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Electrophile-Driven Regioselective Synthesis of Functionalized Quinolines

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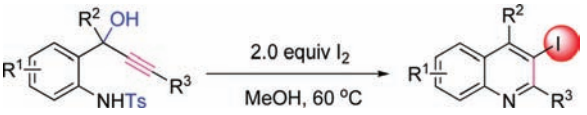
ABSTRACT



Highly substituted 3-iodoquinolines bearing different alkyl and aryl moieties can be synthesized in moderate to excellent yields (up to 99%) by 6-endo-dig iodocyclization of 2-tosylaminophenylprop-1-yn-3-ols with molecular iodine (I_2) under mild conditions. The cyclization is highly regioselective and the resulting 3-iodoquinolines can be further functionalized by various coupling reactions.

Quinoline derivatives are a major class of heterocycles which occur in various natural products, especially in alkaloids. The quinoline skeleton is often used for the construction of many synthetic compounds with diverse pharmacological properties.[1] In particular, halogen-containing quinolines are of special interest because the halogen atom sometimes plays an important role in the compound's bioactivity, and such compounds provide a further avenue for functionalization.[2] As a result, a number of attempts have been made to prepare and functionalize them since the late 1800s. The structural core of quinoline can be synthesized by various conventional methods.[3−8] However, these classical syntheses often make use of elevated temperatures and prolonged reaction times and/or use of strong acids and bases, which cannot be applied to sensitive substrates. There are also many new metal-catalyzed protocols for preparing quinolines.[9−12] Thus, a metal free, mild, and environmentally benign protocol for preparing quinolines from readily available and simple substrates is still of high demand because of their extreme significance. In recent years, the electrophilic cyclization of heteroatom nucleophiles, such as oxygen, nitrogen, and sulfur, with tethered alkynes has proven to be an effective

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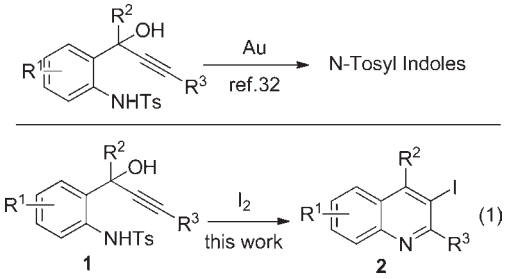
method for the synthesis of heterocyclic compounds.[13−31] We[13] and others have reported that electrophilic cyclization[14] of alkynes can be a very powerful tool for the preparation of a wide variety of important heterocyclic compounds due to the mild, efficient, and clean reactions. Many important heterocycles, such as benzo[*b*]thiophenes,[15] benzofurans,[16] 2,3-dihydropyrroles and pyrroles,[17] furans,[13b,18] dihydropyrans,[13f,19] indoles,[20] isochromenes,[21] isocoumarins and R-pyrones,[22] isoquinolines and quinolines,[23] isoxazoles[24] and oxazoles,[25] furanones,[26] furopyridines,[27] spiro[4,5]trienones,[28] coumestans and coumestrols,[29] naphthols,[30] and naphthalenes,[31] have been reported based on this strategy. Also very recently, Wai's group reported the synthesis of *N*-tosylated indoles using 2-tosylaminophenylprop-1-yn-3-ols as starting materials in the prescence of gold catalyst.[32] We envisioned that the treatment of 2-tosylaminophenylprop-1-yn-3-ol (**1a**) with molecular iodine (I_2) would lead to iodocyclization in a 5-exo-dig manner resulting in an indole derivative. To test the viability of the above hypothesis we treated **1a** with I_2, but unexpectedly the ^{1}H and ^{13}C NMR data revealed quinoline derivative **2a** (Scheme 1). Herein, we report a general and highly regioselective protocol for the synthesis of substituted quinolines by 6- endo-dig iodocyclization of 2-tosylaminophenylprop-1-yn-3-ols. In 2005, although Flynn developed the synthesis of 3-iodoquinolinium salts by a related process,[33] the lengthy preparation of their starting materials, the low substrate scope, and the separation of quinolinium salts make it less attractive synthetically. We were extremely pleased to see that our 2-tosylaminophenylprop-1-yn-3-ols reacted smoothly to gave 3-iodoquinolines in a single step with no quinolinium salts.

To explore suitable reaction conditions for this useful transformation, we started by using 0.2 mmol of **1a** and 1.5 equiv of I_2 in nitrommethane at room temperature; to our

Scheme 1. Design of an Electrophile-Driven Cascade Cyclization



delight, the quinoline derivative **2a** was obtained in 38% yield after 2 h. Increasing the amount of iodine to 2.0 equiv, the yield slightly increased to 41%. Further increasing the amount of iodine resulted in a decrease of yield. The influence of different acids and increase of reaction temperature in nitromethane was studied but no useful results were obtained. We then discovered that the best result can be obtained by carrying out the reaction in methanol at 60 °C. Thus, changing the solvent from polar aprotic to polar protic the yield dramatically increased to 93%. The protic nature of the solvent is most probably involved in the easy removal of hydroxyl group to give intermediate **D** (see the mechanism, Scheme 2). Solvents such as dichloromethane, acetonitrile, and tetrahydrofuran were found to be less effective, whereas dimethylformamide and 1,4-dioxane were found to be ineffective (see the Supporting Information).

To investigate the scope of the cascade iodocyclization a variety of differently aliphatic and aromatic substituted 2-tosylaminophenylprop-1-yn-3-ols were subjected to the

Table 1. Cascade 6-Endo-Dig Iodocyclization of 2-Tosylaminophenylprop-1-yn-3-ols (eq 1)[a]

		alcohol					
entry	no.	R^1	R^2	R^3	time (h)	quinoline	isolated yield (%)
1	**1a**	H	Ph	Ph	6	**2a**	93
2	**1b**	H	Ph	*p*-MeC_6H_4	6	**2b**	94
3	**1c**	H	Ph	*p*-$MeOC_6H_4$	6	**2c**	96
4	**1d**	H	Ph	*p*-ClC_6H_4	6	**2d**	88
5	**1e**	H	Ph	*p*-BrC_6H_4	6	**2e**	81
6	**1f**	H	Ph	*m*-MeC_6H_4	6	**2f**	77
7	**1g**	H	Ph	*m*-$MeOC_6H_4$	6	**2g**	84
8	**1h**	H	Ph	*o*-MeC_6H_4	12	**2h**	66
9	**1i**	H	Ph	*o*-ClC_6H_4	12	**2i**	71
10	**1j**	H	Ph	*o*,*p*-$Cl_2C_6H_3$	12	**2j**	60
11	**1k**	5-Cl	Ph	Ph	12	**2k**	88
12	**1l**	5-Br	Ph	Ph	12	**2l**	76
13	**1m**	H	Ph	*n*-propyl	12	**2m**	62
14	**1n**	H	*p*-MeC_6H_4	Ph	6	**2n**	74
15	**1o**	H	*p*-BrC_6H_4	Ph	6	**2o**	99
16	**1p**	H	Me	Ph	12	**2p**	54
17	**1q**	H	Et	Ph	12	**2q**	40

[a] All reactions were run with 0.2 mmol of the alcohol, 2 equiv of I_2 in 2.0 mL of CH_3OH at 60 °C, followed by addition of 8.0 mL of saturated aqueous $Na_2S_2O_3$ to remove the excess I_2.

standard reaction conditions. The corresponding quinoline products were obtained in moderate to excellent yields as shown in Table 1. The structure of product **2b** was also confirmed by X-ray crystal structure analysis (Figure 1). As evident, R^2 and R^3 can be alkyl or aryl. In the case of R^2 and R^3 as phenyl groups, the reaction can tolerate both electron-donating and electron-withdrawing groups at different positions. The reaction is particularly good in the case of a group with an unshared pair of electrons on the

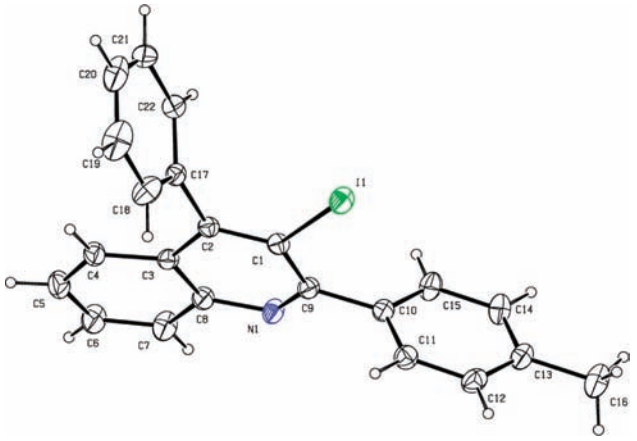
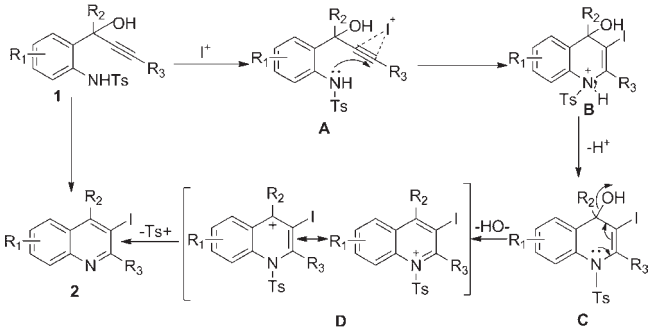


Figure 1. X-ray structure of **2b**.

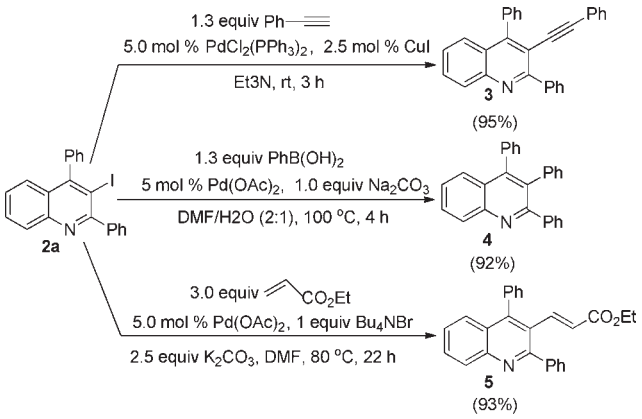
para position of R^2 (Table 1, entry 15). This result indicates that electron donation is needed to stabilize the cyclic intermediate **D** (see the mechanism in Scheme 2). The same fact is also supported by the results that moderate yields are obtained in the case of R^2 as alkyl group (Table 1, entries 16 and 17).

The mechanism of this iodocyclization involves anti attack of the electrophile and the nitrogen of the tosylated amino group on the alkyne moiety of **1** to produce an intermediate **B**, which undergoes a proton removal by the iodide present in the reaction mixture to give compound **C**. The intermediate compound **C** can be isolated if the reaction is carried out in an aprotic solvent such as nitromethane. However, in protic solvents **C** loses hydroxyl ion to give

Scheme 2. Mechanistic Considerations



Scheme 3. Palladium-Catalyzed Reactions of 3-Iodo-2,4-diphenylquinoline (**2a**)



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cation **D**. Finally, **D** gains full aromaticity by eliminating a tosyl group to form quinoline derivative **2** (Scheme 2).

In conclusion, we have discovered an efficient and highly regioselective protocol for preparing quinolines from readily available and simple starting materials. The reaction is metal-free and can produce substituted 3-iodoquinolines in a single step in moderate to excellent yields. The resulting 3-iodoquinolines can be further functionalized by using known organopalladium chemistry, such as Sonogashira[34] and Suzuki[35] cross-couplings and the Heck reaction[36] (Scheme 3). Further exploration of the reaction scope and mechanism is underway.

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Supporting Information Available. Detailed experimental procedures, copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds, and X-ray data of **2b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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