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Synthesis of the trifluoromethylated retinoial aromatic amide—4-[1-(5,6,7,8-tetrahydro-3-trifluoromethyl-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid

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Abstract

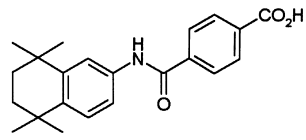
A new methodology was developed for the preparation of an o-trifluoromethylated arylamine. The condensation of 2-amino-3-trifluoromethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene and terephthalic acid monomethyl ester chloride gave the trifluoromethylated retinoial aromatic amide. The key step in the synthesis is the introduction of the aryl trifluoromethyl group.

Keywords: Retinoids; Trifluoromethylation

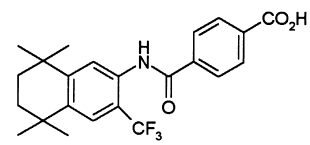
1. Introduction

Retinoids, natural and synthetic analogs of Vitamin A, are potent molecules that can affect a variety of fundamental biological processes including cell differentiation and proliferation and apoptosis [1,2]. Recent evidence has shown that retinoids exert their functions through at least two classes of nuclear receptors: RAR (α,β,γ) and RXR (α,β,γ) [3]. Current research efforts in this field have focused on searching for receptor-specific ligands in order to elucidate the biological functions of each receptor. Several classes of molecules that are specific for the RAR [4] or RXR [5] families of receptors have been described. Among them, aromatic amide, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (Am 80, **1**) binds strongly to two subtypes, RARα and RARβ, but not to RARγ [6].

Due of its high lipophilicity, and powerful electron-withdrawing effect, the trifluoromethyl group is an increasingly popular aromatic substituent in compounds synthesized for improving their biological activity [7]. From this perspective, we became interested in the incorporation of the trifluoromethyl substituted into retinoid **1**, The synthesis of compound **2** is described below:



(1)



(2)

2. Results

Disconnection of the amide bond divides the target molecule **2** into two precursors o-trifluoromethylated arylamine **3** and terephthalic acid monomethyl ester chloride **4**. Compound **4** is commercially available. Thus, we turned our attention to prepare the key precursor o-trifluoromethyl arylamine **3**. Compound **3** was synthesized as outlined in Scheme 1. The bromo compound **5**, was prepared by reaction of bromobenzene with 2,5-dichloro-2,5-dimethylhexane in the presence of aluminum chloride. Nitration of **5** at 60°C gave the nitro product **6** in 75% yield. Reaction of **6** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA [8] afforded the trifluoromethylated product **7** in 85% yield. Reduction of **7** with Fe/HCl gave the o-trifluoromethylated arylamine **3** in 95% yield. The condensation of **3** and terephthalic acid monomethyl ester chloride **4** in the presence of pyridine provided the amide **8**, which on hydrolysis produced the trifluoromethylated retinoial aromatic amide **2**.

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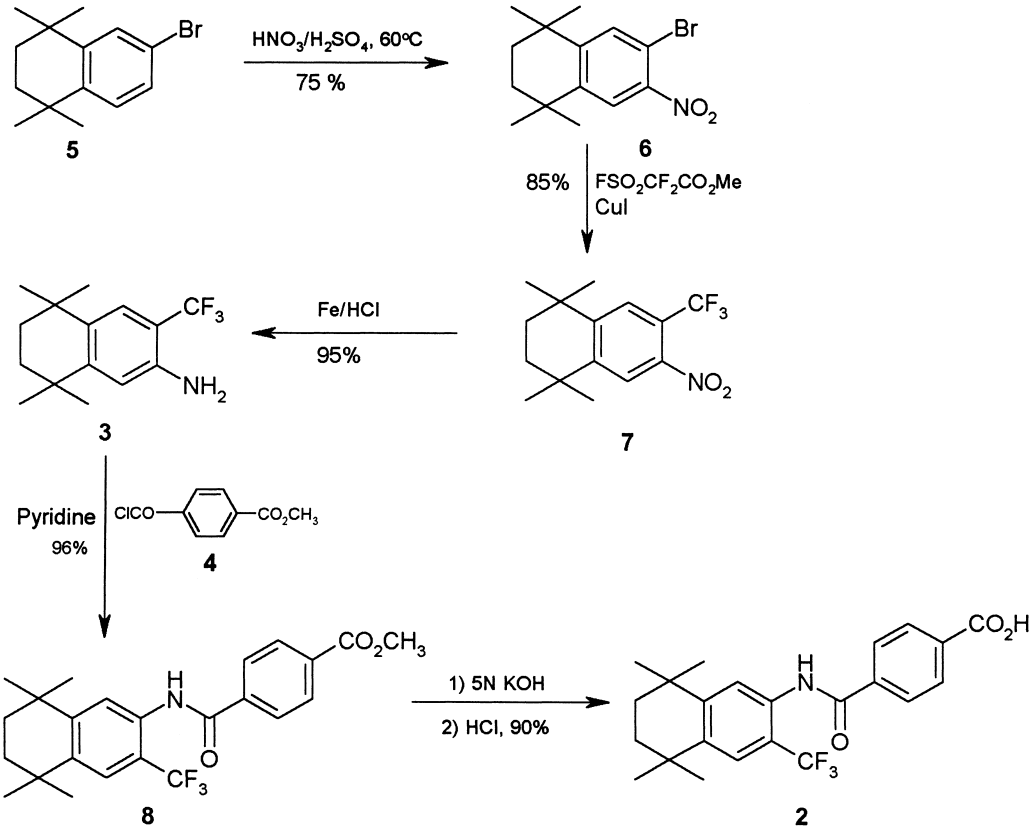

Scheme 1.

3. Experimental

Melting points are uncorrected. ^{19}F NMR spectra (56.4 Hz) were recorded on a Varian-360A instrument using CF_3CO_2H as an external standard, upfield positive. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with tetramethylsilane as the internal standard. All chemical shifts are expressed in ppm. The mass spectra were recorded on a Finnigan-MAT-8430 mass spectrometer. IR spectra were recorded as KBr discs on a Shimadzu IR-440 Spectrometer. Light petroleum ether refers to the fraction with distillation range 60–90°C.

3.1. 2-Bromo-3-nitro-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (6)

Under −10°C, 4 ml concentrated H_2SO_4 was added dropwise to 2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**5**, 4.0 g, 15 mmol). The mixture was vigorously stirred to dissolve compound **5**, then 5 ml of concentrated HNO_3/H_2SO_4 (1 : 1) was slowly added to the mixture while keeping the reaction temperature at about 65°C. After the reaction was complete (TLC analysis), the reaction mixture was poured into 40 ml iced water, the yellow solids were filtered and washed with water to give 3.5 g (75%) of **6** after drying, m.p. 121–123°C; ^1H NMR ($CDCl_3$) δ: 1.25(s, 6H), 1.28 (s, 6H), 1.70 (s, 4H), 7.60 (s, 1H), 7.82 (s, 1H); MS (m/e): 313 (16.8), 311 (17.1), 298 (100), 296 (95.5), 256 (42.5), 141 (28.4); IR: 3458, 3371, 2963, 2928, 1635, 1329, 1273, 1144, 1097, 900, 701 cm^{-1}; Anal. Calc. for $C_{14}H_{18}BrNO_2$: C, 53.86; H, 5.81; N, 4.48; Found: C, 54.00; H, 5.78; N, 4.01%.

3.2. 2-Nitro-3-trifluoromethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (7)

A mixture of $FSO_2CF_2CO_2Me$ (3 ml, 27 mmol), CuI (5.0 g, 27 mmol), HMPA (4.8 ml, 27 mmol) and **6** (1.14 g, 3.7 mmol) in DMF (5 ml) was stirred for 5 h at 70°C. The reaction mixture was then cooled to room temperature, 5 ml of saturated aq. NH_4Cl were added and the mixture was extracted with Et_2O (3 × 20 ml). The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed in vacuo. Flash chromatography with petroleum ether afforded compound **7** (950 mg, 85%), m.p. 89–91°C; ^{19}F NMR ($CDCl_3$) δ:−18.0 (s); ^1H NMR ($CDCl_3$) δ: 1.35(s, 12 H), 1.77 (s, 4H), 7.73 (s, 1H), 7.86 (s, 1H); MS (m/e): 302 (7.0), 312 (3.8), 287 (16.4), 286 (100.0), 282 (23.7), 244 (18.4); IR: 2969, 2940, 1535, 1362, 1296, 1162, 1142, 1083, 910 cm^{-1}; Anal. Calc. for $C_{15}H_{18}F_3NO_2$: C, 59.79; H, 6.02; N, 4.65; Found: C, 59.73; H, 5.92; N, 4.84%.

3.3. 2-Amino-3-trifluoromethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**3**)

A mixture of **7** (2.5 g, 8.3 mmol), concentrated HCl (2ml) and menthol (100 ml) was stirred at reflux, then iron powder (34.0 g) was added in portions to the reaction mixture for 1 h at reflux. After the reaction was complete (TLC analysis), the reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated at reduced pressure until a volume of about 10 ml remained. 10 ml of water were added and the mixture was extracted with Et_2O (2×20 ml). The organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give **3** (2.1 g, 95%), m.p. 61–62°C; ^{19}F NMR ($CDCl_3$) δ: −16.0 (s); ^{1}H NMR ($CDCl_3$) δ: 1.24 (s, 6H), 1.25 (s, 6H), 1.65 (s, 4H), 3.94 (br, 2H), 6.67 (s, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 31.7, 31.9, 33.7, 34.4, 35.0, 35.1, 112.4, 112.8, 115.0, 123.5, 124.7, 127.1, 135.2, 141.7, 150.4; MS (m/e): 271 (21.7), 257 (20.2), 256 (100.0), 227 (11.2); IR: 3485, 3371, 2963, 2928, 1635, 1329, 1273, 1144, 1097, 900 cm^{-1}; HRMS Calc. for $C_{15}H_{20}F_3N$: 271.1549, Found: 271.1518.

3.4. Methyl,4-[1-(5,6,7,8-tetrahydro-3-trifluoromethyl-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoate (**8**)

A mixture of **3** (27 mg, 0.1 mmol), **4** (20 mg, 0.1 mmol), pyridine (0.1 ml, 0.1 mmol) and anhydrous benzene (15 ml) was stirred at room temperature. After the reaction was complete (TLC analysis), 5 ml of water were added and the mixture was extracted with ethyl acetate (2×20 ml). The organic layer was washed successively with 2N HCl, water, 1N $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed in vacuo. Flash chromatography with petroleum ether/ethyl acetate (10 : 1) afforded compound **8** (42 mg, 96%), m.p. 218–220°C; ^{19}F NMR ($CDCl_3$) δ: -18.3 (s); ^{1}H NMR ($CDCl_3$) δ: 1.30(s, 6 H), 1.35 (s, 6H), 1.73 (s, 4H), 3.97 (s, 3H), 7.57 (s, 1H), 7. 97 (d, $J = 8.5$ Hz, 2H), 8.19 (s, 1H), 8.29 (d, $J = 8.5$ Hz, 2H); MS (m/e): 433 (13.9), 419 (19.1), 418 (85.2), 398 (25.8), 163 (100.0); IR: 3437, 2960, 2934, 1724, 1673, 1573, 1517, 1284, 1170, 1118, 722 cm^{-1}; Anal. Calc. for $C_{24}H_{26}F_3NO_3$: C, 66.50; H, 6.05; N, 3.23; Found: C, 66.35; H, 6.14; N, 3.04%.

3.5. 4-[1-(5,6,7,8-tetrahydro-3-trifluoromethyl-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (**2**)

A mixture of **8** (86 mg, 0.2 mmol), ethanol (10 ml) and 2N NaOH (1.5 ml, 0.3 mmol) was stirred at reflux. After the reaction was complete (TLC analysis), the reaction mixture was cooled to room temperature and acidified with 2 N HCl. The mixture was then extracted with ethyl acetate and the solution was washed with water, brine, and dried over Na_2SO_4. The solvent was removed in vacuo. Flash chromatography with petroleum ether/ethyl acetate (1 : 1) afforded compound **2** (80 mg, 95%), m.p. 235–238°C; ^{19}F NMR ($CDCl_3$) δ: -18.5 (s); ^{1}H NMR ($CDCl_3$) δ: 1.31(s, 6 H), 1.35 (s, 6H), 1.73 (s, 4H), 7.58 (s, 1H), 7. 98 (d, $J = 8.2$ Hz, 2H), 8.14 (s, 1H), 8.27 (d, $J = 8.2$ Hz, 2H); MS (m/e): 419 (26.1), 404 (100.0), 384 (24.2), 342 (18.6), 149 (68.3); IR: 3482, 3217, 2964, 1694, 1625, 1581, 1523, 1407, 1320, 1278, 1155, 1102, 1079, 906, 722 cm^{-1}.

Acknowledgements

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