Heteroatom Chemistry
Volume 11, Number 3, 2000

Studies on Organophosphorus Compounds 105: A Facile Synthesis of Dialkyl 6-Substituted-4-hydroxy-2-trifluoromethylquinoline-3-phosphonates

Chengye Yuan, Jingbo Xiao, and Xiaomei Zhang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, China. Fax: +86-21-64166128, Email: yuancy@pub.sioc.ac.cn

Received 5 November 1999; revised 31 December 1999

ABSTRACT: *For the investigation of biological activities of trifluoromethylated heterocyclic compounds bearing a phosphoryl moiety, a series of N-aryliminophosphonates were obtained by reaction of dialkyl 1-methoxycarbonylmethylphosphonates with trifluoroacetimidoyl chlorides using NaH as a deprotonating agent. The resulting intermediates underwent cyclization on refluxing in toluene to give dialkyl 6-substituted-4-hydroxy-2-trifluoromethylquinoline-3-phosphonates.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:240–243, 2000

INTRODUCTION

Quinoline and its derivatives are of considerable interest due to their potential biological and medicinal properties. Beside these, many important applications of this class of compounds have been reported. For example, they can be used as dyestuffs, sensitizers in photographic emulsion, floatation agents, pesticides, and antimalarial drugs [1, 2]. As far as we are aware, the introduction of the trifluoromethyl group [3, 4] and the phosphoryl moiety [5, 6] into organic molecules usually results in the enhancement of the biological activity of the parent compounds. Herein, we wish to report a convenient, general method for the synthesis of dialkyl 6-substituted-4-hydroxy-2-trifluoromethylquinoline-3-phosphonates. To the best of our knowledge, these compounds have not been reported.

RESULTS AND DISCUSSION

Our synthetic approach leading to dialkyl 6-substituted-4-hydroxy-2-trifluoromethylquinoline-3-phosphonates is based on the following sequence of reactions, as shown in Scheme 1.

The intermediates **1,** trifluoromethyl N-substituted imidoyl chlorides, were conveniently prepared by amidation of trifluoroacetic acid with a primary amine, in the presence of carbon tetrachloride, triphenylphosphine, and triethylamine in a one-pot procedure [7]. Dialkyl 1-methoxycarbonylmethylphosphonates were prepared in the usual manner by heating the mixture of trialkyl phosphite and methyl chloroacetate [8]. For the synthesis of compounds **3** and **4** [9, 10], sodium hydride was used as a deprotonating base. The carbanions thus obtained displaced the chloride of compounds **1** at -30 to 20°C to afford a mixture consisting of imines **3** and enamines **4,** which were difficult to separate by column chromatography. The mixture of **3** and **4** thus obtained in various ratios varied greatly, depending on the structure of the *p*-substituent of the phenyl group

Correspondence to: Chengye Yuan.
Contract Grant Sponsor: National Natural Science Foundation of China.
Contract Grant Number: 29832050

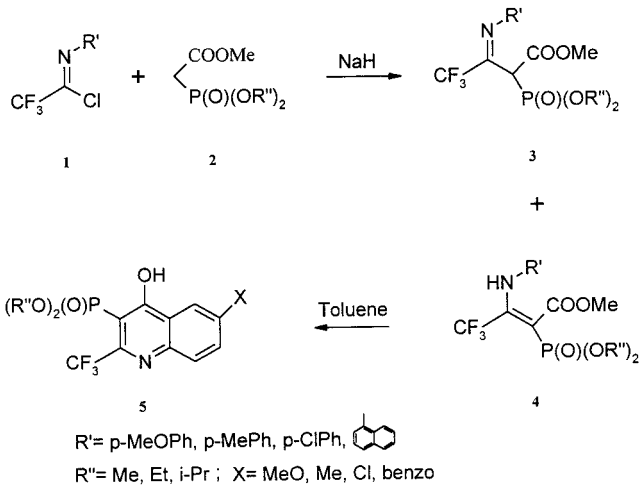
as shown in Table 1. Our trials to synthesize compound **3i** were unsuccessful, probably due to the steric hindrance of the bulky isopropylphosphoryl group that inhibits the reactivity of the neighbor carbanion (Table 1).

By refluxing the mixture of imine (3) and enamine (4) in toluene, we obtained 5. As a result, the thermal cyclization proceeded in a similar manner to that described by Uneyama et al for the synthesis of hydroxyquinoline derivatives. [11, 12] Additionally, we observed that the chemical structure of the N-substituents does not appear to have any significant effect on the yield of the cyclization process.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken on a Shimadzu-440 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 or a JEOL FX-90Q. Chemical shifts for ^{1}H NMR spectra are reported in δ value downfield from TMS. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3COOH as an external standard, positive for downfield shifts. EI-MS were obtained on a HP5989A mass spectrometer.

NaH was purchased as a standard reagent from Merck Co. Other reagents were commercially available from a local source (Shanghai chemical Co). THF was freshly distilled from sodium benzophenone ketyl prior to use.



SCHEME 1

TABLE 1 Preparation of Compounds **3** and **4**

Comps.	*R′*	*R″*	*Yield* (%)	*Ratio of Imine* **3** *and Enamine* **4**[a]
3a + 4a	*p*-MeOPh	Me	73	5:9
3b + 4b	*p*-MePh	Me	71	1:1
3c + 4c	*p*-ClPh	Me	71	7:6
3d + 4d	1-naphthyl	Me	66	3:1
3e + 4e	*p*-MeOPh	Et	82	5:8
3f + 4f	*p*-MePh	Et	78	1:1
3g + 4g	*p*-ClPh	Et	74	6:5
3h + 4h	1-naphthyl	Et	57	1.5:1
3i + 4i	*p*-MePh	i-Pr	0	–

[a]The ratio of **3** and **4** was determined by ^{19}F-NMR.

Dimethyl 1-Methoxycarbonyl-2-(N-p-methoxylphenyl)imino-3,3,3-trifluoropropylphosphonate (**3a** *and* **4a**)

To an oven-dried three-necked flask containing a stir bar, thermometer, and rubber septum, and charged with dry N_2 was added NaH (80% in mineral oil, 0.159 g, 5.28 mmol) and dry THF (10 mL). After the mixture had been cooled to −30°C, dimethyl 1-methoxycarbonylmethylphosphonate (1.802 g, 9.9 mmol) and THF (10 mL) were added dropwise. The reaction temperature was kept at −30°C to −20°C for one hour. Then, the N-*p*-methoxylphenyltrifluoroacetimidoyl chloride (0.784 g, 3.3 mmol) with THF(10 mL) was added dropwise at the same temperature. Stirring was continued at room temperature for two hours, and the THF was removed from the mixture under reduced pressure. After column chromatography (EtOAc:petroleum = 1:3), we obtained a mixture of **3a** and **4a;** yellow liquid; yield, 73%. ^{1}H NMR ($CCl_4/CDCl_3$) δ 3.93 (s, 9H, $3XOCH_3$), 4.03 (s, 3H, OCH_3), 4.49 (d, 1H, J = 26.7 Hz, N=C-CH), 6.95 (d, 2H, J = 14 Hz, ArH), 7.1 (d, 2H, J = 14 Hz, ArH), 10.07 (b, 1H, NH). ^{19}F NMR (CCl_4/TFA) δ − 10.2 (s), −18.9 (s, enamine).

Dimethyl 1-Methoxycarbonyl-2-(N-p-methylphenyl)imino-3,3,3-trifluoropropylphosphonate (**3b** *and* **4b**)

Compounds **3b** and **4b** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 71%. ^{1}H NMR(CCl_4/TMS) δ 2.7 (s, 3H, CH_3), 4.07 (s, 6H, $2XOCH_3$), 4.2 (s, 3H, OCH_3), 4.91 (d, 1H, J = 27.9 Hz, N=C-CH), 7.06 (d, 2H, J = 7.2 Hz, ArH), 7.53 (d, 2H, J = 7.2 Hz, ArH). ^{19}F NMR (CCl_4/TFA) δ − 10.4 (s), −19.5 (s, enamine).

Dimethy 1-Methoxycarbonyl-2-(N-p-chlorophenyl)imino-3,3,3-trifluoropropylphosphonate (**3c** *and* **4c**)

Compounds **3c** and **4c** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 71%. ^{1}H NMR (CCl_4/TMS) δ 3.90 (s, 6H, $2XOCH_3$), 4.01 (s, 3H, OCH_3), 4.57 (d, 1H, J = 28.8 Hz, N=C-CH), 7.21 (d,

2H, J = 8.4 Hz, ArH), 7.5 (d, 2H, J = 8.4 Hz, ArH). ^{19}F NMR (CCl_4/TFA) δ − 10.0 (s), −19.1 (s, enamine).

Dimethyl 1-Methoxycarbonyl-2-(N-1-naphthyl)imino-3,3,3-trifluoropropylphosphonate (**3d** *and* **4d**)

Compounds **3d** and **4d** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 66%. ^{1}H NMR (CCl_4/TMS) δ 3.58 (s, 6H, 2XOCH_3), 4.05 (s, 3H, OCH_3), 4.65 (d, 1H, J = 24.3 Hz, N=C-C$\underline{H}$), 6.98 (b, 1H, NH), 7.41–8.18 (m, 7H, ArH). ^{19}F NMR (CCl_4/TFA) δ − 10.5 (s), −18.6 (s, enamine).

Diethyl 1-Methoxycarbonyl-2-(N-p-methoxylphenyl)imino-3,3,3-trifluoropropylphosphonate (**3e** *and* **4e**)

Compounds **3e** and **4e** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 82%. ^{1}H NMR (CCl_4/TMS): δ 1.43 (t, 6H, J = 6.3 Hz, 2XCH_2C$\underline{H}_3$), 4.77 (d, 1H, J = 24.3 Hz, N=C-C$\underline{H}$), 6.86 (d, 2H, J = 11 Hz, ArH), 7.14 (d, 2H, J = 11 Hz, ArH), 9.94 (b, 1H, NH). ^{19}F NMR (CCl_4/TFA): δ −10.6 (s), −19.1 (s, enamine).

*Diethyl 1-Methoxycarbonyl-2-(*N-p-methylphenyl*)imino-3,3,3-trifluoropropylphosphonate* (**3f** *and* **4f**)

Compounds **3f** and **4f** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 78%. ^{1}H NMR (CCl_4/TMS) δ 2.37 (t, 6H, J = 10.8 Hz, 2XCH_2C$\underline{H}_3$), 2.49 (s, 3H CH_3), 3.88 (s, 3H, OCH_3), 4.15–4.48 (m, 4H, 2XOCH_2), 4.69 (d, 1H, J = 23.4 Hz, N=C-C$\underline{H}$), 6.83 (d, 2H, J = 10.8 Hz, ArH), 7.16 (d, 2H, J = 10.8 Hz, ArH). ^{19}F NMR (CCl_4/TFA) δ −10.8 (s), −19.4 (s, enamine).

Diethyl 1-Methoxycarbonyl-2-(N-p-chlorophenyl)imino-3,3,3-trifluoropropylphosphonate (**3g** *and* **4g**)

Compounds **3g** and **4g** were synthesized analogously as for **3a** and **4a;** yellow liquid; yield, 74%. ^{1}H NMR (CCl_4/TMS): δ 1.51 (t, 6H, 2XCH_2C$\underline{H}_3$), 4.23–4.39 (m, 4H, 2XOCH_2), 4.77 (d, 1H, J = 27 Hz, N=C-C$\underline{H}$), 6.97 (d, 2H, J = 8.1 Hz, ArH), 7.51 (d, 2H, J = 8.1 Hz, ArH). ^{19}F NMR (CCl_4/TFA): δ −8.1 (s), −16.9 (s, enamine).

Diethyl 1-Methoxycarbonyl-2-(N-1-naphthyl)imino-3,3,3-trifluoropropylphosphonate (**3h** *and* **4h**)

Compounds were synthesized analogously as for **3a** and **4a;** yellow liquid; yield 57%. ^{1}H NMR (CCl_4/TMS): δ 1.52 (t, 6H, J = 7.2 Hz, 2XCH_2C$\underline{H}_3$), 4.01 (s, 3H, OCH_3), 4.27–4.55 (m, 4H, 2XCH_2), 4.79 (d, 1H, J = 27 Hz, N=C-C$\underline{H}$), 7.74–7.79 (m, 7H, ArH). ^{19}F NMR (CCl_4/TFA): δ −10.4 (s), −18.2 (s, enamine).

Dimethyl 6-Methoxy-4-hydroxy-2-trifluoromethylquinoline-3-phosphonate (**5a**)

To an 50 mL flask was added **3a** and **4a** (1.915 g, 5mmol) and toluene (20 mL). After the mixture had been refluxed for eight hours, the toluene was removed from the mixture under reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel using EtOAc: petroleum ether (1:15) as an eluent. A pale solid resulted; yield, 91%; m.p., 132–133°C. IR (KBr) *v:* 3540 (OH), 1230 (P=O), 1130 (C-F), 1020 (P–O–C) cm^{-1}. ^{1}H NMR (CCL_4/TMS) δ 3.97 (s, 3H, OCH_3), 4.16 (s, 6H, 2XOCH_3), 7.52 (d, 1H, J = 17.1Hz, ArH). 7.72–7.82 (m, 1H, ArH), 8.16 (d, 1H, J = 9 Hz, ArH). ^{19}F NMR (CCl_4/TFA) δ −13.1 (s). MS, *m/e* (%): 304 (M^+ -OH -OCH_3 + 1), 319 (M^+ -OCH_3 -1), 351 (M^+,100), 352 (M^+ + 1). Anal. Calcd. for $C_{13}H_{13}F_3NO_5P$ (351.2157): C, 44.46; H, 3.73; N, 3.99. Found: C, 44.42; H, 3.69; N, 3.73.

Dimethyl 6-Methyl-4-hydroxy-2-trifluoromethylquinoline-3- phosphonate (**5b**)

Product **5b** was obtained analogously by the similar method as for **5a.** A pale solid; yield, 93%; m.p. 82–83°C. IR (KBr) *v:* 3530 (OH), 1160(P=O), 1120, 1160 (C-F), 1020 (P–O–C) cm^{-1}. ^{1}H NMR (CCl_4/TMS) δ 2.99 (s, 3H, CH_3), 4.23 (s, 6H, 2XOCH_3), 8.48 (s, 1H, ArH), 8.32 (d, 1H, J = 8.1 Hz, ArH), 7.99 (d, 1H, J = 9.0 Hz, ArH). ^{19}F NMR (CCl_4/TFA) δ −13.2 (s). MS, *m/e* (%): 109 [P(O)(OCH_3)$_2$], 266 (M^+ -CF_3), 335 (M^+, 100), 336 (M^+ + 1). Anal. Calcd. for $C_{13}H_{13}F_3NO_4P$ (335.2167): C, 46.60; H, 3.91; N, 4.18. Found: C, 47.16; H, 4.02; N, 3.77.

Dimethyl 6-Chloro-4-hydroxy-2-trifluoromethylquinoline-3-phosphonate (**5c**)

Product **5c** was obtained analogously by the similar method as for **5a.** A yellow solid; yield, 90%; m.p. 109–111°C. IR (KBr) *v:* 1260 (P=O), 1200 (C–F), 1020, (P–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS) δ 4.02 (s, 6H, 2XOCH_3), 7.67 (d, 1H, J = 9.0 Hz, ArH), 7.90 (d, 1H, J = 9.0 Hz, ArH), 8.23 (s, 1H, ArH). ^{19}F NMR ($CDCl_3$/TFA) δ −12.8 (s). MS, *m/e*(%): 109 [P(O)(OCH_3)$_2$], 286 (M^+ − CF_3), 355 (M^+,100), 356 (M^+ + 1). Anal. Calcd. for $C_{12}H_{10}F_3C1NO_4P$ (355.635): C, 40.53; H, 2.83; N, 3.94. Found: C, 40.54; H, 2.77; N, 3.63.

Dimethyl 4-Hydroxy-2-trifluoromethyl-benzoquinoline-3-phosphonate (**5d**)

Product **5d** was obtained analogously by the similar method as for **5a.** A yellow solid; yield, 91%; m.p. 94–96°C. IR (KBr) *v:* 1260 (P=O), 1120 (C–F), 1020, (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 4.03 (s, 6H, $2XOCH_3$), 7.88 (m, 4H, ArH), 8.30 (m, 1H, ArH), 9.35 (m, 1H, ArH). ^{19}F NMR (CCl_4/TFA) δ −13.4 (s). MS, *m/e* (%): 371 (M^+, 100), 372 (M^+ + 1). Anal. Calcd. for $C_{16}H_{13}F_3NO_4P$ (371.2497): C, 51.76; H, 3.53; N, 3.77. Found: C, 51.70; H, 3.35; N, 3.67.

Dimethyl 6-Methoxyl-4-hydroxy-2-trifluoromethylquinoline-3-phosphonate (**5e**)

Product **5e** was obtained analogously by the similar method as for **5a.** A yellow solid; yield, 93%; m.p. 111–112°C. IR (KBr) *v:* 1220 (P=O), 1120 (C–F), 1010 (P-O-C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.38 (t, 6H, J = 14.0 Hz, $2XCH_2\underline{CH_3}$), 3.98 (s, 3H, OCH_3), 4.11–4.31 (m, 4H, $2XOCH_2$). 7.51 (d, 1H, J = 9.0 Hz ArH), 7.62 (s, 1H, ArH), 8.01 (d, 1H, J = 9.0 Hz, ArH) 13.70 (s, 1H, OH). ^{19}F NMR (CCl_4/TFA) δ −14.1 (s). MS, *m/e* (%): 69 (CF_3), 379 (M^+), 380 (M^+ + 1). Anal. Calcd. for $C_{15}H_{17}F_3NO_5P$ (379.2693): C, 47.50; H, 4.52; N, 3.69. Found: C, 47.41; H, 4.38; N, 3.61.

Diethyl 6-Methyl-4-hydroxy-2-trifluoromethylquinoline-3-phosphonate (**5f**)

Product **5f** was obtained analogously by the similar method as for **5a.** A colorless liquid; yield, 96%. IR (film) *v:* 3530 (OH), 1140 (P=O), 1120 (C–F), 1020 (P–O–P) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.5 (t, 6H, J = 8.1 Hz, $2XCH_2\underline{CH_3}$), 2.69 (s, 3H, CH_3), 4.11–4.37 (m, 4H, $2XOCH_2$), 7.70 (d, 1H, J = 9 Hz, ArH), 8.00 (d, 1H, J = 9 Hz, ArH), 8.16 (s, 1H, ArH). ^{19}F NMR (CCl_4/TFA) δ − 13.9 (s). MS, *m/e* (%): 227 [M^+ -$P(O)(OEt)_2$], 335 (M^+ -Et +1), 346 (M^+ -OH), 363 (M^+), 364 (M^+ +1). Anal. Calcd. for $C_{15}H_{17}F_3NO_4P$ (363.2703): C, 49.60; H, 4.72; N, 3.86. Found: C, 49.41; H, 4.46; N, 3.79.

Diethyl 6-Chloro-4-hydroxy-2-trifluoromethylquinoline-3-phosphonate (**5g**)

Product **5g** was obtained analogously by the similar method as for **5a.** A yellow solid; yield, 92%; m.p. 60–62°C. IR (KBr) *v:* 1200 (P=O), 1140 (C–F), 1010 (P–O–C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.33 (t, 6H, J = 9 Hz, $2XCH_2\underline{CH_3}$), 4.12–4.32 (m, 4H, $2XCH_2$), 7.80 (d, 1H, J = 11.1 Hz, ArH), 8.03 (d, 1H, J = 8.9 Hz, ArH), 8.35 (d, 1H, J = 2.2 Hz ArH) 13.85 (s, 1H, OH). ^{19}F NMR (CCl_4/TFA) δ −13.7 (s). MS, *m/e* (%): 355 (M^+ -Et +1), 383 (M^+, 100), 384 (M^+ + 1). Anal. Calcd. for $C_{14}H_{14}F_3ClNO_4P$ (383.6886): C, 43.83; H, 3.68; N, 3.65. Found: C, 43.81; H, 3.58; N, 3.50.

Diethyl 4-Hydroxy-2-trifluoromethyl-benzoquinoline-3-phosphonate (**5h**)

Product **5h** was obtained analogously by the similar method as for **5a.** A yellow solid; yield, 90%; m.p. 72–74°C. IR (KBr) *v;* 1160 (P=O), 1120 (C-F), 1010 (P–O–C). ^1H NMR (CCl_4/TMS) δ 1.52 (t, 6H, J = 8.1 Hz, $2XCH_2\underline{CH_3}$), 4.22–4.41 (m, 4H, $2XCH_2$), 7.87 (m, 4H, ArH), 8.27 (m, 1H, ArH), 9.34 (m, 1H, ArH). ^{19}F NMR (CCl_4/TFA) δ 14.0 (s). MS, *m/e* (%): 263 [M^+ - $P(O)(OEt)_2$ + 1], 399(M^+, 100), 400 (M^+ + 1). Anal. Calcd. for $C_{12}H_{17}F_3NO_4P$ (399.3033): C, 54.14; H, 4.29; N, 3.51. Found: C, 54.09; H, 4.24; N, 3.47.

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