ORGANIC LETTERS

2001
Vol. 3, No. 8
1109−1112

Rh(I)-Catalyzed Coupling Cyclization of *N*-Aryl Trifluoroacetimidoyl Chlorides with Alkynes: One-Pot Synthesis of Fluorinated Quinolines

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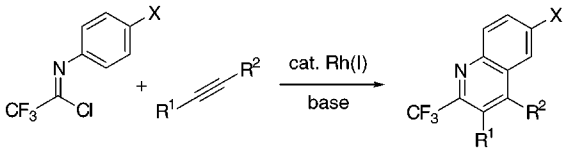
Received November 29, 2000

ABSTRACT



Rh(I) complexes were found to catalyze the coupling cyclization of *N*-aryl trifluoroacetimidoyl chlorides with alkynes to afford 2-trifluoromethylated quinolines in good yields. Various alkynes were applied to this cyclization coupling with regioselectivity.

The quinoline ring system occurs in various natural products, especially alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with pharmacological properties.[1,2] In particular, fluorine-containing quinolines are of significant interest because fluorine atoms sometimes play a pivotal role in bioactive compounds, and they provide a further avenue for structural elaboration.[3] For instance, antiprotozoal drug mefloquine, which has a 2-trifluoromethylquinoline skeleton, is one of the main agents for the current treatment of malaria.[4] Previously, we reported the syntheses of a wide repertoire of fluorinated heterocyclic compounds[5] such as trifluoromethylated quinolines, indoles, imidazoles, triazines, triazoles, and diazepines by the use of trifluoroacetimidoyl halides as a starting material. Considering the significance of bioactive fluorine compounds, we undertook a study of trifluoroacetimidoyl−metal complexes which serve as important agents for C−C bond formation.[6] Herein, we present a novel entry to 2-trifluoromethylated quinoline **3** (and **4**) which involves Rh(I)-catalyzed tandem one-pot coupling−cyclization reaction of trifluoroacetimidoyl chlorides (**1**) with alkynes **2**.[7]

Representative results are summarized in Table 1. A mixture of **1a** and 4-octyne (**2a**) in Et_3N/toluene was heated at 110 °C for 24 h in the presence of catalytic amount of a Rh(I) complex prepared in situ by mixing a dinuclear complex $[Rh(cod)Cl]_2$ with PPh_3 to afford 2-trifluoromethylquinoline **3a** in 29% yield (entry 1). When a neutral Rh(I)

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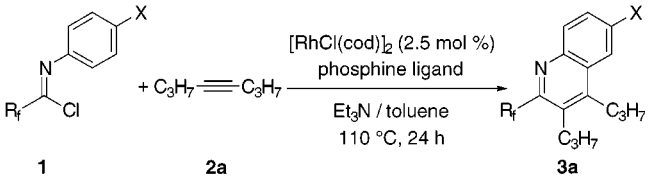
10.1021/ol006936u CCC: $20.00
Published on Web 03/17/2001

Table 1. Rh(I)-Catalyzed Coupling Cyclization of *N*-Aryl Fluorinated Imidoyl Chlorides with 4-Octyne



1 2a 3a

entry	imidoyl chloride 1 R_f	X		phosphine ligand	product 3	%yield[a]
1	CF_3	OMe	(**1a**)	PPh_3 (10 mol %)	**3a**	29
2	CF_3	OMe	(**1a**)	TFP (10 mol %)	**3a**	73
3	CF_3	OMe	(**1a**)	DPPE (5 mol %)	**3a**	72
4	CF_3	H	(**1b**)	TFP (10 mol %)	**3b**	61
5	CF_3	Me	(**1c**)	TFP (10 mol %)	**3c**	70
6	CF_3	Cl	(**1d**)	TFP (10 mol %)	**3d**	6[b]
7	HCF_2	OMe	(**1e**)	TFP (10 mol %)	**3e**	43
8	C_3F_7	OMe	(**1f**)	TFP (10 mol %)	**3f**	78

[a] Isolated yield. [b] This yield was determined by ^{19}F NMR. TFP = tris(2-furyl)phosphine. DPPE = 1,2-bis(diphenylphosphino)ethane.

complex prepared in situ from $[Rh(cod)Cl]_2$ and $P(2\text{-furyl})_3$ (TFP) in a molar ratio of 1:4 (Rh:P = 1:2) was used, a significant increase of the product yield (73% isolated yield) was observed. The use of dppe ($Ph_2P(CH_2)_2PPh_2$) as a phosphine ligand was found to be also effective for the coupling−cyclization reaction (entry 3). The imidoyl chlorides **1** which possess electron-donating substituents (OMe, H, Me) on the aryl ring provide **3a**−**c** in good yields (entries 2−5). In contrast, if the aryl group of **1** has an electron-withdrawing 4-Cl group (entry 6), then **3d** was formed only in 6% yield. Other fluoroalkyl imidoyl chlorides **1e**,**f** (R_f = HCF_2, C_3F_7) were found to give the corresponding quinolines **3e**,**f** (entries 7 and 8).

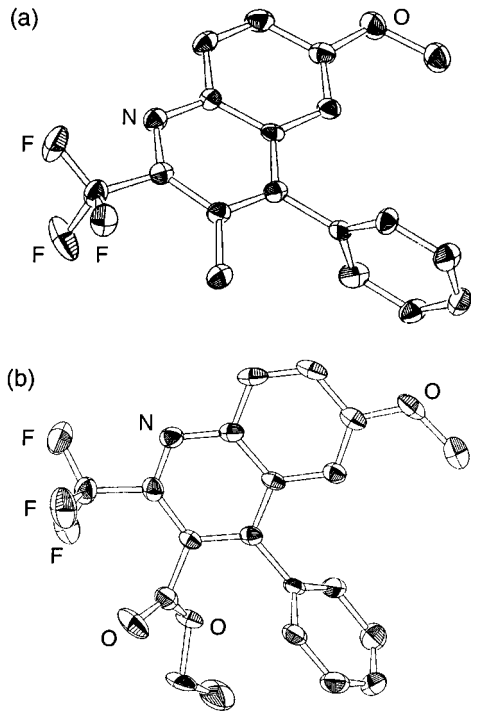
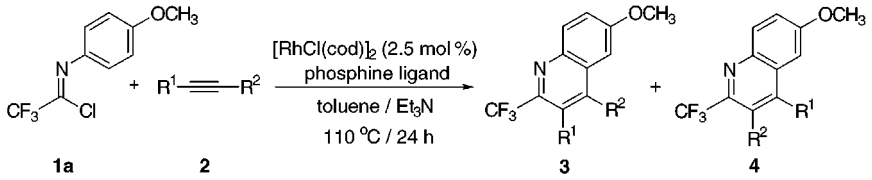


Figure 1. ORTEP drawing of single crystal structures of **3k** (a) and **4l** (b) at 50% probability level. All hydrogen atoms are omitted for clarity.

This one-pot quinoline synthesis worked well for both symmetrical and unsymmetrical alkynes (Table 2). Propargylic ether functionality in **2h** and ester functionalities in **2j**,**l** were compatible with the present reaction conditions (entry 3, 5, and 7).

The reaction of **1a** with an unsymmetrical internal alkyne such as 1-phenyl-1-propyne (**2k**) provided a 64:36 mixture

Table 2. Rh(I)-Catalyzed Coupling Cyclization of **1a** with Internal Alkynes **2**



1a 2 3 4

entry	alkyne 2 R^1	R^2		phosphine ligand	products (**3** and/or **4**)[a]	%yield (**3** + **4**)
1	C_3H_7	C_3H_7	(**2a**)	TFP (10 mol %)	**3a**	73
2[b]	Et	Et	(**2g**)	TFP (10 mol %)	**3g**	55
3	CH_2OMe	CH_2OMe	(**2h**)	DPPE (5 mol %)	**3h**	65
4	Ph	Ph	(**2i**)	DPPE (5 mol %)	**3i**	35
5[c]	CO_2Me	CO_2Me	(**2j**)	DPPE (20 mol %)[d]	**3j**	22
6	Me	Ph	(**2k**)	DPPE (5 mol %)	**3k** + **4k**[e] (64:36)	80
7[c]	Ph	CO_2Et	(**2l**)	DPPE (5 mol %)	**3l** + **4l** (1: >99)	82

[a] Ratio of the products (**3**:**4**) indicated in parentheses. [b] The reaction was carried out in a sealed glass tube. [c] Na_2CO_3 was used instead of Et_3N. [d] 10 mol % of $[RhCl(cod)]_2$ was used (140 °C in xylene). [e] Regiochemistries of the products (**3** and **4**) were determined by NOE difference NMR spectroscopy.

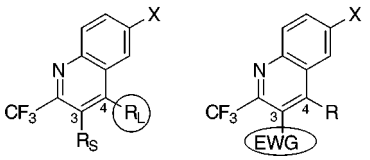


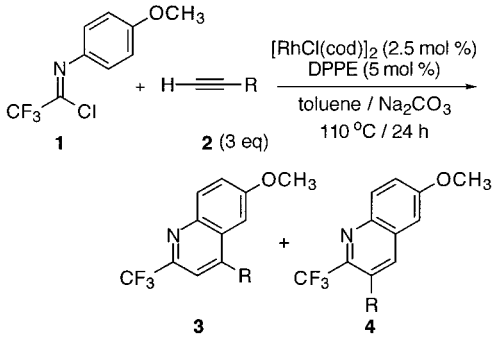
Figure 2.

of two regioisomers **3k** and **4k** (entry 6). Very interestingly, the reaction with **2l** led to the exclusive formation of the product **4l** in 82% yield (entry 7). Besides NOE experiments, the regiochemistries of **3k** and **4l** were determined by the X-ray crystal structure analyses shown in Figure 1.[8,9]

In addition, unsymmetrical alkynes **2** show a relatively great tendency to undergo regioselective additions with a bulkier group (R_L in **2**) attached to the quinoline 4-position and with an electron-withdrawing group attached to the quinoline 3-position (Figure 2).

As shown in Table 3, a terminal alkyne such as 1-octyne (**2m**) reacted with **1a** to give **3m** in high regioselectivity (**3m**/**4m** = 94/6), and the combined product yield was 68% (entry 1). Similarly, use of terminal alkynes **2n**−**r** as a reactant gave **3n**−**r** as a major product (with the distribution of **3**/**4** being 95/5 to >99/1, as described in entries 2−6).

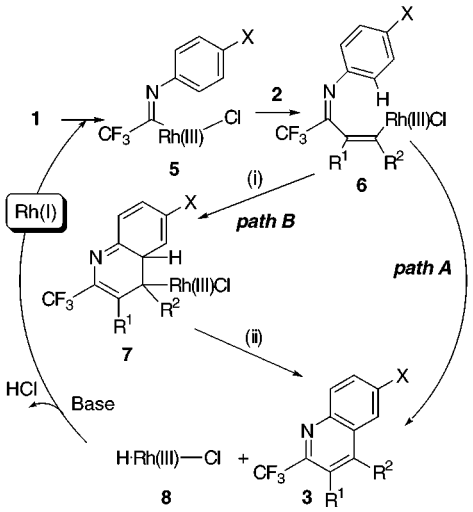
Table 3. Rh(I)-Catalyzed Coupling Cyclization of **1a** with Terminal Alkynes **2**



entry	alkyne **2** R		products (**3** and/or **4**)[a]	%yield (**3** + **4**)
1[b]	C_6H_{13}	(**2m**)	**3m** + **4m** (94:6)	68
2[c]	$SiMe_3$	(**2n**)	**3n** + **4n** (95:5)	82
3	CH_2SiMe_2Ph	(**2o**)	**3o** + **4o** (>99:1)	46[d]
4	$(CH_2)_2OSiMe_2{}^tBu$	(**2p**)	**3p** + **4p** (95:5)	52
5	Ph	(**2q**)	**3q** + **4q** (>99:1)	42
6	$CH(OEt)_2$	(**2r**)	**3r** + **4r** (>99:1)	70
7[e]	CO_2Et	(**2s**)	**3s** + **4s**[f] (29:71)	70

[a] Ratio of the products (**3**:**4**) indicated in parentheses. Regiochemistries of the products (**3** and **4**) were determined by NOE difference NMR spectroscopy. Each ratio was determined by ^{19}F NMR and GC analysis. [b] Et_3N was used instead of Na_2CO_3. [c] The reaction was carried out in a sealed glass tube at 140 °C. [d] Desilylated quinoline (R = Me) was also obtained in 6% yield. [e] 10 mol % of $[RhCl(cod)]_2$ was used (140 °C in xylene). [f] Determined by comparison with the authentic **3s** (ref 10)

Scheme 1



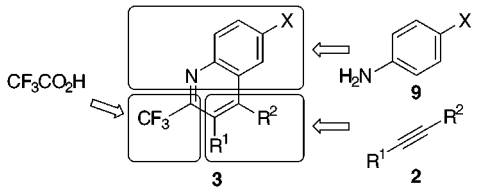
path A: Electrophilic Substitution or C-H Bond Activation
path B: (i) 6π-Cyclization, (ii) β-H Elimination

rhodium(I) undergoes an oxidative addition with the imidoyl chloride **1** to give the trifluoroacetimidoyl rhodium(III) species (**5**).[11] Next, intermolecular alkyne insertion into the Rh−C bond of the imidoyl−rhodium(III) complex gives rise to the vinylrhodium (**6**). Extrusion of the product quinoline **3** from the resultant vinylrhodium (**6**) then occurs to furnish H−Rh(III)−Cl complex (**8**) which can regenerate an active Rh(I) species after reductive elimination of HCl to complete the catalytic cycle.[12] There are two possible routes from the intermediate **6** to H−Rh(III)−Cl (**8**); intramolecular electrophilic substitution at the ortho position of the aromatic ring of the imine moiety with the vinyl rhodium(III) moiety in **6** (path A), or intramolecular thermal 6π-electrocyclization of **6** and subsequent β-hydride elimination to afford the quinoline **3** (path B). The experimental observation that imidoyl chloride **2d**, which possesses an electron-withdrawing substituent on the aryl ring of the imine moiety, provided **3d** in poor yield whereas **2a**−**c**, which possess electron-donating substituents, provided **3a**−**c** in good yields led us to consider that participation of path A (electrophilic substitution) is plausible for this coupling−cyclization reaction.

One of the well-established methods to construct 2-trifluoromethylated quinoline ring systems is Lewis acid-catalyzed aza-Diels−Alder reaction of trifluoromethylated aldimine derivatives with electron-rich olefins.[3b−d] Compared to available methods, the present methodology has several advantages: (i) the trifluoromethylated quinolines which possess a functional group such as silyl or electron-

withdrawing alkoxycarbonyl group (CO_2R) are obtained; (ii) the starting materials **1** are stable compounds and are easily prepared in high yields by refluxing a mixture of commercially available TFA, arylamines, PPh_3, and Et_3N in CCl_4.[13] Only the use of a catalytic amount of Rh(I) complexes without further functionalization of imidoyl chlorides **1** allowed formation of the fluorinated quinolines **3** (and **4**). Thus, the construction of quinolines was formally achieved by the coupling of three components, i.e., CF_3CO_2H, arylamines **9**, and alkynes **2** as shown in Scheme 2.

Scheme 2



In conclusion, Rh(I)-catalyzed tandem one-pot coupling−cyclization reaction of trifluoroacetimidoyl chlorides (**1**) with alkynes **2** was developed, and it gave a new catalytic access to 2-trifluoromethylated quinolines.

Acknowledgment. This work has been supported by Ministry of Education, Science, Sports and Culture of Japan (Encouragement of Young Scientists, No. 11750748). We also thank the SC-NMR laboratory of Okayama University for ^{19}F NMR analysis and the Venture Business Laboratory of Graduate School of Okayama University for X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures, details of compound characterization for **3**/**4** (PDF), and crystallographic data for **3k** and **4l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystal data for **3k**: $C_{18}H_{14}F_3N_1O_1$: $M_r = 317.31$; monoclinic, $P21/n$ (No.14), $a = 10.182(2)$ Å, $b = 9.790(4)$ Å, $c = 30.84(1)$ Å, $\beta = 91.70(2)°$, $V = 3073(1)$ Å^3, $Z = 8$, $D = 1.371$ g/cm^3. The structure was solved by direct methods (SIR 92), yielding $R = 0.063$, $R_w = 0.062$ for 4740 independent reflections with $I > 3\sigma(I)$.

(9) Crystal data for **4l**: $C_{20}H_{16}F_3N_1O_3$: $M_r = 375.35$; monoclinic, $P21/n$ (No.14), $a = 11.729(1)$ Å, $b = 8.5412(4)$ Å, $c = 17.731(2)$ Å, $\beta = 92.027(4)°$, $V = 1775.1(2)$ Å^3, $Z = 4$, $D = 1.404$ g/cm^3. The structure was solved by direct methods (SIR 92), yielding $R = 0.069$, $R_w = 0.093$ for 2495 independent reflections with $I > 3\sigma(I)$.

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