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Synthesis of Substituted Quinolines by Electrophilic Cyclization of *N*-(2-Alkynyl)anilines

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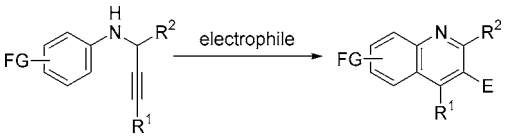
ABSTRACT

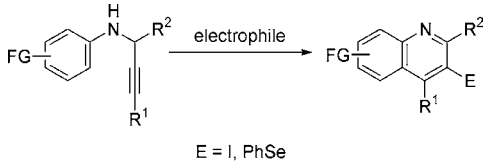


Quinolines substituted in the 3-position by an iodo or phenylseleno group are readily prepared in good to excellent yields by the reaction of propargylic anilines with appropriate electrophiles under mild reaction conditions.

Quinolines and their derivatives occur in numerous natural products, and many of them display interesting biological activity.[1] In particular, halogen-containing quinolines are of significant interest because the halogen atom sometimes plays a pivotal role in the compound's bioactivity, and such compounds provide a further avenue for structural elaboration.[2] Many methods for the synthesis of quinolines are known,[3] but due to their importance, the development of new synthetic approaches using mild reaction conditions remains an active research area.[4]

Although simple 3-bromoquinolines can be obtained by the bromination of quinoline hydrochlorides,[5] the site-selective aromatic halogenation of substituted quinolines remains a synthetic challenge.[6] 3-Haloquinolines have also been synthesized by a photochemical method,[7] a modified Skraup quinoline synthesis employing halo-substituted acroleins and anilines,[8] and the Friedländer quinoline synthesis.[2c] Some of these methods suffer relatively low yields, poor regioselectivity, and/or rather lengthy synthetic sequences.

Scheme 1



The cyclization of aryl-substituted alkynes via intramolecular hydroarylation has proven to be an efficient method for the construction of carbocycles and heterocycles.[9] Our work and that of others on the electrophilic cyclization of functionally substituted alkynes has recently showed that this is a very promising route to isoquinolines,[10] benzothiophenes,[11] polycyclic aromatics,[12] indoles,[13] naphthalenes,[14] furopy-

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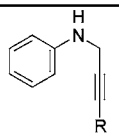
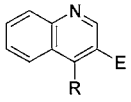
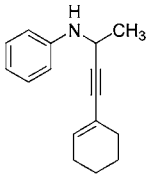
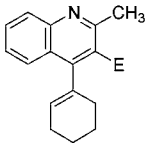
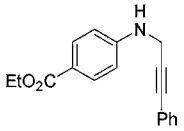
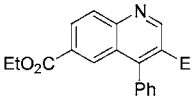
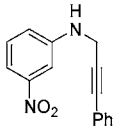
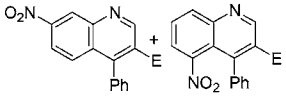
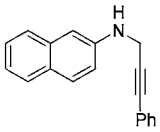
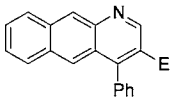
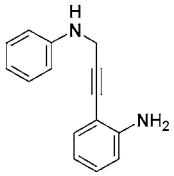
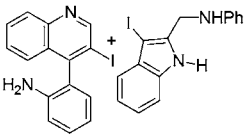
Table 1. Synthesis of Quinolines by Electrophilic Cyclization of *N*-(2-Alkynyl)anilines

entry	propargylic aniline		electrophile	product(s)			% yield
					E		
1	R = Ph	**1**	I_2[a]	R = Ph	I	**2**	76
2			ICl[b]		I	**2**	83
3	R = *p*-$MeOC_6H_4$	**3**	I_2[a]	R = *p*-$MeOC_6H_4$	I	**4**	71
4			ICl[b]		I	**4**	73
5			PhSeBr[c]		PhSe	**5**	74
6	R = *p*-FC_6H_4	**6**	I_2[a]	R = *p*-FC_6H_4	I	**7**	78
7	R = *p*-$CH_3COC_6H_4$	**8**	I_2[a]	R = *p*-$CH_3COC_6H_4$	I	**9**	57
8	R = *n*-Bu	**10**	I_2[a]	R = *n*-Bu	I	**11**	43
9		**12**	I_2[a]		I	**13**	80
10		**14**	I_2[a]		I	**15**	88
11			PhSeBr[c]		PhSe	**16**	56
12		**17**			I	**18+19**	8+71
13		**20**	I_2[a]		I	**21**	75
14		**22**	I_2[a]		I	**23+24**	55+0

[a] Reactions were run under the following conditions: 0.3 mmol of the propargylic aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN were stirred at room temperature. [b] To 0.3 mmol of propargylic aniline and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN was added 2 equiv of ICl in 1 mL of CH_3CN dropwise at room temperature. [c] To 0.3 mmol of propargylic aniline and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN was added 2 equiv of PhSeBr in 1 mL of CH_3CN dropwise at room temperature.

ridines,[15] and isochromenes.[16] This encouraged us to examine the cyclization of propargylic anilines by electrophiles in order to obtain 3-haloquinolines and derivatives (Scheme 1).

The requisite *N*-(2-alkynyl)anilines can be easily prepared by the reaction of propargylic mesylates or bromides with anilines.[17] We initially studied the reaction of *N*-(3-phenyl-2-propynyl)aniline (**1**) and I_2. The reaction has been examined with or without various bases such as $NaHCO_3$, $NaOCO_2CH_3$, triethylamine, and pyridine and in the presence of different solvents and varying amounts of I_2. The optimal

reaction conditions developed thus far include stirring of 0.30 mmol of the propargylic aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature. The reaction is complete in 0.5 h in all cases when finely ground iodine powder is employed. The results are summarized in Table 1.

We proceeded to examine the scope of the cyclization in terms of the alkyne substituent. The iodocyclization of both phenyl- (**1**) and 4-methoxyphenyl-substituted propargylic anilines (**3**) using I_2 generated the corresponding 3-iodoquinolines in 76 and 71% yields, respectively, with only a trace of any side products (entries 1 and 3, Table 1). Good results have also been obtained with the 4-fluorophenyl substrate **6** (entry 6). In contrast, introducing a stronger electron-withdrawing acetyl group in the *para* position of the aromatic ring significantly lowered the yield to 57% (entry 7). This reaction was accompanied by the formation of 25% of the corresponding 3,6-diiodoquinoline and 14% of the *N*-(3-aryl-2-propynyl)-4-iodoaniline. Cyclization with I_2 still proceeds when the terminus of the carbon−carbon triple bond is substituted by an alkyl group. Thus, 4-butyl-3-iodoquinoline can be synthesized in a moderate 43% yield by the cyclization of aniline **10** (entry 8) together with a 26% yield of 3,6-diiodoquinoline. The reaction also proceeded smoothly with vinylic substitution on the alkyne terminus. Thus, substrate **12** was cleanly converted to 4-(1-cyclohexenyl)-3-iodo-2-methylquinoline in an 80% yield (entry 9). In general, those alkyne substituents that can better stabilize an iodonium intermediate (see the latter mechanistic discussion) increase the reactivity of the carbon−carbon triple bond and produce higher yields of the desired quinoline. The *n*-butyl- and 4-acetylphenyl-substituted alkynes underwent competitive electrophilic aromatic substitution on the activated aniline ring, followed by iodocyclization to produce diiodoquinoline side products.

We continued to elucidate the scope of the reaction by examining the effect of various substituents on the aniline ring. Cyclization on relatively electron-poor anilines has also been successful. For example, quinoline **15** was generated exclusively in an 88% yield from substrate **14** bearing an ester group (entry 10).

The regioselectivity of this cyclization has also been investigated. Very interestingly, 3-nitroaniline **17** afforded regioisomers **18** and **19** in a 79% combined yield with cyclization primarily ortho to the nitro group (9:1 ratio of *ortho* to *para*) (entry 12). Only one isomer was observed in the cyclization of 2-naphthylamine **20** with ring closure occurring selectively in the less sterically hindered 3-position of the naphthalene ring (entry 13).

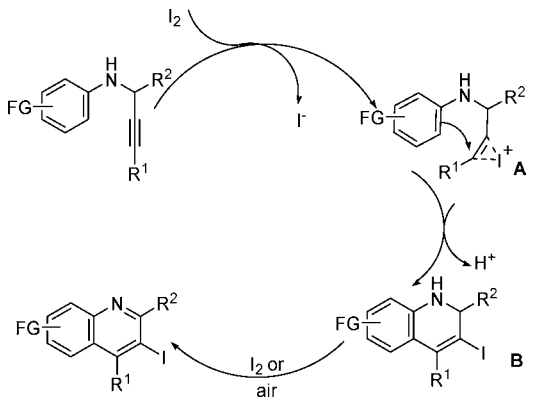
The reaction of diamine **22** has also been examined (entry 14). Presumably, both the aromatic ring and the amino group could attack the iodonium intermediate to form quinoline **23** and/or indole derivative **24**[13b] as products. However, under our reaction conditions, quinoline **23** is the only observed product, being formed in a 55% isolated yield.

The stronger electrophile ICl has also been employed in this cyclization. The ICl reaction conditions include stirring of 0.30 mmol of the propargylic aniline, 2 equiv of ICl, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature. Once again, good results were obtained at room temperature. Thus, iodoquinolines **2** and **4** have been obtained in slightly higher yields using ICl (entries 2 and 4). Lowering the temperature to 0 or −78 °C did not improve the yields. Yields comparable to those obtained using I_2 (compare entry 1 with 2 and entry 3 with 4) have been obtained, and the reactions are much faster, being complete in about 5 min. PhSeBr has also been used as an electrophile in this cyclization process. Satisfactory results have been obtained using substrates bearing either an electron-donating group on the phenyl ring of the side chain (entry 5) or an electron-withdrawing group (entry 11) on the aniline ring.

We propose the following mechanism for this process: (1) coordination of the carbon−carbon triple bond of the propargylic aniline to the iodine cation, generating an iodonium intermediate **A**, (2) intramolecular nucleophilic attack of the aromatic ring of the aniline on the activated triple bond to form dihydroquinoline **B**, and (3) in the presence of I_2 or ICl, oxidation of the dihydroquinoline **B** to the corresponding quinoline[18] (Scheme 3). It is possible that the dihydroquinoline is not oxidized to the quinoline until it is exposed to air during the workup.

To obtain a dihydroquinoline, we have also examined the cyclization on the mesyl-protected aniline **25** (Scheme 4).

Scheme 2



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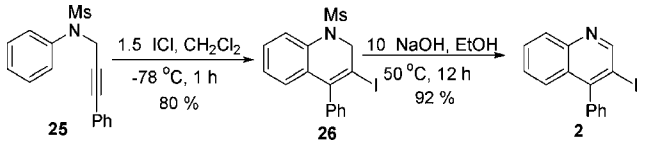
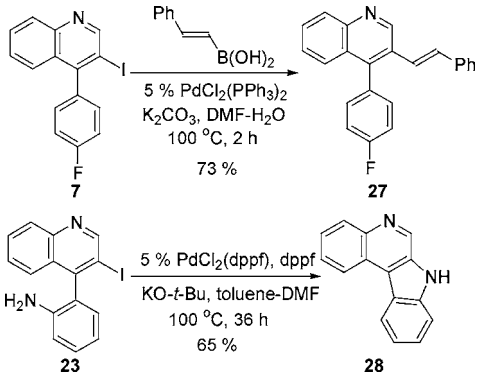
Scheme 3



Scheme 4



Thus, the reaction of **25** with ICl at −78 °C for 1 h afforded sulfonamide **26** in an 80% yield. Subsequent treatment with NaOH in EtOH at 50 °C for 12 h in the presence of O_2 converted this sulfonamide into the corresponding quinoline **2** in a 92% isolated yield.

3-Iodo- and selenoquinolines offer considerable potential for further elaboration. For example, iodoquinoline **7** undergoes a facile Suzuki reaction[19] to afford styryl-substituted quinoline **27** in a 73% yield (Scheme 5). Iodoquinoline **23** readily undergoes an intramolecular palladium-catalyzed Buchwald−Hartwig amination[20] to produce the interesting tetracyclic diamine **28** in a 65% yield.

In summary, we have developed a new approach to 3-substituted quinolines, which are difficult to prepare using previous methods. The reaction takes place under very mild reaction conditions and tolerates considerable functionality. The iodocyclization of propargylic anilines, followed by palladium-catalyzed substitution, affords a rapid increase in molecular complexity and provides a powerful tool for the preparation of a wide range of functionalized, multisubstituted quinolines. Further work is in progress to extend this method to the synthesis of more complex molecular structures.

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Supporting Information Available: General experimental procedures and spectral data for all of the starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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