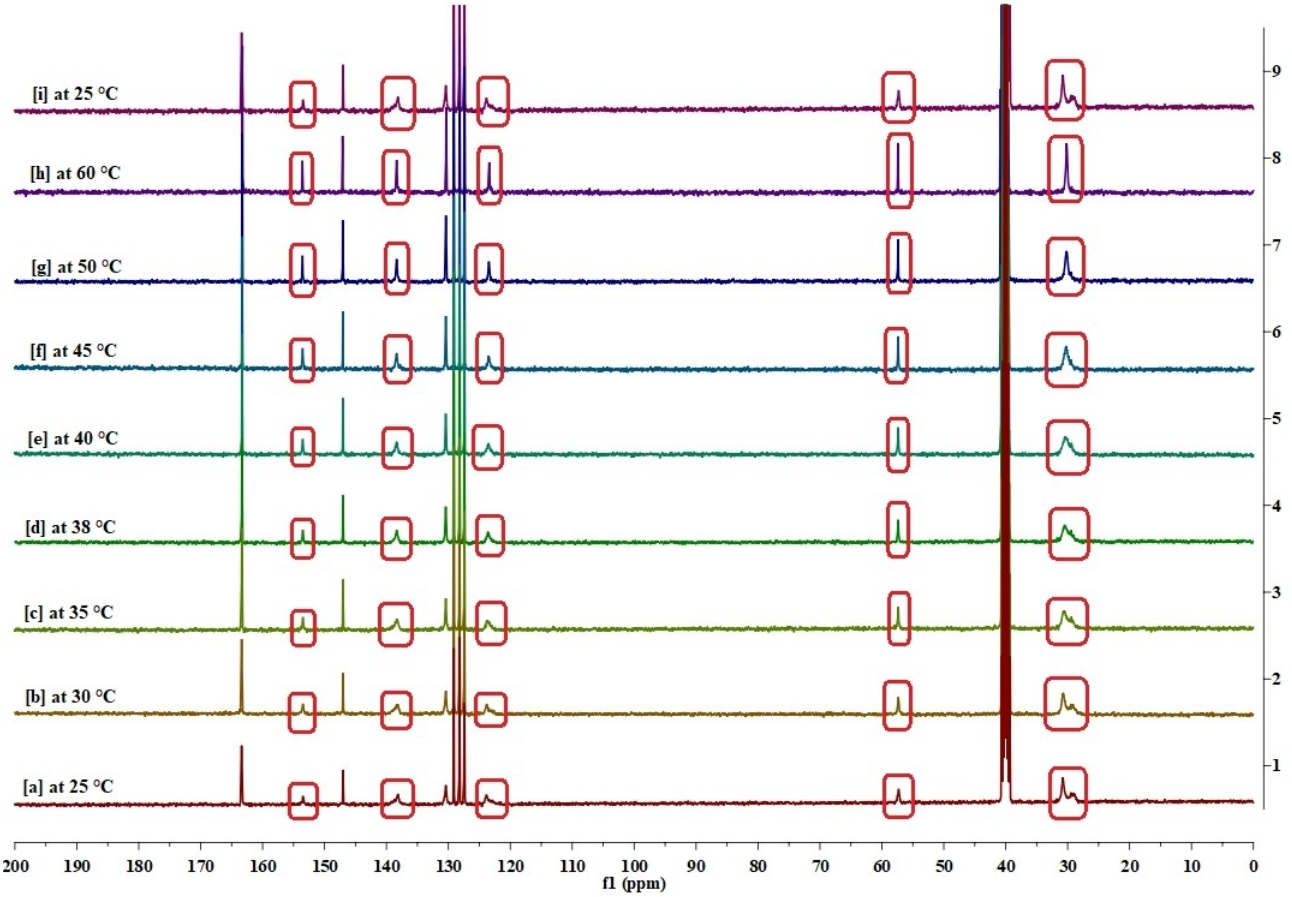
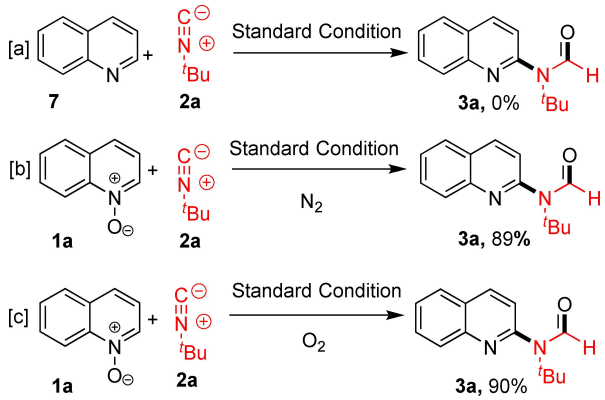


Figure 4. Variable-temperature ^{13}C NMR spectra of **3 a** in DMSO-d_6 from 25 °C to 60 °C demonstrating the presence of rotamers.



Scheme 6. Control experiments. Reaction conditions: 0.5 mmol of **1 a**, 0.5 mmol of **2 a**, I_2 (10 mol%) and 2 mL of DMF at 70 °C for 6 h. (a) Quinoline **7** (0.5 mmol); (b) Under 1 atm nitrogen; (c) under 1 atm oxygen.

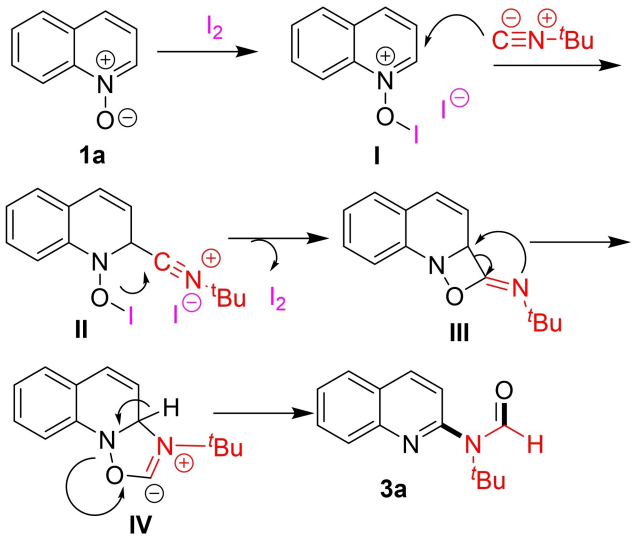
under the standard conditions, no reaction was observed, which indicated the role of *N*-oxide in this transformation (Scheme 6a). Finally, reactions were carried out under nitrogen and oxygen to find out the role of oxygen, the yield of product **3 a** was unchanged.

On the basis of our control experiments and previous literature,[16,23] a plausible mechanism of the iodine catalysed conversion of quinoline *N*-oxides to *N*-(2-quinolinyl)formamides is illustrated in Scheme 7.

The catalytic cycle initiates with the reaction of quinoline *N*-oxide **1a** with molecular iodine to produce intermediate **I**, then nucleophilic addition between **I** and isocyanide results in the formation of intermediate **II**. Later, the nucleophilic oxygen of *N*-oxide subsequently attacked on the carbon of isocyanide to form intermediate **III**, which readily undergoes rearrangement to form more stable intermediate **IV**. Finally, the intermediate **IV** undergoes re-aromatization to obtain the desired product **3 a.**

Conclusion

In summary, we have demonstrated a molecular iodine catalyzed regioselective C2 amino formylation of quinoline *N*-oxides with diversified isocyanides. This metal-free reaction affords rapid access to quinoline 2-formamides with exceptional functional group tolerance, broad substrate scope. This protocol provides 100% atom-economy. A library of 33 *N*-(2-quinolinyl) formamides are synthesized.



Scheme 7. Proposed Reaction Mechanism.

Experimental Section

General Procedure for the Synthesis of *N*-(2-Quinolinyl)formamides (3 a–p and 5 a–q)

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), I_2 (10 mol%), alkyl isocyanides (0.5 mmol) and DMF (2 mL). The mixture was stirred at 70 °C for the appropriate time (4–10 h). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature and treated with saturated $Na_2S_2O_3$, later extracted with ethyl acetate (3 × 10 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexanes and ethyl acetate as an eluent.

General Procedure for Hydrolysis of Formamides

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate *N*-(2-quinolinyl) formamide (0.5 mmol) in ethanol (2 mL) and aqueous (1.0 mL) sodium hydroxide (20 mg; 0.5 mmol). The reaction mixture was stirred at 70 °C for 2 h. The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexanes and ethyl acetate as an eluent.

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RESEARCH ARTICLE

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