Synthesis of 2-Trifluoromethyl Quinoline by the Reaction of Fluorinated Imine with Alkyne Catalyzed by Indium(III) Triflate

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Abstract: Preparation of 2-trifluoromethyl-4-aryl quinolines from a variety of readily available alkynes and *N*-aryl trifluoroethylimine has been achieved via indium(III) triflate catalyzed Diels–Alder reactions.

Key words: alkynes, quinolines, indium, Diels–Alder reaction, imines

The performance of organofluorine compounds in all aspects of chemicals industry, such as materials, pharmaceuticals, agrochemicals, and fine chemicals, is phenomenal. Organofluorine compounds are rare in natural products, but 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. As the incorporation of fluorine and/or fluorine-containing groups into an organic molecule often drastically alters the chemical, physical, and biological properties of the parent compound, it is only logical to conclude that such modifications necessitate the invention of novel reagents and materials endowed with fluorine imparting properties. For example, 2-trifluoromethyl quinolines are of significant pharmacological interest for their use as potent antimalarial agents (mefloquine, **1**),[1] PDE4 inhibitors **2**,[2] antituberculosis agents **3** (Figure 1),[3] DPP-IV inhibitors,[4] and leishmanicidal agents.[5]

Since Skraup reported the synthesis of quinoline in 1880 for the first time,[6] there have been great achievements in this area.[7] However, the usual method for synthesis of 2-trifluoromethyl quinoline was the Combes' method.[8] Till recently, several methods have been developed.[9] In 2001, Uneyama et al. reported a one-pot synthesis of highly substituted fluorinated quinolines by Rh(I)-catalyzed cyclization of *N*-aryl trifluoroacetimidoyl chlorides with alkynes.[10] In 2009, Likhar et al. reported a method for the synthesis of highly substituted 2-perfluoroalkyl quinolines by electrophilic iodocyclization of perfluoroalkyl propargyl imines or amines.[11] Recently, our group developed a process for synthesis of multisubstituted 2-trifluoromethyl quinolines via palladium-catalyzed domino Sonogashira–alkyne carbocyclization of β-trifluoromethly β-enamino ketones with alkyne.[12] The drawbacks of many of these methods are either the limited availability of starting materials or poor substrate scope. Consequently, the development of an efficient and facile synthesis of 2-perfluoroalkyl-substituted quinolines using mild reaction conditions remains an active research area. Herein we wish to report a versatile method for synthesis of multisubstituted 2-trifluoromethyl quinolines by the reaction of fluorinated imine with alkyne under catalysis of indium(III) triflate.

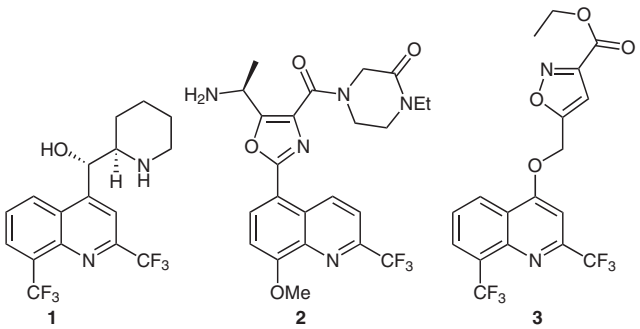

Figure 1 Representative of 2-trifluoromethyl quinoline in medicinal chemistry

Initially, we chose phenylacetylene **5a** and *N*-aryl trifluoroethylimine **4a** which was obtained by the condensation of the commercial trifluoroacetaldehyde ethyl hemiacetal with arylamine, as the model substrates to optimize the reaction conditions at 60 °C in toluene. As shown in Table 1, when CuOTf was used as the catalyst, 27% of desired 2-trifluoromethyl quinoline **6a** was obtained after column chromatography (Table 1, entry 1). Switching to $Cu(OTf)_2$ as the catalyst, the yield of **6a** was raised to 35% (Table 1, entry 2). Under this condition, *N*-*p*-methoxyphenyl trifluoroethylamine was also formed. It was reasoned that **5a** reacted with **4a** to form dihydroquinoline firstly, which was then oxidized to **6a**. At the same time some **4a** was reduced to *N*-*p*-methoxyphenyl trifluoroethylamine. So we supposed that the yield of this reaction may be improved by adding an oxidant to the reaction system. As expected, the yield of **6a** was increased to 64%, when two equivalents of 2,3-dichloro-5,6-dicyanoquinone (DDQ) was added. Subsequently, other catalysts were further scanned. It was found that when CuI or $La(OTf)_3$ was used as catalyst, product **6a** was formed in trace amount (Table 1, entries 5, 6). However, when $In(OTf)_3$ was used as the catalyst, the yield of **6a** was improved to 88% (Table 1, entry 7), the yield of **6a** was further raised

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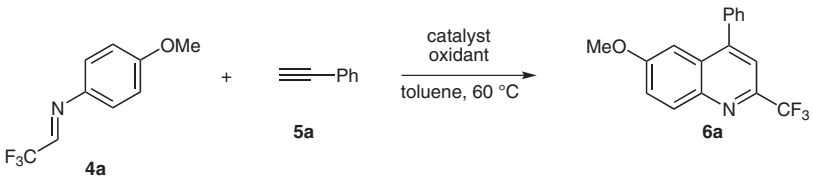
Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Oxidants	Solvent	Yield (%)[b]
1	CuOTf	–	toluene	27
2	$Cu(OTf)_2$	–	toluene	35
3	$Cu(OTf)_2$	DDQ	toluene	64
4	$Cu(OTf)_2$	BQ	toluene	64
5	CuI	DDQ	toluene	trace
6	$La(OTf)_3$	DDQ	toluene	trace
7	$In(OTf)_3$	DDQ	toluene	88
8	$In(OTf)_3$	BQ	toluene	92

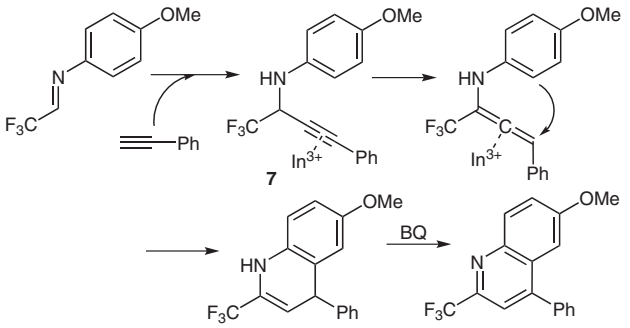
[a] Unless otherwise specified, reactions were performed on a 1.0 mmol scale of *N*-aryl trifluoroethylimine, alkyne (2.0 mmol), toluene (5 mL).
[b] Isolated yield calculated on the basis of *N*-aryl trifluoroethylimine.

to 92%, when two equivalents of *para*-benzoquinone (BQ) was used as oxidant (Table 1, entry 8). Then the optimization conditions were ascertained as $In(OTf)_3$ (10 mol%), BQ (2 equiv) in toluene at 60 °C.

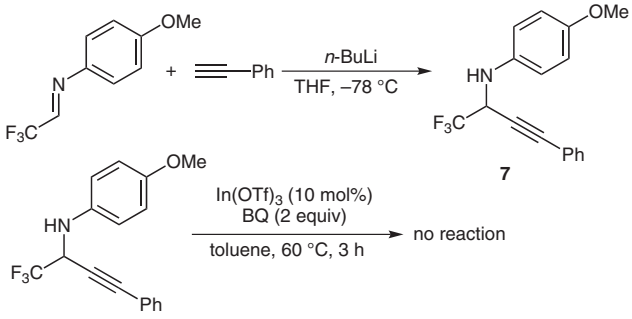
Having established suitable reaction conditions, the scope and generality of this methodology were explored. As shown in Table 2, most substrates examined provided moderate to excellent yields under the standard reaction conditions. In an effort to understand the scope of the reaction, the effect of various substituents on the benzene ring of the imine was scrutinized. Generally, electron-donating substitutent on the benzene ring of the imine, such as methoxy (Table 2, entry 1) and methyl (Table 2, entry 3) proceeded well. On the other hand, electron-withdrawing substituted on the benzene ring of the imine, including chloro (Table 2, entry 4), fluoro (Table 2, entry 5), and trifluoromethyl (Table 2, entry 5) would reduce the yield. Next, the effect of various substituents on the aryl ring of the alkynes was examined.

The substituents on the aryl ring of the alkynes such as methoxy (Table 2, entries 7, 11), methyl (Table 2, entry 8), and chloro (Table 2, entries 9, 12) also proceeded well, while 4-fluorophenylacetylene provided lower yield (Table 2, entry 10). Notably, it was interesting to note that 2-naphthylacetylene (Table 2, entry 13) or 2-thienylacetylene (Table 2, entry 14) could also afford **6** in excellent yield.

There are two possible reaction routes for this reaction. The first one was a stepwise mechanism (Scheme 1). In this case, propargylic amine **7** which was produced via an intermediate that was formed by successive complexation of substrates to the metal center was formed firstly.[7g,h,13] Subsequent cyclization step may occur directly through a Friedel–Crafts-type addition affording dihydroquinoline, which was then oxidized to the desired products by BQ. To confirm this proposed mechanism (Scheme 1), the intermediate propargylic amine **7** was synthesized (Scheme 2). But the experiment revealed that propargylic amine **7** did not react under the same reaction conditions. This result provided a concrete evidence to exclude this mechanism.

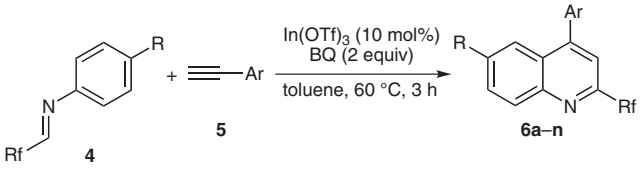


Scheme 1 Possible stepwise mechanism



Scheme 2 The synthesis of intermediate propargylic amines **7** and its reaction

Table 2 $In(OTf)_3$-Catalyzed Synthesis of 2-Trifluoromethyl Quinolines[a]



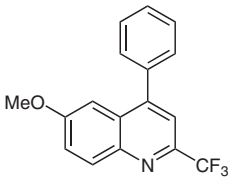
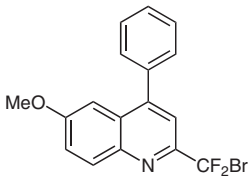
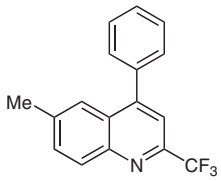
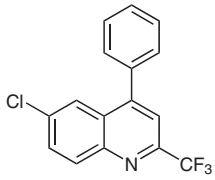
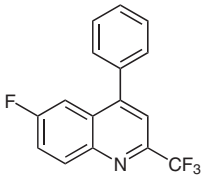
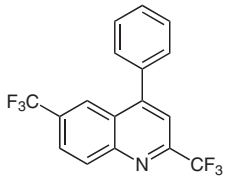
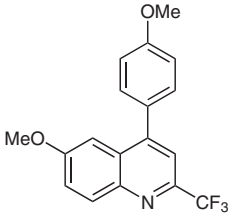
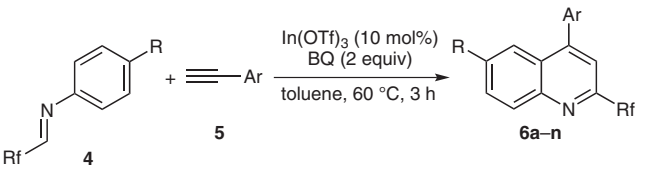
Entry		Product	Yield (%)[b]
1	**6a**		92
2	**6b**		94
3	**6c**		91
4	**6d**		85
5	**6e**		75
6	**6f**		66
7	**6g**		93

Table 2 $In(OTf)_3$-Catalyzed Synthesis of 2-Trifluoromethyl Quinolines[a] (continued)



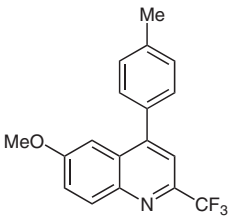
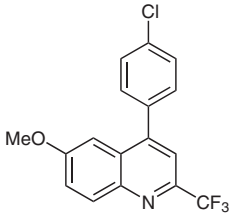
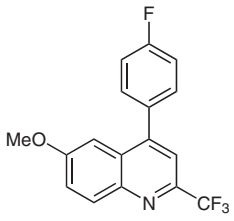
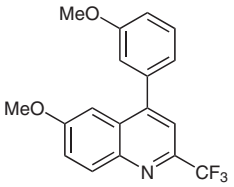
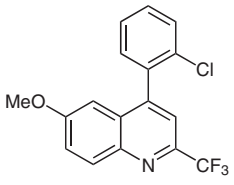
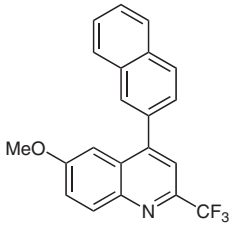
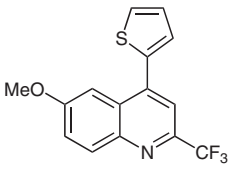
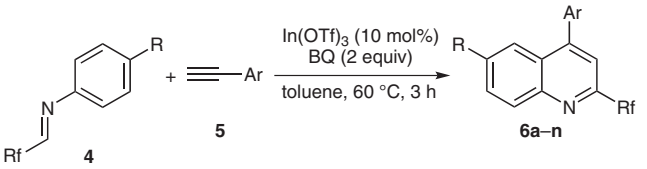
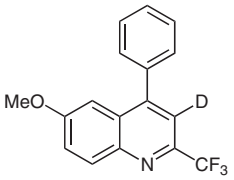
Entry		Product	Yield (%)[b]
8	**6h**		93
9	**6i**		82
10	**6j**		60
11	**6k**		92
12	**6l**		91
13	**6m**		90
14	**6n**		90

Table 2 $In(OTf)_3$-Catalyzed Synthesis of 2-Trifluoromethyl Quinolines[a] (continued)



Entry	Product	Yield (%)[b]
15	**6o** 	91

[a] Reaction conditions: *N*-aryl trifluoroethylimine (1.0 mmol), alkyne (2.0 mmol), $In(OTf)_3$ (0.1 mmol), BQ (2.0 mmol), toluene (5mL), 60 °C.

[b] Isolated yield calculated on the basis of *N*-aryl trifluoroethylimine.

Another route of this transformation is a concerted mechanism, dihydroquinoline was formed via a Diels–Alder-type addition between imine and phenylacetylene under the catalyst of $In(OTf)_3$, which was then oxidized to the desired product by BQ. To gain further evidence for this mechanism, phenylacetylene-*d* was used as substrate, the corresponding product's NMR spectrum showed that more than 95% deuterium was retained at the 3 position of final product quinoline. This result indicated that this reaction did not involve alkynide anion, which provides concrete evidence to support the concerted mechanism (Scheme 3). This kind of reaction belongs to the IEDDA reactions family.[14] The reaction mechanism may be similar to Povarov reaction. Although the Povarov reaction is an organic reaction described as a formal cycloaddition between an aromatic imine and an alkene, this reaction may be a formal cycloaddition between an aromatic imine and an alkyne.

In summary, a facile and efficient method for synthesis 2-trifluoromethyl-4-aryl quinolines from a variety of readily available alkynes and *N*-aryl trifluoroethylimine was developed. The reaction proceeded under mild conditions and gave the desired quinoline products in high yields. Through intermediate propargylic amines and deuterium-labeling studies, a Diels–Alder reaction mechanism was proposed.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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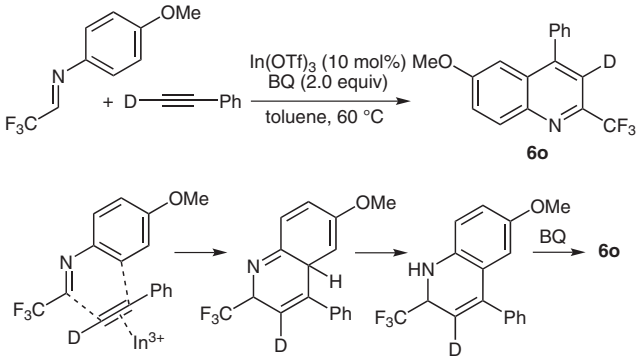

Scheme 3 Deuterium-labeled reaction

References

(1) Ohnmacht, C. J.; Patel, A. R.; Lutz, R. E. *J. Med. Chem.* **1971**, *14*, 926.

(2) (a) Dyke, H. J.; Montana, J. G. WO 2000026208, **2000**. (b) Kuang, R.; Blythin, D.; Shih, N. Y.; Shue, H. J.; Chen, X.; Cao, J.; Gu, D.; Huang, Y.; Schwerdt, J. H.; Ting, P. C.; Wong, S. C.; Xiao, L. WO 2005116009, **2005**.

(3) (a) Mao, J. L.; Wan, B. J.; Wang, Y. H.; Franzblau, S. G.; Kozikowski, A. P. *ChemMedChem* **2007**, *2*, 811. (b) Lilienkampf, A.; Mao, J. L.; Wan, B. J.; Wang, Y. H.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 2109.

(4) Sakashita, H.; Yoshida, T.; Kitajima, H.; Takeuchi, M.; Tanaka, Y.; Yoshimura, T.; Akahoshi, F.; Hayashi, Y. WO 2003024942, **2003**.

(5) Dade, J.; Provot, O.; Moskowitz, H.; Mayrargue, J.; Prina, E. *Chem. Pharm. Bull.* **2001**, *49*, 480.

(6) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086.

(7) (a) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (b) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1591. (c) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G.; Ruggieri, F. *J. Org. Chem.* **1992**, *57*, 1842. (d) Linkert, F.; Laschat, S.; Kotila, S.; Fox, T. *Tetrahedron* **1996**, *52*, 955. (e) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Naveenkumar, V.; Nagaiah, K. *Synthesis* **2003**, 1610. (f) Basuli, F.; Aneetha, H.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17992. (g) Cao, K.; Zhang, F. M.; Tu, Y. Q.; Zhuo, X. T.; Fan, C. A. *Chem. Eur. J.* **2009**, *15*, 6332. (h) Huang, H.; Jiang, H. L.; Chen, K. X.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476.

(8) Combes, A. *Bull. Soc. Chim. Fr.* **1883**, *49*, 89.

(9) (a) Crousse, B.; Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, *39*, 5765. (b) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Eur. J. Org. Chem.* **1999**, 937. (c) Crousse, B.; Begue, J. P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009. (d) El Kharrat, S.; Skander, M.; Dahmani, A.; Laurent, P.; Blancou, H. *J. Org. Chem.* **2005**, *70*, 8327. (e) Loska, R.; Majcher, M.; Makosza, M. *J. Org. Chem.* **2007**, *72*, 5574. (f) Yanai, H.; Mimura, H.; Kawada, K.; Taguchi, T. *Tetrahedron* **2007**, *63*, 2153.

(10) (a) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109. (b) Isobe, A.; Takagi, J.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2008**, *10*, 2657.

(11) Likhar, P. R.; Subhas, M. S.; Roy, S.; Kantam, M. L.; Sridhar, B.; Seth, R. K.; Biswas, S. *Org. Biomol. Chem.* **2009**, *7*, 85.

(12) Chen, Z.; Zhu, J.; Xie, H.; Li, S.; Wu, Y.; Gong, Y. *Chem. Commun.* **2010**, *46*, 2145.

(13) (a) Ji, J. X.; Au-Yeung, T. L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42. (b) Rueping, M.; Antonchick, A. R.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903.

(14) (a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (b) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116. (c) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.