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# Synthesis of Isoquinolines and Naphthyridines by Electrophilic Ring Closure of Iminoalkynes

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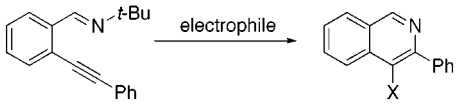
## ABSTRACT

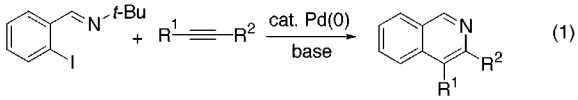



X = H, I, PhS, *p*-$O_2NC_6H_4S$, PhSe

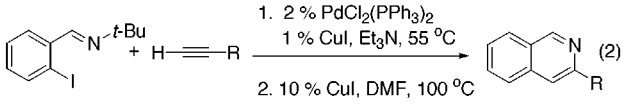
**Substituted isoquinolines and naphthyridines have been prepared in good to excellent yields by the reaction of iminoalkynes with a variety of electrophiles under mild reaction conditions.**

The isoquinoline backbone appears in numerous natural products. Thus, the synthesis of isoquinolines has received much recent attention.[1] Although classical methods[2] have been frequently employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks.

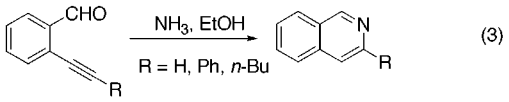
Recently, substituted isoquinolines have been synthesized by employing palladium chemistry.[3] We have reported the formation of numerous 3,4-disubstituted isoquinolines by the palladium-catalyzed annulation of internal alkynes (eq 1).[4]




(1)



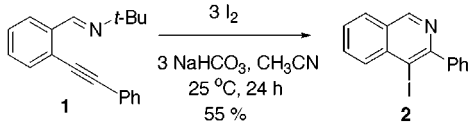

(2)




(3)

3-Substituted isoquinoline derivatives can be prepared by the palladium- and copper-catalyzed cross coupling of terminal alkynes and subsequent ring closure by catalytic CuI (eq 2)[5] or by the reaction of *o*-(1-alkynyl)benzaldehydes with $NH_3$ (eq 3).[6a]

During the course of this latter study, we discovered an interesting reaction which utilizes an external electrophile, $I_2$, to cyclize an iminoalkyne to a 3,4-disubstituted isoquinoline in modest yield (eq 4). The requisite iminoalkynes can




(4)

be easily prepared by the Sonogashira reaction of a 2-halobenzaldehyde and a terminal alkyne, followed by reaction

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(3) (a) Diederen, J. J. H.; Sinkeldam, R. W.; Frühauf, H.-W.; Hiemstra, H.; Vrieze, K. *Tetrahedron Lett.* **1999**, *40*, 4255. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238. (c) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565. (d) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941.

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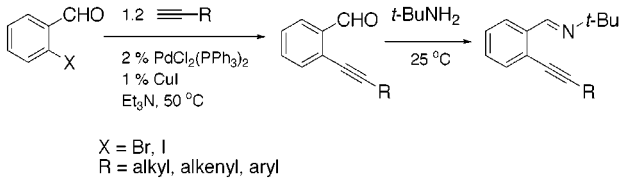
**Scheme 1**




X = Br, I
R = alkyl, alkenyl, aryl

with *tert*-butylamine (Scheme 1).[5] This efficient approach to a 4-iodoisoquinoline encouraged us to investigate this process, improve the reaction conditions, and extend the reaction to other electrophiles. Herein we report the results of that study.

First, we studied the reaction of iminoalkyne **1** and $I_2$. A variety of bases, such as $NaHCO_3$, $Na_2CO_3$, $K_2CO_3$, $NaOCO_2CH_3$,[7] pyridine, 2,4,6-trimethylpyridine, and triethylamine, different solvents, and different amounts of $I_2$ have been examined. This work has afforded a general procedure for the preparation of 4-iodoisoquinolines and 4-iodonaphthyridines. The following are the optimal reaction conditions: 0.25 mmol of the iminoalkyne, 6 equiv of $I_2$, and 3 equiv of $NaOCO_2CH_3$ in 7 mL of $CH_3CN$ are stirred at room temperature for an appropriate amount of time. The results of these $I_2$ cyclization reactions are summarized in Table 1, entries 1, 8, and 12. The reaction is complete in 0.5 h and affords good to excellent yields of 4-iodonaphthalenes and 8-iodonaphthyridines.

ICl, a stronger electrophile, has also been employed, and the corresponding cyclization products have been observed in yields comparable to those obtained using $I_2$. The reaction times are also essentially identical to those of $I_2$. The results are summarized in Table 1, entries 2, 13, and 16.

The next electrophile studied was PhSeCl. Very similar yields, 74% and 78%, respectively, of isoquinoline **3** were obtained from iminoalkyne **1** using 1 or 2 equiv of PhSeCl. The concentration of the reactants seems to play a role in this reaction. A more concentrated reaction gave a slightly lower yield. Thus, we chose 0.25 mmol of the iminoalkyne and 2 equiv of PhSeCl in 7 mL of $CH_2Cl_2$ at room temperature as our standard reaction conditions for the reaction of PhSeCl. The results from various cyclizations using this procedure are summarized in Table 1, entries 3, 6, 7, and 14. In general, the reaction of iminoalkynes and PhSeCl requires 1−3 days, and good to excellent yields of selenium-containing isoquinolines and naphthyridines are obtained.

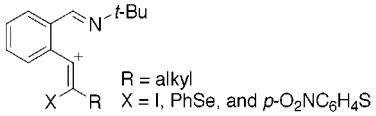
The electrophile *p*-$O_2NC_6H_4SCl$ has been examined under the optimum reaction conditions for PhSeCl. The isoquinoline product **5** expected from iminoalkyne **1** was obtained in a rather low yield of 47%. An increase in the reaction temperature or the addition of a Lewis acid to induce the cyclization had little effect on the product yield. PhSCl has also been employed as an electrophile. The results are summarized in Table 1, entries 9 and 15. In general, these reactions take 24 h and afford only modest yields of the corresponding sulfides.

In earlier work, we reported that catalytic amounts of CuI would close these same iminoalkynes to isoquinolines with a hydrogen in the 4 position.[5] We now wish to report that catalytic amounts of $AgNO_3$ will effect the same transformation and the reaction occurs under milder reaction conditions, is more general, and the yields are higher. Thus, 0.25 mmol of iminoalkyne **1** has been allowed to react with 2 equiv of $AgNO_3$ in 7 mL of $CHCl_3$ at 50 °C. After 1 day, isoquinoline **4** was obtained in 90% yield. Further study indicated that 5 mol % of $AgNO_3$ is enough to close the six-membered ring in good yield. Thus, the following standard conditions have been employed in all subsequent experiments: 0.25 mmol of the iminoalkyne and 5 mol % of $AgNO_3$ were stirred at 50 °C in 7 mL of $CHCl_3$ for the appropriate reaction time. The reaction takes approximately 24 h at 50 °C and gives decent yields of the corresponding cyclization products (entries 4, 10, and 11).

A variety of isoquinolines and naphthyridines have been prepared by this electrophilic ring closure reaction. The results are summarized in Table 1. Iodine and ICl close the six-membered ring the fastest. These reactions are complete in 0.5 h, although the yields from iminoalkyne **1** are somewhat less than those of PhSeCl (entry 3) and $AgNO_3$ (entry 4). PhSCl and *p*-$O_2NC_6H_4SCl$ are the least efficient electrophiles for this reaction. Their reactions are still incomplete after 3 days, and yields of sulfides are generally low.

The introduction of electron-donating groups onto the phenyl group directly attached to the triple bond of the alkyne increased the yield using PhSeCl from 76% (entry 3) to 95% (entry 6). This indicates that electron-rich aryl groups facilitate cyclization. From entries 7−9, one can see that imine **8** containing an enyne moiety reacts well with PhSeCl, $I_2$, and PhSCl, affording the desired products in fair to good yields.

To further test the scope of this electrophilic ring closure, alkyl-substituted acetylenes such as iminoalkynes **12** and **14** have been allowed to react with some of these same electrophiles. Cacchi[8] has reported that alkyl-substituted *o*-(1-alkynyl)phenols can react with $I_2$ to give substituted benzofurans. However, in our chemistry, $I_2$ does not react with either iminoalkyne **12** or **14**, and neither do PhSeCl or PhSCl. Since a phenyl group is a better electron donor than an alkyl group, the reaction of $I_2$ with the carbon−carbon triple bond in iminoalkynes such as **12** and **14** most likely forms a cationic intermediate such as **A**, where the positive charge is located on the carbon next to the aromatic ring. Obviously,




**A**

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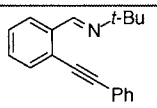
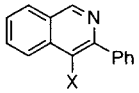
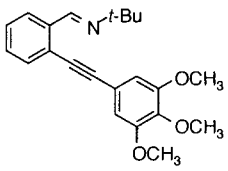
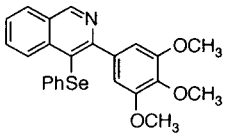
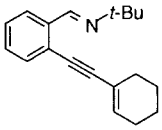
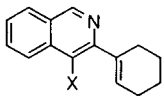
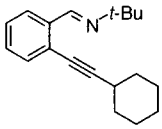
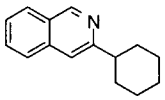
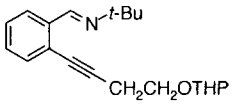
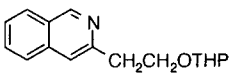
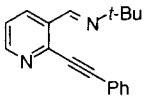
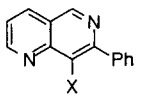
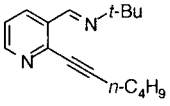
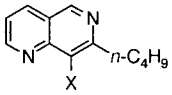
(6) (a) Sakamoto, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311. (b) Sun, Q.; LaVoie, E. J. *Heterocycles* **1996**, *43*, 737. (c) Anderson, C. D.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1331.
(7) Brillon, D.; Sauvé, G. *J. Org. Chem.* **1990**, *55*, 2246.

**Table 1.** Synthesis of Substituted Isoquinolines and Naphthyridines[a]

| entry | iminoalkyne | | electrophile | time (h) | product | | % isolated yield |
|---|---|---|---|---|---|---|---|
| 1 |  | (**1**) | $I_2$[b] | 0.5 |  | X = I (**2**) | 68 |
| 2 | | | ICl[c] | 0.5 | | X = I (**2**) | 67 |
| 3 | | | PhSeCl | 24 | | X = PhSe (**3**) | 76 |
| 4 | | | $AgNO_3$[d] | 24 | | X = H (**4**) | 82 |
| 5 | | | $p$-$O_2NC_6H_4SCl$ | 72 | | X = $p$-$O_2NC_6H_4S$ (**5**) | 47 |
| 6 |  | (**6**) | PhSeCl | 48 |  | (**7**) | 95 |
| 7 |  | (**8**) | PhSeCl | 24 |  | X = PhSe (**9**) | 96 |
| 8 | | | $I_2$[b] | 0.5 | | X = I (**10**) | 67 |
| 9 | | | PhSCl | 24 | | X = PhS (**11**) | 45 |
| 10 |  | (**12**) | $AgNO_3$[d] | 24 |  | (**13**) | 75 |
| 11 |  | (**14**) | $AgNO_3$[d] | 24 |  | (**15**) | 62 |
| 12 |  | (**16**) | $I_2$[b] | 0.5 |  | X = I (**17**) | 90 |
| 13 | | | ICl[c] | 0.5 | | X = I (**17**) | 92 |
| 14 |  | (**18**) | PhSeCl | 72 |  | X = PhSe (**19**) | 61 |
| 15 | | | PhSCl | 24 | | X = PhS (**20**) | 40 |
| 16 | | | ICl[c] | 0.5 | | X = I (**21**) | 76 |

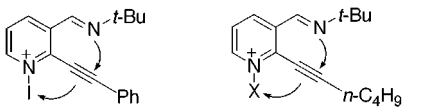
[a] The reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the iminoalkyne and 2 equiv of electrophile in 7 mL of $CH_2Cl_2$ at room temperature. [b] 0.25 mmol of the iminoalkyne, 6 equiv of $I_2$, and 3 equiv of $NaOCO_2CH_3$ in 7 mL of $CH_3CN$ at room temperature. [c] 4 equiv of ICl was used. [d] 0.25 mmol of the iminoalkyne and 5 mol % of $AgNO_3$ in 7 mL of $CHCl_3$ at 50 °C.

the formation of isoquinolines from such an intermediate is impossible. However, $AgNO_3$ reacts with iminoalkynes **12** and **14** to give the expected monosubstituted isoquinolines in good yields (entries 10 and 11). The success of the silver-catalyzed cyclization suggests that silver forms a complex in which the silver simply coordinates to the triple bond, rather than forming a carbon-bearing cation.

From entries 12 and 13, one can see that the introduction of a pyridine ring into the starting material results in relatively high yields when either $I_2$ or ICl is employed as the

(8) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

electrophile. This might be explained by an intermediate such as **B**. The pyridine nitrogen being close to the phenylethynyl




**B** X = I, PhSe, and PhS

**C**

group might first coordinate to the electrophile to form an ammonium cation. Because of this coordination, electrophilic attack of the triple bond might then occur in an intramolecular fashion. Alternatively, the presence of an electron-deficient pyridine ring may simply be disfavoring a structure such as **A** and favoring formation of the cationic intermediate on the carbon necessary for formation of the six-membered ring. Whatever the reason, the presence of the pyridine ring significantly increases the yields from the reactions of $I_2$ and ICl from 68% and 67% for iminoalkyne **1** (entries 1 and 2) to 90% and 92% for iminoalkyne **16** (entries 12 and 13), respectively. This is very encouraging, since it broadens the potential applications of this cyclization and improves its efficiency.

As described above, iminoalkynes derived from *o*-iodobenzaldehyde and acetylenes bearing simple alkyl groups do not react with PhSeCl, $I_2$, or PhSCl. However, imine 1**8** (entries 14−16) can be cyclized by $I_2$, PhSeCl, and PhSCl in yields ranging from 40% to 76%. Again, we believe that the key is either coordination of the electrophile to the pyridine nitrogen and formation of an intermediate, such as **C**, or destabilization of a cation closer to the pyridine ring.

In conclusion, efficient syntheses of isoquinolines and naphthyridines using mild reaction conditions have been developed. This methodology accommodates a variety of iminoalkynes and affords the anticipated substituted isoquinolines in moderate to excellent yields. Further studies into the scope and limitations of this electrophilic cyclization reaction are underway.

**Acknowledgment.** We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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

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