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Synthesis of 2-trifluoromethyl-1(substituted aryl)-4(1*H*)-quinolones using trifluoroacetamidoyl chlorides

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Abstract

A simple two-step procedure for the preparation of 2-trifluoromethyl-1(substituted aryl)-4(1*H*)-quinolones utilizing electrophilic trifluoroacetamidoyl chlorides as the starting materials is described. The cyclization of trifluoromethyl enaminone intermediates with potassium carbonate in hot dimethylformamide produce the trifluoromethylated 4(1*H*)-quinolones in good to excellent yields.

Keywords: Trifluoroacetamidoyl chloride; Trifluoromethyl; 4(1*H*)-quinolone

1. Introduction

Syntheses of 4(1*H*)-quinolones have received significant attention from organic and medicinal chemists, mainly for their high pharmacological value [1–4]. Several efforts have been made for the introduction of a trifluoromethyl group on position 2 of 4(1*H*)-quinolones [5–9]. The chemical literature reports the utility of trifluoroacetamidoyl chlorides [10,11] as excellent nucleophilic acceptors for Grignard's reagents and other stabilized anions [12–14]. Uneyama's group in Japan have observed its utility in the synthesis of 1-unsubstituted 2-trifluoromethylated-quinolones [6]. The stability and electrophilic character of trifluoroacetamidoyl chlorides as building blocks, prompted us to examine their utility in the preparation of 2-trifluoromethyl-1(substituted aryl)-4(1*H*)-quinolones, starting from readily available acetophenones.

2. Results and discussion

The enolate generated by treatment of commercially available acetophenones **1a** and **b** with sodium hydride in dry THF was made to react with the corresponding trifluoroacetamidoyl chlorides **2a–d**, to obtain enaminones **3a–h** exclusively as the geometric *Z*-isomer (Table 1). These enaminone building blocks incorporate the trifluoromethyl group necessary for position 2 of the desired quinolones The corresponding *Z*-geometry assigned for **3a–h**, was based on previous works [9,15] (Scheme 1).

The compounds **3a–h** were subjected to cyclization with potassium carbonate in hot dimethylformamide to obtain trifluoromethyl-quinolones **4a–h** (Table 2), in good to excellent yields. This simple, two-step procedure shows the use of trifluoroacetamidoyl chlorides as building blocks for the construction of trifluoromethylated heterocycles, such as *N*-aryl-quinolones, and will be used for the preparation of their 3-carboxylated analogues. A more extended application of this methodology is being carried out in our laboratories and will be published elsewhere.

3. Experimental

Melting points were determined with a Fischer–Johns micro hot-stage apparatus and are uncorrected. IR spectra were recorded on a Magna Nicolet 750 FT/IR spectrometer as potassium bromide discs. NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in deuterated chloroform, operating at 400 MHz (^{1}H, internal standard TMS) and 376 MHz (^{19}F, internal standard $CFCl_3$); δ values in ppm relative to the internal standard are given. The high resolution

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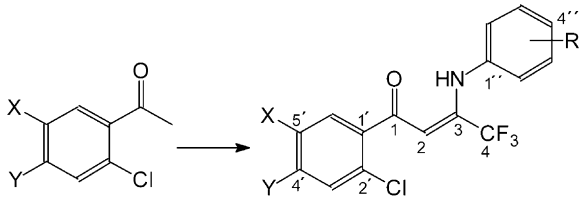
Table 1



1a : X=Cl; Y=H
1b : X=H; Y=Cl

3a-h

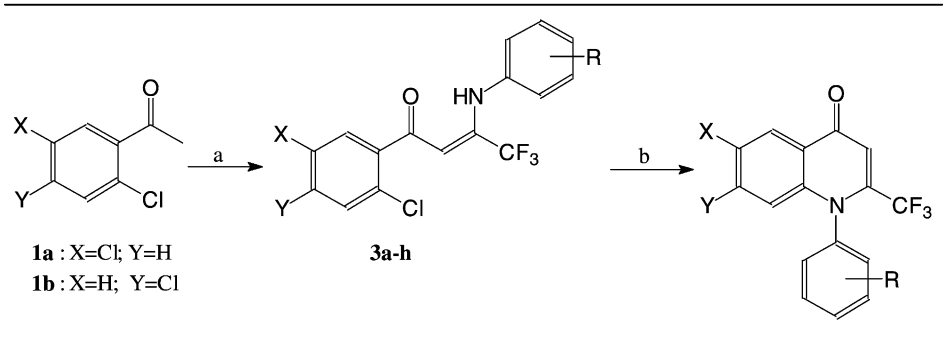
Compound	X	Y	R	Purification methodology		mp (°C)	Yield (%)
3a	Cl	H	4″-OMe	Column chromatography	Hex:AcOEt 8:2	54–56	49
3b	Cl	H	3″-OMe	Column chromatography	Pet. ether:Et_2O 99:1	53–54	47
3c	Cl	H	3″-Cl	Recrystallization	EtOH:acetone:H_2O	66–68	58
3d	Cl	H	4″-F	Recrystallization	EtOH:H_2O	67–69	83
3e	H	Cl	4″-OMe	Recrystallization	Hexanes	69–70	57
3f	H	Cl	3″-OMe	Column chromatography	Pet. ether:Et_2O 99:1	Oil	69
3g	H	Cl	3″-Cl	Column chromatography	*n*-Hexane	35–36	43
3h	H	Cl	4″-F	Column chromatography	Hex:EtOAc 95:5	70–71	40

mass spectra were obtained on a JEOL JMS-AX505WA mass spectrometer. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA, USA); the results fell in the range ±0.4% of the required theoretical values. Silica gel plates ALUGRAM® SIL G/UV_{254} (Macherey–Nagel GmbH & Co., Germany) were used for TLC testing. Reagents obtained from Aldrich (Milwaukee, MI, USA) or Merck (Darmstadt, Germany) were used without further purification. Solvents were distilled prior to use. Trifluoroacetamidoyl chlorides **2a–d** were prepared according to the literature procedure [10].

3.1. General experimental procedures

3.1.1. General procedure for the preparation of enaminones *3a–h*

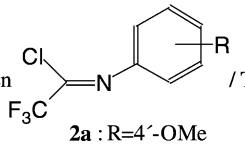
To an ice cooled suspension of NaH (1.2 mmol) in dry THF (20 ml) was slowly added a solution of acetophenone **1a** and **b** (1 mmol). To the resulting suspension stirred for 30 min at 0 °C, was slowly added a solution of the corresponding trifluoroacetamidoyl chloride **2a–d** (1 mmol) in dry THF and then further stirred the resulting yellow-orange solution at room temperature for 1 h. Water was added (20 ml), the



1a : X=Cl; Y=H
1b : X=H; Y=Cl

3a-h

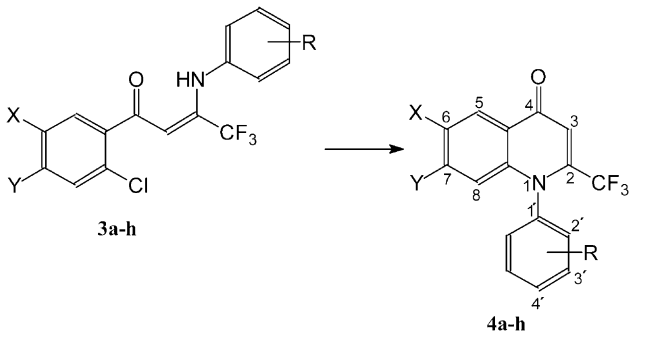
4a-h

Conditions: a. NaH, THF, then  / THF, rt, 1 h.; b. K_2CO_3, Me_2NCHO, 100 °C, 2 h.

2a : R=4′-OMe
2b : R=3′-OMe
2c : R=3′-Cl
2d : R=4′-F

Scheme 1.

Table 2



Compound	X	Y	R	mp (°C)	Yield (%)
4a	Cl	H	4′-OMe	168–169	91
4b	Cl	H	3′-OMe	178–179	89
4c	Cl	H	3′-Cl	186–188	91
4d	Cl	H	4′-F	223–224	75
4e	H	Cl	4′-OMe	185–186	46
4f	H	Cl	3′-OMe	188–190	76
4g	H	Cl	3′-Cl	196–197	94
4h	H	Cl	4′-F	225–226	74

solution was concentrated at reduced pressure and extracted with $CHCl_3$ (2 × 20 ml). The organic extract was separated, dried over anhydrous magnesium sulfate, and evaporated, obtaining a yellow oil which was further purified either by recrystallization or column chromatography (silicagel).

*3.1.1.1. 3-(4-Methoxyphenylamino)-1-(2,5-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3a**).* 0.19 g (49% yield), purified by column chromatography (Hex:AcOEt 8:2), yellow crystals, mp 54–56 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 6.07 (s, 1H, H-2), 6.89 (d, 2H, $J = 8.8$ Hz, H-arom.), 7.19 (d, 2H, $J = 8.8$ Hz, H-arom.), 7.33 (dd, 1H, $J = 2.2$ Hz, $J = 8.4$ Hz, H-4′), 7.36 (d, 1H, $J = 8.4$ Hz, H-3′), 7.52 (d, 1H, $J = 2.2$ Hz, H-6′), 11.97 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.37 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{12}Cl_2F_3O_2N$: C, 52.33; H, 3.10; N, 3.59. Found: C, 52.40; H, 3.08; N, 3.64.

*3.1.1.2. 3-(3-Methoxyphenylamino)-1-(2,5-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3b**).* 0.18 g (47% yield), purified by column chromatography (petroleum ether:diethyl ether 99:1), yellow solid, mp 53–54 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 6.12 (s, 1H, H-2), 6.81 (bs, 1H, H-arom.), 6.86 (dd, 1H, $J = 2.2$ Hz, $J = 8.4$ Hz, H-arom.), 7.32–7.35 (m, 2H, H-arom.), 7.36 (d, 1H, $J = 8.4$ Hz, H-3′), 7.53 (d, 1H, $J = 2.5$ Hz, H-6′), 12.09 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.00 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{12}Cl_2F_3O_2N$: C, 52.33; H, 3.10; N, 3.59. Found: C, 52.25; H, 3.12; N, 3.52.

*3.1.1.3. 3-(3-Chlorophenylamino)-1-(2,5-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3c**).* 0.23 g (58% yield), recrystallized from EtOH:acetone:water, yellow crystals, mp 66–68 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 1H, H-2), 7.16–7.20 (m, 1H, H-arom.), 7.29–7.33 (m, 3H, H-arom.), 7.35 (dd, 1H, $J = 2.2$ Hz, $J = 8.1$ Hz, H-4′), 7.37 (d, 1H, $J = 8.1$ Hz, H-3′), 7.52 (d, 1H, $J = 2.2$ Hz, H-6′), 12.03 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.98 (s, 3F, CF_3). Anal. Calcd. for $C_{16}H_9Cl_3F_3ON$: C, 48.70; H, 2.30; N, 3.55. Found: C, 48.59; H, 2.37; N, 3.46.

*3.1.1.4. 3-(4-Fluorophenylamino)-1-(2,5-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3d**).* 0.31 g (83% yield), recrystallized from EtOH:water, yellow crystals, mp 67–69 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 1H, H-2), 7.06–7.10 (m, 2H, H-arom.), 7.24–7.27 (m, 2H, H-arom.), 7.34 (dd, 1H, $J = 2.2$ Hz, $J = 8.8$ Hz, H-4′), 7.37 (d, 1H, $J = 8.8$ Hz, H-3′), 7.52 (d, 1H, $J = 2.2$ Hz, H-6′), 11.95 (s, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.25 (s, 3F, CF_3), −113.55 (s, 1F, F-4″). Anal. Calcd. for $C_{16}H_9Cl_2F_4ON$: C, 50.82; H, 2.40; N, 3.70. Found: C, 50.93; H, 2.36; N, 3.58.

*3.1.1.5. 3-(4-Methoxyphenylamino)-1-(2,4-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3e**).* 0.22 g (57% yield), recrystallized from cooled hexanes, yellow crystals, mp 69–70 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.09 (s, 1H, H-2), 6.89 (d, 2H, H-2″, H-6″, $J = 8.8$ Hz), 7.19 (d, 2H, $J = 8.8$ Hz, H-3″, H-5″), 7.32 (dd, 1H, $J = 1.8$ Hz, $J = 8.4$ Hz, H-5′), 7.45 (d, 1H, $J = 1.8$ Hz, H-3′), 7.50 (d, 1H, $J = 8.4$ Hz), 11.99 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.12 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{12}Cl_2F_3O_2N$: C, 52.33; H, 3.10; N, 3.59. Found: C, 52.46; H, 3.14; N, 3.68.

*3.1.1.6. 3-(3-Methoxyphenylamino)-1-(2,4-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3f**).* 0.27 g (69% yield), purified by column chromatography (petroleum ether:diethyl ether 99:1), yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 6.14 (s, 1H, H-2), 6.81–6.87 (m, 3H, H-arom.), 7.28 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz, H-5″), 7.32 (dd, 1H, $J = 1.8$ Hz, $J = 8.4$ Hz, H-5′), 7.45 (d, 1H, $J = 1.8$ Hz, H-3′), 7.51 (d, 1H, $J = 8.4$ Hz, H-6′), 12.12 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.98 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{12}Cl_2F_3O_2N$: C, 52.33; H, 3.10; N, 3.59. Found: C, 52.21; H, 3.07; N, 3.64.

*3.1.1.7. 3-(3-Chlorophenylamino)-1-(2,4-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3g**).* 0.17 g (43% yield), purified by column chromatography (*n*-hexane), yellow crystals, mp 35–36 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H, H-2), 7.16–7.20 (m, 1H, H-arom.), 7.28–7.34 (m, 4H, H-arom.), 7.46 (d, 1H, $J = 1.8$ Hz, H-3′), 7.50 (d, 1H, $J = 8.1$ Hz, H-6′), 12.05 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.00 (s, 3F, CF_3). Anal. Calcd. for $C_{14}H_9Cl_3F_3ON$: C, 48.70; H, 2.30; N, 3.55. Found: C, 48.82; H, 2.37; N, 3.40.

*3.1.1.8. 3-(4-Fluorophenylamino)-1-(2,4-dichlorophenyl)-4,4,4-trifluoro-2-buten-1-one (**3h**).* 0.15 g (40% yield),

purified by column chromatography (Hex:EtOAc 95:5), yellow crystals, mp 70–71 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 1H, H-2), 7.07 (dd, 2H, H-arom.), 7.07 (dd, 2H, $J = 8.4$ Hz, $J = 8.4$ Hz, H-3″, H-5″), 7.23–7.27 (m, 2H, H-arom.), 7.33 (dd, 1H, $J = 1.4$ Hz, $J = 8.4$ Hz, H-5′), 7.46 (d, 1H, $J = 1.4$ Hz, H-3′), 7.51 (d, 1H, $J = 8.4$ Hz, H-6′), 11.97 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.25 (s, 3F, CF_3), −113.62 (s, 1F, F-4″). Anal. Calcd. for $C_{16}H_9Cl_2F_4ON$: C, 50.82; H, 2.40; N, 3.70. Found: C, 50.67; H, 2.35; N, 3.81.

*3.1.2. General procedure for the preparation of 2-trifluoromethyl-1(substituted aryl)-4(1H)-quinolones (**4a–h**)*

To a solution of the corresponding enamine **3a–h** (1 mmol) in DMF (5 ml) was added potassium carbonate (1.2 mmol). The reaction mixture was heated (100 °C) and stirred for 2 h, then cooled to room temperature and poured into crushed ice, The resulting solid was filtered, washed with water, dried in vacuo and recrystallized from acetone:-water.

*3.1.2.1. 6-Chloro-2-trifluoromethyl-1-(4-methoxyphenyl)-4(1H)-quinolone (**4a**).* 0.32 g (91% yield), needles, mp 168–169 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H, OCH_3), 6.67 (d, 1H, $J = 9.2$ Hz, H-8), 6.84 (s, 1H, H-3), 7.07 (d, 2H, $J = 9.1$ Hz, H-2′, H-6′), 7.25 (d, 2H, $J = 9.1$ Hz, H-3′, H-5′), 7.42 (dd, 1H, $J = 2.6$ Hz, $J = 9.2$ Hz, H-7), 8.36 (d, 1H, $J = 2.6$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.43 (s, 3F, CF_3). HRMS: Calcd. for $C_{17}H_{11}ClF_3O_2N$: 353.0400. Found 352.9906.

*3.1.2.2. 6-Chloro-2-trifluoromethyl-1-(3-methoxyphenyl)-4(1H)-quinolone (**4b**).* 0.31 g (89 % yield), white needles, mp 178–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H, OCH_3), 6.68 (d, 1H, $J = 9.2$ Hz, H-8), 6.77–6.95 (m, 3H, H-3, H-arom.), 7.14 (d, 1H, $J = 7.7$ Hz, H-arom.), 7.39–7.51 (m, 2H, H-arom.), 8.31(s, 1H, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.38 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{11}ClF_3O_2N$: C, 57.72; H, 3.13; N, 3.96. Found: C, 57.87; H, 3.16; N, 3.84.

*3.1.2.3. 6-Chloro-2-trifluoromethyl-1-(3-chlorophenyl)-4(1H)-quinolone (**4c**).* 0.33 g (91% yield), creamy solid, mp 186–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, 1H, $J = 9.2$ Hz, H-8), 6.83 (s, 1H, H-3), 7.29 (d, 1H, $J = 8.1$ Hz, H-6′), 7.40 (s, 1H, H-2′), 7.44 (dd, 1H, $J = 2.6$ Hz, $J = 9.2$ Hz, H-7), 7.56 (dd, 1H, $J = 8.1$ Hz, H-4′), 8.34 (d, 1H, $J = 2.6$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.23 (s, 3F, CF_3). Anal. Calcd. for $C_{16}H_8Cl_2F_3ON$: C, 53.66; H, 2.25; N, 3.91. Found: C, 53.43; H, 2.17; N, 4.03.

*3.1.2.4. 6-Chloro-2-trifluoromethyl-1-(4-fluorophenyl)-4(1H)-quinolone (**4d**).* 0.26 g (75% yield), mp 223–224 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, 1H, $J = 9.2$ Hz, H-8), 6.84 (s, 1H, H-3), 7.27–7.38 (m, 4H, H-arom.), 7.45 (dd, 1H, $J = 2.6$ Hz, $J = 9.2$ Hz, H-7), 8.36 (d, 1H, $J = 2.6$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.23 (s, 3F, CF_3), −108.31 (s, 1F, F-4′). Anal. Calcd. for $C_{16}H_8ClF_4ON$: C, 56.24; H, 2.36; N, 4.10. Found: C, 56.35; H, 2.40; N, 3.95.

*3.1.2.5. 7-Chloro-2-trifluoromethyl-1-(4-methoxyphenyl)-4(1H)-quinolone (**4e**).* 0.16 g (46 % yield), white needles, mp 185–186 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H, OCH_3), 6.69 (s, 1H, H-8), 6.82 (s, 1H, H-3), 7.07–7.09 (m, 2H, H-arom.), 7.25–7.34 (m, 3H, H-arom.), 8.32 (d, 1H, $J = 8.4$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.53 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{11}ClF_3O_2N$: C, 57.72; H, 3.13; N, 3.96. Found: C, 57.98; H, 3.07; N, 4.03.

*3.1.2.6. 7-Chloro-2-trifluoromethyl-1-(3-methoxyphenyl)-4(1H)-quinolone (**4f**).* 0.27 g (76% yield), creamy solid, mp 188–190 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.69 (s, 1H, H-8), 6.81 (s, 1H, H-3), 6.87–6.95 (m, 2H, H-arom.), 7.15 (d, 1H, $J = 7.7$ Hz, H-arom.), 7.31 (d, 1H, $J = 8.1$ Hz, H-arom.), 7.50 (dd, 1H, $J = 7.7$ Hz, $J = 8.1$ Hz, H-5′), 8.31 (d, 1H, $J = 8.4$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.45 (s, 3F, CF_3). Anal. Calcd. for $C_{17}H_{11}ClF_3O_2N$: C, 57.72; H, 3.13; N, 3.96. Found: C, 57.90; H, 3.18; N, 3.85.

*3.1.2.7. 7-Chloro-2-trifluoromethyl-1-(3-chlorophenyl)-4(1H)-quinolone (**4g**).* 0.35 g (94 % yield), creamy solid, mp 196–197 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, 1H, $J = 1.8$ Hz, H-8), 6.84 (s, 1H, H-3), 7.29 (d, 1H, $J = 8.4$ Hz, H-arom.), 7.36 (dd, 1H, $J = 1.8$ Hz, $J = 8.8$ Hz, H-6), 7.39 (s, 1H, H-2′), 7.58 (dd, 1H, $J = 8.1$ Hz, $J = 8.1$ Hz, H-5′), 7.65 (d, 1H, $J = 8.4$ Hz, H-arom.), 8.35 (d, 1H, $J = 8.8$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.30 (s, 3F, CF_3). HRMS: Calcd. for $C_{16}H_8Cl_2F_3ON$: 356.9900. Found: 356.9475 (100).

*3.1.2.8. 7-Chloro-2-trifluoromethyl-1-(4-fluorophenyl)-4(1H)-quinolone (**4h**).* 0.25 g (74% yield), needles, mp 225–226 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, 1H, $J = 1.8$ Hz, H-8), 6.82 (s, 1H, H-3), 7.28–7.39 (m, 5H, H-arom.), 8.32 (d, 1H, $J = 8.8$ Hz, H-5). ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.38 (s, 3F, CF_3), −108.147 (s, 1F, F-4′). Anal. Calcd. for $C_{16}H_8ClF_4ON$: C, 52.24; H, 2.36; N, 4.10. Found: C, 52.39; H, 2.32; N, 4.18.

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References

[1] T.E. Renau, J.P. Sanchez, J.W. Gage, J.A. Dever, M.A. Shapiro, S.J. Gracheck, J.M. Domagala, J. Med. Chem. 39 (1996) 729.
[2] S.K. Srivastawa, P.M.S. Chauhan, A.P. Bhaduri, N. Fatima, R.K. Chatterjee, J. Med. Chem. 43 (2000) 2275.
[3] V. Cecchetti, C. Parolin, S. Moro, T. Pecere, E. Filipponi, A. Calistri, O. Tabarrini, B. Gatto, M. Palumbo, A. Fravolini, G. Palur, J. Med. Chem. 43 (2000) 3799.
[4] Y.-L. Chen, K.-C. Fang, J.-Y. Sheu, S.-L. Hsu, C.-C. Tzeng, J. Med. Chem. 44 (2001) 2374.
[5] G.S. Bajwa, M.M. Joullie, J. Heterocycl. Chem. 9 (1972) 1403.
[6] K. Uneyama, O. Morimoto, F. Yamashita, Tetrahedron Lett. 30 (1989) 4821.
[7] D.W. Combs, M.S. Reed, D.H. Klaubert, Synth. Commun. 22 (1992) 323.
[8] H. Gildemeister, H. Knorr, H. Mildenberger, G. Salbeck, Liebigs Ann. Chem. (1982) 1656.
[9] E.J. Latham, S.P. Stanforth, J. Chem. Soc., Perkin Trans. 1 (1997) 2059.
[10] K. Tamura, H. Mizukami, K. Maeda, H. Watanabe, K. Uneyama, J. Org. Chem. 58 (1993) 32.
[11] F. Clemence, R. Deraedt, A. Allais, O. Lemartrer, Eur. Pat. Appl. 12,639 (CI. C07D215/56), Chem. Abstr. 94 (1981) 15590g.
[12] K. Uneyama, F. Yamashita, K. Sugimoto, O. Morimoto, Tetrahedron Lett. 31 (1990) 2717.
[13] P. Bravo, G. Cavicchio, M. Crucianelli, A.L. Markovsky, A. Volonterio, M. Zanda, Synlett (1996) 887.
[14] P. Bravo, S. Capelli, S.V. Meille, P. Seresini, A. Volonterio, M. Zanda, Tetrahedron: Asymmetry 7 (1996) 2321.
[15] J.J. Bozell, L.S. Hegedus, J. Org. Chem. 46 (1981) 2561.