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Efficient Synthesis of 2-Fluoromethylated Quinolines *via* Copper-Catalyzed Alkynylation and Cyclization of Fluorinated Imidoyl Iodides

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Abstract: 2-Fluoromethylated quinolines were synthesized through the reaction of *N*-aryl-fluorinated imidoyl iodides with terminal alkynes in good yields by the catalysis of copper(I) iodide (CuI) alone.

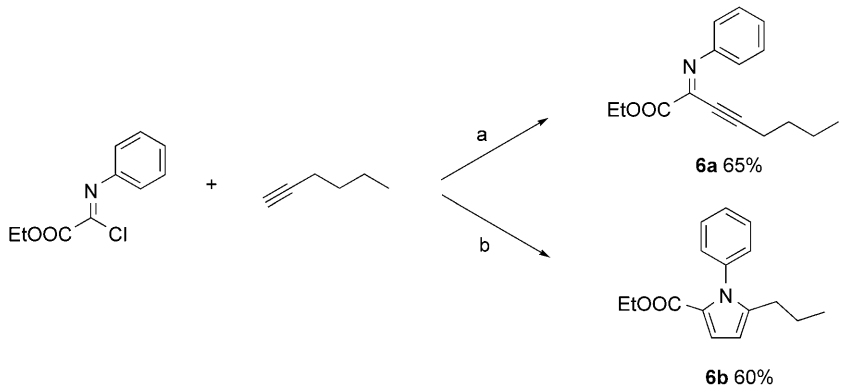
Keywords: copper; coupling reactions; cyclization; fluorinated alkynylimines; fluorinated quinolines

Quinolines are important heterocycles that are frequently found in natural products.[1] The quinoline skeleton is often used in the design of many synthetic compounds with pharmacological properties.[2,3] Recently, the fluorine-containing quinolines have been attracted much attention due to their interesting biological activities.[4] It was considered that the fluorine atom or fluorinated substituent plays a pivotal role in bioactive compounds, and that they provide an avenue for further structural elaboration.[5,6] The 2-trifluoromethylated quinolines, mefloquine, for example, are of significant pharmacological interest for their use as potent antimalarial agents.[7]

Although the synthesis of various quinolines has been largely described in the literature through many different strategies,[8] methods leading to the trifluoromethylated substrates are limited.[9] The conventional method is based on a trifluoromethylated building blocks strategy. Some of them can be prepared in good yields.[10] In 2001, Uneyama et al reported a one-pot method for the synthesis of 2-trifluoromethylated quinolines from *N*-aryl-trifluoroacetimidoyl chlorides and alkynes catalyzed by an Rh complex.[11] This procedure gave the desired products in good yields, however, only moderate regioselectivity was achieved. Herein, we wish to report a Cu(I)-catalyzed coupling reaction and subsequent cyclization to construct 2-fluoromethylated quinolines.

During the course of our study on the reactivity of fluorinated alkynylimines,[12] it was found that 2-bromodifluoromethylated *N*-aryl-alkynylimines could be readily converted to quinolines *via* an intramolecular cyclization reaction catalyzed by CuI. And it was also found in our previous work that fluorinated imidoyl halides could react with terminal alkynes in the presence of CuI.[13] We envisioned that these two reactions might be combined into a one-pot protocol. The reaction of *N*-(*p*-methylphenyl)-2-bromo-2.2-difluoroacetimidoyl iodides with 1-hexyne was selected as the model system. Et_3N was the base, several Lewis acids such as $ZnBr_2$, $AlCl_3$, CuI were used as the catalyst separately to test this transformation, and the results are listed in Table 1. Gratifyingly, CuI could indeed catalyze this transformation. Extensive investigations indicated that, in the presence of 10 mol% of CuI, the 2-bromodifluoromethylated quinoline was isolated in 93% yield while the two-step one-pot reaction was conducted in Et_3N/MeCN at 50 °C. In addition, when inorganic bases like K_3PO_4, K_2CO_3 were used, alkynylimine (**3aba**) was afforded as the final product, and K_3PO_4 is superior to K_2CO_3.

To investigate the scope of the established strategy, a number of fluorinated imidoyl iodides and terminal alkynes were tested (Table 2). Both electron-donating and electron-withdrawing groups on the arene of the imidoyl iodides were tolerated in this reaction. It was interesting to note that electron-donating groups on the benzene ring of the imidoyl iodides could raise the yields of the isolated products (Table 2, entries 2,



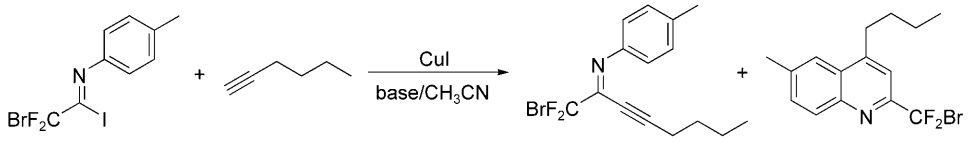
Scheme 1. CuI-catalyzed the coupling reaction of unfluorinated imidoyl chloride with 1-hexyne. *Reaction conditions:* imidoyl chlorides (1.0 mmol), 1-hexyne (1.2 mmol), CuI (30 mol%), KI (1.0 equiv.), K_3PO_4 (a) or Et_3N (b) (1.2 mmol), CH_3CN (3.0 mL), 60 °C.

4, 8, 14, 17, 20, 24, 26, 27, 30, and 31). Electron-withdrawing groups would lead to lower yields of the isolated products (Table 2, entries 3, 6, 9, 11, 12, 16, 18, 23, and 25). If a strong electron-withdrawing group (Table 2, entry 7) was involved in the substrate, no product could be obtained and the alkynylimines were found to undergo decomposition in the presence of triethylamine. The protocol gave equally good yields with substances bearing the *para*, *meta*, and *ortho* substituents. For instance, 6-methylquinoline and 8-methylquinoline were obtained in almost the same yields (Table 2, entries 2 and 4). Regretfully, this reaction was also suffered from moderate regioselectivity. For the benzene ring with a substituent at the *meta*-position, two isomers (5- and 7-substituted quinolines) were obtained (Table 2, entries 5 and 11). The reaction was compatible with a range of functional groups on the alkynes, such as hydroxy (Table 2, entries 17, 18, and 26–28) and carboxylate groups (Table 2, entries 8–12, 22, 23, and 31) albeit with lower yields. In this reaction, CF_2Br, CF_2Cl, CF_3 exhibit a similar reactivity.

It was very interesting to note that, when non-fluorinated alkynylimines were used as starting material, pyrroles were formed as the sole product under the same conditions.[14] This might be due to the strong electron-withdrawing effect of the R_f group, whereby the electronic density and nucleophilicity of nitrogen in fluorinated alkynylimine was reduced dramatically, so that the allene is attacked by the benzene ring instead of the N atom (Scheme 1).

It was found that the presence of the terminal alkyne α-H was essential for the success of the reaction. For example, no quinoline could be obtained

Table 1. CuI-catalyzed the coupling reaction of imidoyl iodide with 1-hexyne.[a]

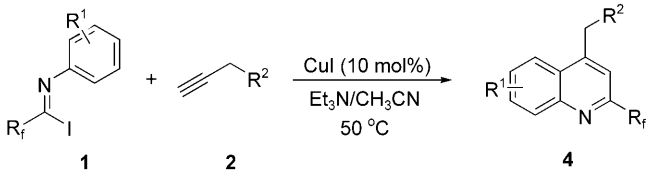


1ab **2a** **3aba** **4aba**

Entry	Catalyst	Base	Temperature [°C]	**3aba**[b] [%]	**4aba**[b] [%]
1	$AlCl_3$ (1.2 equiv.)	Et_3N	r.t.	–	–
2	$ZnBr_2$ (1.2 equiv.)	Et_3N	r.t.	–	-
3	CuI (1.2 equiv.)	Et_3N	r.t.	–	50
4	CuI (0.3 equiv.)	Et_3N	70	–	86
5	CuI (0.1 equiv.)	Et_3N	70	–	70
6	CuI (0.1 equiv.)	Et_3N	50	–	93
7	CuI (0.1 equiv.)	K_2CO_3	50	40	–
8	CuI (0.1 equiv.)	K_3PO_4	50	92	–
9	CuI (0.1 equiv.)	KO-*t*-Bu	50	–	–

[a] *Reaction conditions:* imidoyl iodide (1.0 mmol), 1-hexyne (1.2 mmol), and base (1.2 mmol) under nitrogen.
[b] Isolated yields.

Table 2. CuI-catalyzed the coupling reaction to synthesize quinolines.[a]



1 2 4

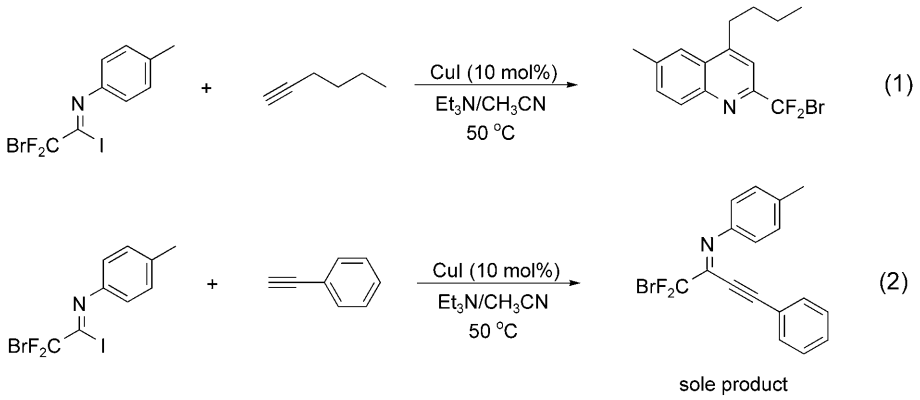
Entry	R_f	R^1	R^2	Product	Yield [%][b]
1	$BrCF_2$	H	*n*-Pr	**4aaa**	82.7
2		*p*-CH_3		**4aba**	92.4
3		*p*-Cl		**4aca**	82.6
4		*o*-CH_3		**4ada**	86.4
5		*m*-CH_3		**4aea**	83.9 (10:3)[c]
6		*o*-Cl		**4afa**	72.1
7		*p*-NO_2		–	–
8		*p*-OCH_3	$OCOCH_3$	**4aab**	90.9
9		*p*-Cl		**4abb**	70.7
10		*o*-CH_3		**4acb**	72.6
11		*m*-Cl		**4adb**	66.5 (1:1)[c]
12		*o*-Cl		**4aeb**	60.0
13		H	Ph	**4aac**	81.7
14		*p*-CH_3		**4abc**	87.8
15		*o*-CH_3		**4acc**	88.7
16		*p*-Cl		**4adc**	62.9
17		*p*-CH_3	$CH(OH)(CH_2)_2CH_3$	**4aad**	66.5[d]
18		*o*-Cl		**4abd**	41.3[d]
19	CF_3	H	*n*-Pr	**4baa**	86.9
20		*p*-CH_3		**4bba**	90.0
21		*p*-Cl		**4bca**	83.4
22		*p*-OCH_3	$OCOCH_3$	**4bab**	82.5
23		*p*-Cl		**4bbb**	70.5
24		*p*-OCH_3	Ph	**4bac**	75.8
25		*o*-Br		**4bbc**	74.4
26		*p*-OCH_3	$CH(OH)(CH_2)_2CH_3$	**4bad**	75.1[d]
27		*p*-CH_3		**4bbd**	56.2[d]
28		*o*-CH_3		**4bcd**	64.6[d]
29	$ClCF_2$	H	*n*-Pr	**4caa**	85.4
30		*p*-CH_3		**4cba**	91.8
31		*p*-OCH_3	$OCOCH_3$	**4cab**	89.5

[a] *Reaction conditions:* fluorinated imidoyl iodides (1.0 mmol), alkynes (1.2 mmol), CuI (10 mol%), Et_3N (1.2 mmol), CH_3CN (3.0 mL), $T = 50$ °C, and under nitrogen.
[b] Isolated yield.
[c] Estimated by ^{19}F NMR.
[d] CuI (30 mol%).

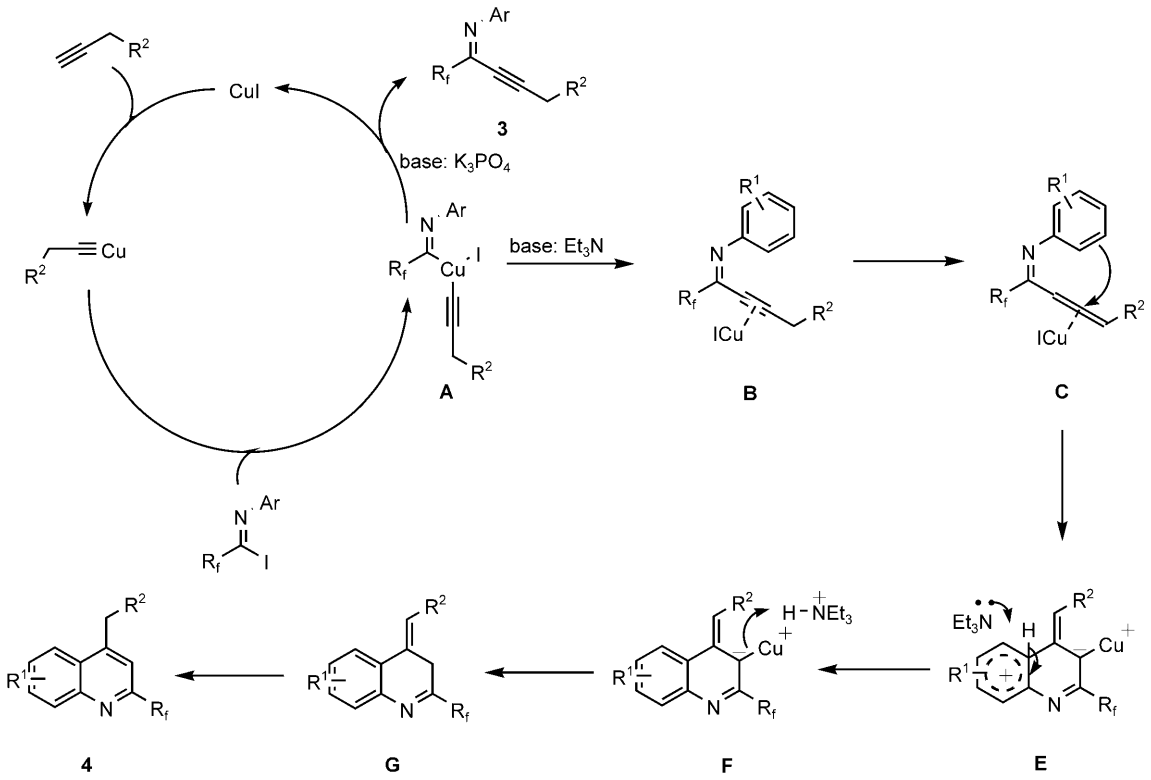
when phenylacetylene was used as substrate, while alkynylimine was formed in high yield (Scheme 2).

Based on above study, the mechanism of this reaction was proposed as shown in Scheme 3. Copper alkynide inserted to the C–I bond of imidoyl iodides by oxidant addition to form an intermediate **A**. After the reductive elimination, alkynylimine **3** was formed. When triethylamine was used as the base, the solubility of the copper salt was increased by the complexation effect of Et_3N, which in turn allowed the formation of the intermediate **B**. Then **B** underwent a base-induced propargyl-allenyl isomerization to form an allene intermediate **C**. Intermediate **C** is expected to undergo a nucleophilic attack by the carbon atom of the benzene ring to the central carbon of the allene moiety. This process is similar to the Friedel–Crafts reaction. As mentioned earlier, the presence of the α-H of the triple bond in the substrate was a key factor for the success of the current transformation, which supports the proposed mechanism. After protonation and isomerization, quinoline **4** was formed.

In conclusion, we have developed a convenient and efficient approach for the one-pot synthesis of fluorinated quinolines catalyzed by CuI. The absence of



Scheme 2. Effect of terminal alkynes.



Scheme 3. Proposed mechanism for the synthesis of quinolines.

noble metals (such as Pd, Rh) and expensive ligands renders this approach highly attractive for the further development of fluorinated quinolines.

Experimental Section

General Procedure

To a Schenk tube, CuI (20 mg, 0.1 mmol), CH_3CN (3.5 mL), Et_3N (1.2 mmol), imidoyl iodides (1.0 mmol), and terminal alkyne (1.2 mmol) were added successively under a nitrogen atmosphere. Then the system was heated to 50 °C, the consumption of imidoyl iodides being monitored by TLC until the corresponding spot was no longer observable. When the reaction had finished, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give the desired products.

Acknowledgements

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[13] Our work demonstrated that, with K_3PO_4 as the base, fluorinated imidoyl iodides can react with terminal alkynes catalyzed by CuI in CH_3CN at 50 °C to afford the alkynylimine with good to excellent yields (in preparation), which is detailed in the Supporting Information.

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