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Zn(II)-Mediated Alkynylation−Cyclization of *o*-Trifluoroacetyl Anilines: One-Pot Synthesis of 4-Trifluoromethyl-Substituted Quinoline Derivatives

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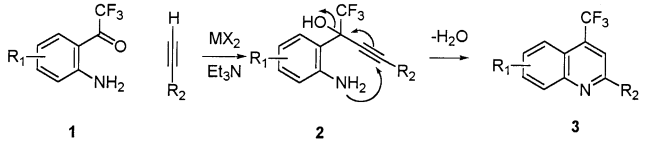
Abstract: A novel efficient route to 4-trifluoromethyl-substituted quinoline derivatives through the Zn(II)-mediated alkynylation−cyclization of *o*-trifluoroacetyl anilines is described.

Fluorine-containing heteroaromatic compounds have received a great deal of interest in the medicinal, agricultural, and material sciences.[1] Trifluoromethylated quinolines are particularly attractive because introducing fluorine atoms into an organic substrate can dramatically affect its physical, chemical, and biological properties.[2] For example, the antiprotozomal drug mefloquine[3] and some antileishmanial compounds[4,5] have a quinoline skeleton bearing a trifluoromethyl group. Recently, quinoline metal complexes have been used as highly efficient phosphorescent sensitizers for an organic light-emitting diode.[6] Considering the significant physical and chemical properties of fluorine-containing compounds, there has been considerable interest in developing an efficient method for the synthesis of trifluoromethylated quinoline derivatives. The methodologies of Skraup, Doebner-von Milller, and Combes provide rapid access to a simple quinoline skeleton. However, all of these methods suffer from low regioselectivity; if the aniline bears a meta substitute, two different ortho positions would be available for cyclization.[7] To the best of our knowledge, the regioselective synthesis of trifluoromethylated quinoline is very limited. Recently, Uneyama found that Rh(I) complexes could catalyze the coupling cyclization of *N*-aryl trifluoroacetylimidoyl chloride with alkynes to give 2-trifluoromethylated quinolines in good yields.[8] The development of cost-effective and simple processes is important in modern synthetic technology. We envisioned that 4-trifluoromethylated quinoline could be prepared by a tandem reaction of *o*-trifluoroacetyl aniline with acetylene by alkynylation and intramolecular cyclization (Scheme 1). We report here a novel efficient method for the synthesis of 4-CF_3 quinolines that involves a Zn(II)-mediated one-pot reaction of alkynes with *o*-trifluoroacetyl anilines.

SCHEME 1



1 2 3

Considerable progress has been made in the alkynylation of aldehydes using organometallic compounds in combination with a base.[9] Initially, treatment of 2-trifluoroacetyl-4-chloroaniline **1a** with phenyl acetylene and Et_3N using $Zn(OTf)_2$ as a catalyst in toluene at 25 °C for 4 h gave the desired cyclization product 4-trifluoromethylquinoline **3a** in only 10% yield, with trifluoromethyl propargylic alcohol **2a** as a major product (50%) (Scheme 1). In subsequent investigations, we found that trifluoromethyl propargylic alcohol **2a** could be easily converted into quinoline **3a** in 82% yield by heating with 1.2 equiv of $Zn(OTf)_2$ and 1.2 equiv of Et_3N in toluene at 50 °C, while the quinoline was not formed under acidic conditions, such as TsOH/MeOH/50 °C, CF_3CO_2H/CH_2Cl_2/25 °C, or HCl/MeOH/50 °C. This result prompted us to investigate the one-pot synthesis of quinoline. Thus, we found that when the reaction was carried out at 25 °C for 4 h in toluene, followed by heating at 50 °C for an additional 4 h, the quinoline **3a** was obtained as a major product in 53% yield. Neither $Cu(OTf)_2$ nor $Sn(OTf)_2$ promoted this reaction. It is important to note that inexpensive $ZnCl_2$ efficiently promoted the reaction and gave **3a** in good yield (60%). When the reaction was performed with *o*-acetylaniline, only the starting material was recovered. This can be explained by the ready formation of the enolate of alkyl ketone with the base, which inhibited the acetylene addition reaction.

The reactions of a series of *o*-trifluoroacetyl aniline substrates with terminal alkynes under optimal conditions are summarized in Table 1. As shown, the use of $ZnCl_2$ as a catalyst led to a higher yield than with $Zn(OTf)_2$. An aryl ring bearing an electron-donating group gave a higher yield than that with an electron-withdrawing group. Cyclopropanyl acetylene was more reactive

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TABLE 1. Preparation of 4-Trifluoromethylated Quinoline 3[a]

entry	R_1 in aniline **1**	R_2 in acetylene	ZnX_2	yield of **3** (%)[b]
1	*p*-Cl (**1a**)	Ph	$Zn(OTf)_2$	53 (**3a**)
2			$ZnCl_2$	60 (**3a**)
3	*p*-Cl (**1a**)	*c*-C_3H_5	$Zn(OTf)_2$	69 (**3b**)
4			$ZnCl_2$	81 (**3b**)
5	*p*-MeO (**1b**)	Ph	$Zn(OTf)_2$	60 (**3c**)
6			$ZnCl_2$	65 (**3c**)
7	*p*-MeO (**1b**)	*c*-C_3H_5	$Zn(OTf)_2$	79 (**3d**)
8			$ZnCl_2$	82 (**3d**)
9	*o*-MeO (**1c**)	Ph	$Zn(OTf)_2$	41 (**3e**)
10			$ZnCl_2$	41 (**3e**)
11	*o*-MeO (**1c**)	*c*-C_3H_5	$Zn(OTf)_2$	79 (**3f**)
12			$ZnCl_2$	82 (**3f**)
13	H (**1d**)	Ph	$Zn(OTf)_2$	55 (**3g**)
14			$ZnCl_2$	60 (**3g**)
15	H (**1d**)	*c*-C_3H_5	$Zn(OTf)_2$	67 (**3h**)
16			$ZnCl_2$	70 (**3h**)
17	*p*-CF_3 (**1e**)	Ph	$Zn(OTf)_2$	38 (**3i**)
18			$ZnCl_2$	45 (**3i**)
19	*p*-CF_3 (**1e**)	*c*-C_3H_5	$Zn(OTf)_2$	55 (**3j**)
20			$ZnCl_2$	61 (**3j**)

[a] All reactions were carried out with 1 equiv of **1**, 1.2 equiv of acetylene, 1.2 equiv of $ZnCl_2$ or 1.2 equiv of $Zn(OTf)_2$, and 1.2 equiv of Et_3N at 25 °C for 4 h and at 50 °C for an additional 4 h. [b] Isolated yield.

than phenylacetylene, and gave the corresponding quinoline in good yield.

In conclusion, this is the first report of a convenient alkynylation−cyclization method for preparing 4-trifluoromethylated quinolines via the reaction of *o*-trifluoroacetyl aniline using zinc(II) salt and triethylamine. The salient features of the present protocol are (1) the facile synthesis and high regioselectivity of 4-trifluoromethylated quinolines under mild conditions and with simple manipulation and (2) rapid access to a wide range of functionalized 4-trifluoromethylated quinolines.

Experimental Section

2-(2′-Amino-5′-chlorophenyl)-1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (2a). Under argon atmosphere, a flame-dried flask was charged with phenyl acetylene (122 mg, 1.2 mmol), anhydrous $Zn(OTf)_2$ (436 mg, 1.2 mmol), triethylamine (167 μL, 1.2 mmol), and toluene (2.5 mL). The resulting mixture was stirred at 50 °C for 2 h and cooled to 25 °C, then 2-trifluoroacetyl-4-chloroaniline **1a** (223 mg, 1 mmol) was added. The reaction mixture was stirred at 25 °C for 4 h. Water (10 mL) was added and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was purified by flash chromatography on silica gel to give **2a** (163 mg, 50%). Mp 119.2−120.9 °C; IR (KBr) 3504, 3406, 3343, 2931, 2233, 1708, 1617, 1491, 1249, 1178 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.60 (br, 2H), 6.81 (d, J = 8.9 Hz, 1H), 7.15 (dd, J = 8.6 and 2.4 Hz, 1H), 7.42 (m, 3H), 7.58 (m, 2H), 7.71 (d, J = 2.2 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 66.2, 76.1, 80.0, 109.9, 110.8, 111.8, 112.8 114.6, 118.4, 120.6, 121.4, 121.6, 121.8, 123.6, 138.4; ^{19}F NMR (acetone-d_6) δ −2.90 (s, 3F); MS (EI) *m/e* 325 (M^+, 28), 256 (65), 105 (100). Anal. Calcd for $C_{16}H_{11}NClF_3O$: C, 59.08; H, 3.38; N, 4.31. Found: C, 59.11; H, 3.32; N, 4.29.

General Procedure for Preparation of 3a−j. Under argon atmosphere, a flame-dried flask was charged with alkyne (1.2 mmol), anhydrous zinc(II) salt (1.2 mmol), triethylamine (167 μL, 1.2 mmol), and toluene (2.5 mL). The resulting mixture was stirred at 50 °C for 2 h and cooled to 25 °C, then *o*-trifluoroacetylaniline **1** (1 mmol) was added. The reaction mixture was stirred at 25 °C for 4 h, then at 50 °C for 4 h. After being cooled to room temperature, the mixture was added to water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford quinolines **3**.

2-Phenyl-4-trifluoromethyl-6-chloroquinoline (3a): mp 116.6−118.4 °C; IR (KBr) 1611, 1376, 1267, 1152, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54−7.60 (m, 3H), 7.77 (dd, J = 9.0 and 2.3 Hz, 1H), 8.12 (m, 1H), 8.17−8.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 116.8, 121.5, 122.4, 123.0, 125.2, 127.5, 129.1, 130.4, 131.5, 132.2, 134.1, 138.0, 147.6, 156.9; ^{19}F NMR ($CDCl_3$) δ −67.4 (s, 3F); MS (EI) *m/e* 307 (M^+, 100). Anal. Calcd for $C_{16}H_9NClF_3$: C, 62.43; H, 2.92; N, 4.55. Found: C, 62.14; H, 3.43; N, 4.24.

2-Cyclopropyl-4-trifluoromethyl-6-chloroquinoline (3b): mp 62.1−63.9 °C; IR (KBr) 2928, 1618, 1411, 1317, 1157, 1139, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24−1.28 (m, 4H), 2.27 (m, 1H), 7.55 (s, 1H), 7.68 (dd, J = 8.7 and 1.5 Hz, 1H), 7.96−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.2, 18.2, 118.1, 121.5, 121.9, 122.9, 125.1, 131.0, 131.1, 133.0, 147.3, 163.4; ^{19}F NMR ($CDCl_3$) δ −67.4 (s, 3F); MS (EI) *m/e* 271 (M^+, 100). Anal. Calcd for $C_{13}H_9NClF_3$: C, 57.46; H, 3.31; N, 5.16. Found: C, 57.73; H, 3.70; N, 4.96.

2-Phenyl-4-trifluoromethyl-6-methoxyquinoline (3c): mp 115.7−117.2 °C; IR (KBr) 1626, 1366, 1238, 1141, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (s, 3H), 7.38−7.59 (m, 5H), 8.15−8.19 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 54.6, 100.9, 115.0, 121.5, 122.1, 124.2, 126.2, 127.9, 128.6, 131.1, 132.7, 137.6, 144.4, 153.1, 157.8; ^{19}F NMR ($CDCl_3$) δ −67.9 (s, 3F); MS (EI) *m/e* 303 (M^+, 100). Anal. Calcd for $C_{17}H_{12}NF_3O$: C, 67.33; H, 3.96; N, 4.62. Found: C, 67.27; H, 4.59; N, 4.22.

2-Cyclopropyl-4-trifluoromethyl-6-methoxyquinoline (3d): mp 73.5−74.6 °C; IR (KBr) 1623, 1613, 1406, 1319, 1240, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09−1.20 (m, 4H), 2.26 (m, 1H), 3.95 (s, 3H), 7.30 (m, 1H), 7.39 (dd, J = 9.2 and 2.4 Hz, 1H), 7.48 (s, 1H), 7.95 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3, 17.8, 55.5, 102.0, 117.2, 122.0, 122.4, 125.7, 131.0, 132.6, 145.2, 157.8, 160.0; ^{19}F NMR ($CDCl_3$) δ −68.0 (s, 3F); MS (EI) *m/e* 267 (M^+, 100). Anal. Calcd for $C_{14}H_{12}NF_3O$: C, 62.92; H, 4.49; N, 5.24. Found: C, 62.55; H, 4.90; N, 5.02.

2-Phenyl-4-trifluoromethyl-8-methoxyquinoline (3e): mp 104.4−105.7 °C; IR (KBr) 2924, 1615, 1556, 1472, 1369, 1270, 1126, 1116, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (s, 3H), 7.16 (d, J = 7.8 Hz, 1H), 7.47−7.60 (m, 4H), 7.68 (m, 1H), 8.18−8.21 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 56.3, 108.7, 115.0, 116.5, 121.7, 123.0, 125.4, 127.6, 128.2, 128.9, 129.9, 134.7, 138.6, 141.1, 155.5, 155.9; ^{19}F NMR ($CDCl_3$) δ −67.3 (s, 3F); MS (EI) *m/e* 303 (M^+, 100). Anal. Calcd for $C_{17}H_{12}NF_3O$: C, 67.33; H, 3.96; N, 4.62. Found: C, 67.11; H, 4.17; N, 4.43.

2-Cyclopropyl-4-trifluoromethyl-8-methoxyquinoline (3f): mp 123.5−124.9 °C; IR (KBr) 1620, 1563, 1319, 1275, 1151, 1129 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12−1.25 (m, 4H), 2.45 (m, 1H), 4.08 (s, 3H), 7.10 (m, 1H), 7.35 (s, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 10.6, 18.8, 18.9, 56.2, 108.6, 115.5, 121.7, 122.4, 125.3, 127.0, 134.3, 140.5, 155.0, 161.9; ^{19}F NMR ($CDCl_3$) δ −67.4 (s, 3F); MS (EI) *m/e* 267 (M^+, 100). Anal. Calcd for $C_{14}H_{12}NF_3O$: C, 62.92; H, 4.49; N, 5.24. Found: C, 62.97; H, 4.81; N, 5.16.

2-Phenyl-4-trifluoromethylquinoline (3g): mp 37.2−39.0 °C; IR (KBr) 1612, 1375, 1361, 1141,1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52−7.60 (m, 3H), 7.67 (m, 1H), 7.83 (m, 1H), 8.14−8.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 115.5, 121.4, 123.4, 125.0, 127.1, 127.4, 128.6, 129.5, 129.9, 130.2, 134.6, 138.0, 148.7, 156.2; ^{19}F NMR ($CDCl_3$) δ −67.2 (s, 3F); MS (EI) *m/e* 273 (M^+, 100). Anal. Calcd for $C_{16}H_{10}NF_3$: C, 70.33; H, 3.66; N, 5.13. Found: C, 70.33; H, 3.93; N, 4.94.

2-Cyclopropyl-4-trifluoromethylquinoline (3h): mp 38.9−40.5 °C; IR (KBr) 1616, 1409, 1319, 1257, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09−1.26 (m, 4H), 2.25 (m, 1H), 7.48−7.55 (m, 2H), 7.70 (m, 1H), 8.02 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.9, 18.1, 18.1, 117.0, 121.7, 123.8, 125.4, 126.7, 129.5, 129.9, 133.9, 148.8, 162.9; ^{19}F NMR ($CDCl_3$) δ −67.2 (s, 3F); MS (EI) *m/e* 237 (M^+, 100). Anal. Calcd for $C_{13}H_{10}N F_3$: C, 65.82; H, 4.22; N, 5.91. Found: C, 65.99; H, 4.44; N, 5.82.

2-Phenyl-4,6-bis(trifluoromethyl)quinoline (3i): mp 99.5−100.8 °C; IR (KBr) 1615, 1325, 1154, 1116 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 7.56−7.63 (m, 3H), 8.00 (dd, J = 9.1 and 1.7 Hz, 1H), 8.21−8.23 (m, 3H), 8.37−8.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 117.0, 120.8, 121.3, 121.8, 124.9, 125.5, 126.2, 127.6, 129.1, 130.7, 131.7, 135.8, 137.5, 149.9, 158.6; ^{19}F NMR ($CDCl_3$) δ 14.6 (s, 3F), 13.4 (s, 3F); MS (EI) *m*/*e* 341 (M^+, 100). Anal. Calcd for $C_{17}H_9NF_6$: C, 59.82; H, 2.64; N, 4.10. Found: C, 60.16; H, 3.03; N, 3.90.

2-Cyclopropyl-4,6-bis(trifluoromethyl)quinoline (3j): mp 51.3−52.8 °C; IR 1618, 1482, 1415, 1319, 1171, 1143 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.18−1.33 (m, 4H), 2.29 (m, 1H), 7.64 (s, 1H), 7.90 (dd, J = 9.1 and 2.1 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.6, 11.7, 18.3, 118.5, 120.2, 121.2, 121.7, 124.8, 125.6, 128.5, 130.6, 134.3, 149.7, 165.6; ^{19}F NMR ($CDCl_3$) δ 13.5 (s, 3F), 14.5 (s, 3F); MS (EI) *m*/*e* 305 (M^+, 100). Anal. Calcd for $C_{14}H_9NF_6$: C, 55.08; H, 2.95; N, 4.59. Found: C, 55.22; H, 3.17; N, 4.51.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **2a** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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