Synthetic Methods

DOI: 10.1002/anie.200701392

Synthesis of 1,3,4-Trisubstituted Isoquinolines by Iodine-Mediated Electrophilic Cyclization of 2-Alkynyl Benzyl Azides**

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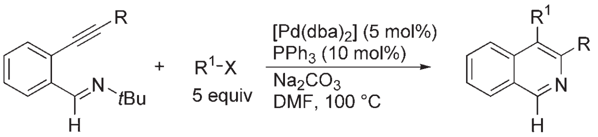
Isoquinolines are an important class of alkaloids commonly found in natural products.[1] Their biological activities have resulted in them often being used as building blocks in pharmaceutical compounds,[2] as chiral ligands for transition-metal catalysts,[3] and their iridium complexes in organic light-emitting diodes (OLEDs).[4]

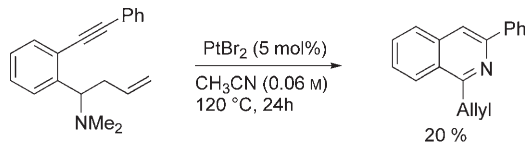
A general and flexible approach to this class of heterocycles is highly desirable for the syntheses of delicate natural products as well as for the fine-tuning of the biological and/or physical properties of the compounds for final application.

Although many ways have been developed to synthesize isoquinolines, classical methods such as the Pomernanz–Fritsch reaction have considerable drawbacks, for example, the use of strong acids and elevated temperature,[5] which are not suitable for sensitive substrates. In recent years, new transition-metal-catalyzed reactions have been developed to synthesize substituted isoquinolines from phenylacetylene substrates (Scheme 1).[6] These reactions have proven to be extremely efficient in the synthesis of a wide variety of 3,4-substituted isoquinolines and other carbo- and heterocycles.[7] It is, however, not possible to synthesize 1,3,4-trisubstituted isoquinolines by these methods.



Scheme 1. Transition-metal-catalyzed synthesis of isoquinolines. dba = *trans,trans*-benzylideneacetone.

During our research into forming functionalized indenes by using platinum as a catalyst,[8] we observed in one case the formation of a 1,3-substituted isoquinoline (Scheme 2).[9] Only aldimine-type substrates are currently known to undergo the transformation shown in Scheme 1. This has prompted us to develop a new mild method to synthesis 1,3,4-trisubstituted isoquinolines.

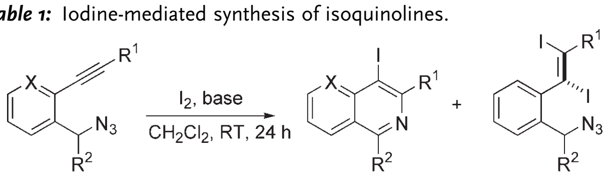


Scheme 2. $PtBr_2$-catalyzed synthesis of isoquinolines.

After considering the pathway of the transformation, we focused our attention on using azides as the leaving group most likely to achieve high yields and conversions. To gain access to 1,3,4-trisubstituted isoquinolines, we considered using an electrophile as a reaction mediator, since it would be incorporated into the final product. The iodonium ion is well suited for this purpose, and it offers clear potential for the further introduction of molecular diversity at C4.

Initial cyclization studies of **1a** using five equivalents of iodine and five equivalents of K_3PO_4 as a base in CH_2Cl_2 provided the desired isoquinoline **2a** in an excellent yield of 95% (Table 1, entry 1). Compounds **1a** and **1f** were used as model substrates to optimize the reaction conditions. The reactions were always carried out for 24 h to ensure complete

Table 1: Iodine-mediated synthesis of isoquinolines.



1 2 3

Entry	1	R^1	R^2	X	Yield[a] [%] 2	Yield[a] [%] 3
1[b]	**1a**	Ph	H	CH	95	–
2[b]	**1b**	*p*-OMePh	H	CH	94	–
3[b,d]	**1c**	*p*-CF_3Ph	H	CH	95	–
4[b]	**1d**	1-cyclohexenyl	H	CH	82	–
5[c]	**1e**	Ph	Me	CH	69	–
6[c]	**1f**	Ph	Hex	CH	73	–
7[c]	**1g**	Ph	Ph	CH	68[e]	–
8[b]	**1h**	Ph	H	N	92	–
9[b]	**1i**	2-pyridinyl	H	CH	–	86
10[b]	**1j**	H	H	CH	–	56[f]

[a] Yield of isolated product. [b] I_2 (5 equiv), K_3PO_4 (5 equiv), CH_2Cl_2 (0.1 M), 24 h, RT. [c] I_2 (5 equiv), $NaHCO_3$ (1 equiv), CH_2Cl_2 (0.1 M), 24 h, RT. [d] Reaction time 72 h. [e] Two side products were formed, which could not be separated; yield determined by NMR spectroscopic analysis. [f] The crystal structure is shown in the Supporting Information. Hex = *n*-hexyl.

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[**] We thank the Japanese Society for the Promotion of Science and the Center of Excellence for financial support.

Supporting information for this article (including general experimental procedures, spectroscopic data for all new compounds, and crystal structural data for **3j**) is available on the WWW under http://www.angewandte.org or from the author.

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conversion. The use of CH_2Cl_2 as the solvent and five equivalents of iodine at room temperature gave the best results. Other solvents, less iodine, or a different temperature either did not improve the yield or even lowered it.

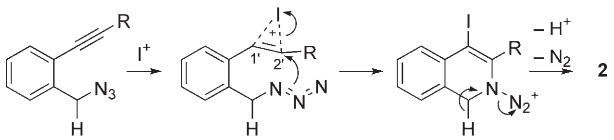
The choice of base used in the reactions was found to depend on the substrate: of the different bases tested, K_3PO_4 and $NaHCO_3$ gave the best results for primary and secondary azides, respectively, while using Al_2O_3 or NEt_3, for example, resulted in lower yields or even inhibited the reaction completely.

For primary azides (R^1 = aryl) the originally selected reaction conditions gave the best results with excellent yields of around 95% (entries 1–3); a longer reaction time of 72 h was required to achieve full conversion in the case of the electron-deficient substrate **1c**. The reaction even proceeded very smoothly with R^1 = 1-cyclohexenyl to give **2d** in a yield of 82% (entry 4).

For secondary azides, and using the weaker base $NaHCO_3$ (entries 5–7), the yields of the trisubstituted isoquinolines **2e–g** ranged from 68 to 73%. In the case of **1g**, two uncharacterized side products were formed, which could not be separated from **2g**. Therefore, the yield of **2g** had to be determined by NMR spectroscopy.

We were also interested in incorporating additional nitrogen atoms into the product. Replacing the carbon atom at position X (Table 1) with a nitrogen atom did not affect the cyclization reaction, it still proceeded very smoothly and afforded the 7,8-substituted 1,6-naphthyridine **2h** in a yield of 92% (entry 8). However, only the bis-iodine product **3i** was obtained from the 2-pyridine-substituted substrate **1i** (entry 9). The structure of the axial chiral product **3i** was determined by X-ray crystal-structure analysis of **3j** (entry 10, see also the Supporting Information) and by comparison of the ^{1}H NMR spectral data.

The formation of bis-iodine product **3i** was unexpected, but can be explained by a plausible reaction pathway. The I^+ ion initially coordinates at the alkyne, thereby activating the triple bond towards nucleophilic ring closure of the azide at the C2′ carbon atom. Subsequent elimination of N_2 and H^+ then results in the formation of isoquinoline **2** (Scheme 3).[10]



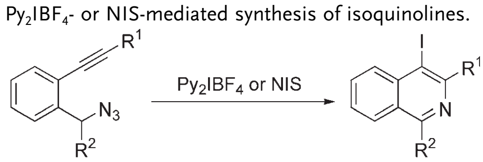
Scheme 3. Plausible reaction pathway.

The proximity of the pyridinyl substituent to the reaction center enables the basic nitrogen atom to coordinate to the iodonium ion, thereby holding it close to the C2′ carbon atom and preventing the azide from forming the new C2′−N bond. Instead, I^- is added at the C1′ carbon atom to form the bis-iodine adduct **3**. If a nitrogen atom is incorporated into the aromatic system of the benzyl azide itself (**1h**), the reaction proceeds smoothly in 92% yield (entry 8).

Besides the formation of 3-aryl- and 3-alkenyl-substituted isoquinolines, we were interested in the formation of 3-alkyl-substituted isoquinolines and isoquinolines. Similar to the 2-pyridine substrate **1i**, a cation in position 2′ is less favored in the case of alkyl-substituted substrates, and thus the formation of **2** will be hindered. Initial experiments showed that under the original reaction conditions the products **2** and **3** were formed in a ratio of approximately 1:4 (R^1 = Me). Attempts to transform the bis-iodine adduct **3** into isoquinoline **2** by prolonged heating or abstraction of iodide by silver resulted only in decomposition of **3**.

To prevent the formation of product **3**, we investigated the use of electrophiles with less nucleophilic counterions. While ICl led to a mixture of iodo- and chloro-substituted isoquinolines and *N*-bromosuccinimide (NBS) gave no conversion, the Barluenga reagent (Py_2IBF_4/HBF_4) in CH_2Cl_2 at −78 °C and *N*-iodosuccinimide (NIS) in $(CH_2Cl)_2$ at 50 °C produced the desired isoquinoline **2** as a single product. The alkyl-substituted isoquinolines were formed in moderate to fair yields (Table 2). In general, the use of the Barluenga reagent

Table 2: Py_2IBF_4- or NIS-mediated synthesis of isoquinolines.



1 **2**

Entry	1	R^1	R^2	Yield[a] [%] Py_2IBF_4	Yield[b] [%] NIS
1	**1k**	Me	H	55	42
2	**1l**	*n*-butyl	H	67	66
3	**1m**	*t*-butyl	H	71 (I_2, 21 days)[c]	
4	**1n**	CH_2TMS	H	69	62
5	**1o**	Ph	CH_2OAc	62	18[d]

[a] Py_2IBF_4 (2 equiv), HBF_4 in Et_2O (2 equiv), CH_2Cl_2, −78 °C, Ar; yield of isolated product. [b] NIS (5 equiv), $NaHCO_3$ (1 equiv), $(CH_2Cl)_2$ (0.1 M), 50 °C, Ar; yield of isolated product. [c] I_2 (5 equiv), $NaHCO_3$ (1 equiv), CH_2Cl_2 (0.1 M), 21 days, RT, 96% conversion. [d] 80% conversion. TMS = trimethylsilyl.

under acidic conditions produced the desired isoquinolines in higher yields then when NIS was used under basic conditions. This finding may result from the shorter reaction time and lower reaction temperature required. However, the yield of substrate **1l** under the two reaction conditions was almost identical (Table 2, entry 2). In contrast, the yield of the methyl-substituted isoquinoline **2k** decreased significantly from 55% (Py_2IBF_4) to 42% (NIS, entry 1). I_2 was used as the electrophile for substrate **1m**, which bears the bulky *tert*-butyl substituent, since the bis-iodine adduct **3m** was not formed. Product **2m** was formed in a good yield of 71% with 96% conversion after 21 days at room temperature (entry 3).

The easily accessible substrates **1n** and **1o** were tested as examples of substrates bearing functional groups. Both substrates were converted into the corresponding isoquinolines **2n** and **2o** in reasonable yields of 69% and 62%, respectively, when Py_2IBF_4 was used (entries 4 and 5). The yield of substrate **1n** dropped slightly to 62% when NIS was used, while substrate **1o** was not compatible to the reaction

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conditions employed, and gave **2n** in a yield of only 18% after 80% conversion (entries 4 and 5).

On considering the obtained results, it becomes clear that the substrates must satisfy certain requirements for the iodine-mediated cyclization: R^1 needs to be either a transition-state-stabilizing (Table 1, entries 1–8) or a bulky (Table 2, entry 3) substituent; otherwise different iodine sources have to be used (Table 2, entries 1, 2, 4, 5). Only when R^1 contained a coordinating substituent or was unsubstituted (Table 1, entries 9 and 10) did the reaction not proceed at all.

In conclusion, we have presented a general and flexible approach to highly substituted isoquinoline building blocks, which can be further functionalized. Depending on the nature of the substrate employed, acidic, basic, or neutral reaction conditions can be used, which makes this method compatible with sensitive, highly functionalized molecules. Additional studies on this method to broaden the scope even further is currently underway.

Experimental Section

Azide **1e** (7.22 mg, 0.29 μmol) was dissolved in CH_2Cl_2 (0.1 M) and $NaHCO_3$ (1 equiv) added. Iodine (5 equiv) was added and the solution stirred in the dark for 24 h. After complete conversion (as evident by TLC) the reaction was quenched with $Na_2S_2O_3$ solution, the product extracted with ethyl acetate, dried over $MgSO_4$, and purified by column chromatography (SiO_2) to yield 6.9 mg (69%) of **2e**.

Barluenga reagent (Py_2IBF_4, 2 equiv) was dissolved in CH_2Cl_2 (0.16 M) cooled to −78°C under argon and then HBF_4 (54% in Et_2O; 2 equiv) added. The solution was transferred to a solution of azide **1o** (25 mg, 82 μmol) in CH_2Cl_2 (1.33 M) at −78°C. After 1 h, the reaction was quenched with $Na_2S_2O_3$ solution, the product extracted with ethyl acetate, dried over $MgSO_4$, and purified by column chromatography (SiO_2) to yield 20.1 mg (61%) of **2o**.

Received: March 31, 2007
Published online: May 22, 2007

Keywords: azides · cyclization · heterocycles · iodine · isoquinolines

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