Synthesis of α-(4-hydroxyphenyl)-β,β,β-trifluoro-α-alanine derivatives

V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin*

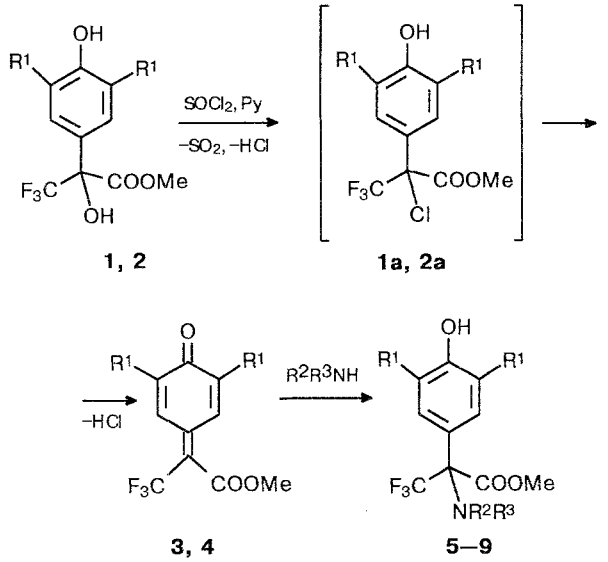
A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085

2,6-Dimethyl- and 2,6-dimethoxy-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinones have been synthesized. These compounds easily react with ammonia, morpholine, and *p*-toluidine to afford the corresponding α-(4-hydroxyphenyl)-β,β,β-trifluoro-α-alanine derivatives.

Key words: 2,6-dimethyl-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinone; 2,6-dimethoxy-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinone; ammonia; morpholine; *p*-toluidine; α-(4-hydroxyphenyl)-β,β,β-trifluoro-α-alanine derivatives.

Fluorine-containing α-aminoacids are of interest as biologically active compounds with bactericidal, antiviral, and antitumor action. Some of these substances are already used in medicine.[1] Studies of compounds of this type, first started in the 60s, are now being intensely conducted.[2—4]

This paper concerns a synthesis of previously unknown derivatives of α-(4-hydroxyphenyl)-β,β,β-trifluoro-α-alanine. The method consists of the addition of ammonia or amines to 2,6-disubstituted α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinones (**3**, **4**). Earlier, it has been shown that α-alkyl substituted 2,6-di-*tert*-butyl-*p*-methylenequinones are stable and rather reactive under normal conditions.[5,6] Electron-accepting α-substituents like CN or CF_3 increase the stability of methylenequinones while retaining their rather high reactivity.[7—9] Previously unknown *p*-methylenequinones were synthesized in 90 % yields from methyl α-hydroxy-α-(4-hydroxy-2,6-dimethyl- and 2,6-dimethoxyphenyl)-β,β,β-trifluoropropionates (**1**, **2**) (which have been prepared by us previously) by refluxing with $SOCl_2$ in the presence of pyridine.



R^1 = Me (**1**, **3**, **5**, **6**, **8**); OMe (**2**, **4**, **7**, **9**);
R^2 = R^3 = H (**5**); R^2, R^3 = —$(CH_2)_2O(CH_2)_2$— (**6**, **7**);
R^2 = *p*-MeC_6H_4, R^3 = H (**8**, **9**)

Compound **3** is an oily orange liquid with a specific odor. Compound **4** is obtained as bright-yellow crystals. It is noteworthy that under these conditions α,α-bis(trifluoromethyl)-4-hydroxy-3,5-dimethylbenzyl alcohol is quantitatively transformed into the corresponding benzyl chloride, which undergoes dehydrochlorination into *p*-methylenequinone only in an alkaline medium.[8] The presence of the COOMe group apparently increases the mobility of the Cl atom in intermediates **1a** and **2a**, thus substantially facilitating dehydrochlorination.

Addition of amines to α,α-bis(fluoroalkyl)-*p*-methylenequinones has been described previously.[8] As a rule, it proceeds when the reagents are mixed at room temperature. With methylenequinones **3** and **4**, a competitive reaction at the methoxycarbonyl function is possible, since under the mild conditions used the amidation of fluorosubstituted acids also occurs.[11] However, we found that ammonia adds to *p*-methylenequinone **3** (20 °C, an aprotic solvent) exclusively at the α-position to afford α-(4-hydroxy-3,5-dimethylphenyl)-β,β,β-trifluoro-α-alanine methyl ester (**5**) in 83 % yield. Morpholine also interacts smoothly with compounds **3** and **4** leading to the corresponding adducts **6** and **7**, whose yields amount to 84—85 %. (The end of the reaction was judged from the disappearance of the yel-

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 9, pp. 1631—1633, September, 1994.

1066-5285/94/4309-1543 $12.50 © 1995 Plenum Publishing Corporation

low coloration of the reaction mixture caused by the presence of methylenequinones **3** and **4**). *p*-Toluidine also adds to compounds **3** and **4**, but less efficiently. While methylenequinone **3** reacts with morpholine in 3—5 min in an exothermic manner, its reaction with *p*-toluidine goes to completion only after 30 min to afford *N*-(*p*-tolyl)-α-(4-hydroxy-3,5-dimethylphenyl)-β,β,β-trifluoro-α-alanine methyl ester (**8**). Methylenequinone **4** reacts with *p*-toluidine even more slowly to give the corresponding β,β,β-trifluoro-α-alanine methyl ester (**9**) in 90 % yield. It should be mentioned that when solutions of methylenequinones **3** or **4** (in hexane, CCl_4, or benzene) are mixed with aniline or *p*-toluidine, dark-red coloration appears in the reaction mixture, which disappears at the end of the reaction. The absence of this coloration in the reactions of **3** or **4** with morpholine seems to attest that the color change is caused by distortion of the electron system of arylamine, but not that of methylenequinone. Thus, the addition of ammonia and amines to α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinones is a convenient method for the synthesis of hitherto unknown derivatives of (4-hydroxyphenyl)-β,β,β-trifluoro-α-alanine.

Experimental

^{13}C NMR spectra were recorded on a Bruker-200 SY spectrometer at 50.31 MHz. ^1H and ^{19}F NMR spectra were obtained using a Bruker-AC-200F instrument at 200.00 and 188.31 MHz, respectively. Chemical shifts for ^1H and ^{13}C are referred to tetrametylsilane as the internal standard, those for ^{19}F are referred to CF_3COOH as the external standard. IR spectra were recorded on a UR-20 spectrophotometer in CCl_4. R_f values for compounds obtained are reported for TLC on Silufol UV_{254} plates (Kavalier) in acetone—CCl_4 (1:3) as the eluent. Physicochemical and spectral characteristics of compounds **3—9** are listed in Tables 1 and 2.

2,6-Dimethyl-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinone (3). Methyl α-(4-hydroxy-3,5-dimethylphenyl)-α-hydroxy-β,β,β-tifluoropropionate (8.34 g, 0.03 mmol) was dissolved in $SOCl_2$ (10 mL, 0.083 mol), and pyridine (2.4 g, 0.03 mol) was added on cooling. The reaction mixture was refluxed for 40—50 min, cooled to 20 °C and poured onto ice. The reaction products were extracted with benzene (3×30 mL), the combined extracts were washed with concentrated solution of $NaHCO_3$. The benzene solution was dried with Na_2SO_4 and passed through a layer of silica gel (l = 10 mm, d = 15 mm). Removal of the solvent afforded 7.1 g of compound **3** as an orange chromatographically pure oil. ^{13}C NMR ($(CD_3)_2CO$), δ: 184.84 (C-1); 162.31 (COO); 140.27, 139.91 (C-2, C-6); 135.58 (C-4); 130.13, 127.48 (C-3, C-5); 126.40 (α-C, $^2J_{C,F}$ = 32.0 Hz); 121.19 (CF_3, $^1J_{C,F}$ = 272.0 Hz); 52.40 (OMe); 14.72 (Me); 14.33 (Me). IR (CCl_4), ν/см$^{-1}$: 1740 (CO); 1645 (C=O).

2,6-Dimethoxy-α-methoxycarbonyl-α-trifluoromethyl-*p*-methylenequinone (4) was obtained analogously to ester **3**. ^{13}C NMR ($(CD_3)_2CO$), δ: 173.54 (C-1); 162.82 (COO); 153.22 (C-2, C-6); 136.70 (C-4); 121.80 (α-C, $^2J_{C,F}$ = 32.0 Hz); 121.75 (CF_3, $^1J_{C,F}$ = 272.0 Hz); 103.71, 101.51 (C-3, C-5); 54.70 (2 OMe); 52.17 (OMe).

α-(4-Hydroxy-3,5-dimethylphenyl)-β,β,β-trifluoro-α-alanine methyl ester (5). Dry NH_3 was passed through a solution of compound **3** (2.6 g, 0.01 mol) in hexane (15 mL) a at room temperature until the disappearance of the yellow color of the reaction mixture (TLC monitoring). The mixture was filtered to give 2.3 g of compound **5** as white crystals. ^{13}C NMR ($(CD_3)_2CO$), δ: 168.9 (COO); 152.23 (C-4); 125.19 (C-2, C-6); 124.20 (C-1); 122.70 (CF_3, $^1J_{C,F}$ = 281.50 Hz); 122.12 (C-3, C-5); 65.12 (C*—CF_3, $^2J_{C,F}$ = 27.5 Hz); 50.66 (OMe), 14.21 (2 Me).

***N*-[1-(4-Hydroxy-3,5-dimethylphenyl)-1-methoxycarbonyl-2,2,2-trifluoroethyl]morpholine (6).** A solution of compound **3** (1.3 g, 0.005 mol) in benzene (1.5 mL) was added to a solution of morpholine (0.44 g, 0.005 mol) in benzene (1 mL).

Table 1. Physicochemical characteristics of compounds **3—9**

Compound	Yield (%)	M.p./°C (solvent)	R_f	Found / Calculated (%)				Molecular formula
				C	H	N	F	
3	90.0	*	0.66	55.20 55.38	4.16 4.23	— —	22.24 21.92	$C_{12}H_{11}F_3O$
4	91.0	102—104 (CCl_4)	0.45	49.20 49.32	3.53 3.77	— —	19.74 19.52	$C_{12}H_{11}F_3O_5$
5	83.0	103—105 (C_6H_6)	0.30	51.47 51.38	5.05 5.05	4.70 5.05	— —	$C_{12}H_{14}F_3NO_3$
6	85.0	123—125 (hexane)	0.50	55.36 55.33	5.80 5.76	3.96 4.03	15.86 16.43	$C_{16}H_{20}F_3NO_4$
7	84.4	105—107 (hexane)	0.35	50.61 50.66	5.27 5.28	3.52 3.69	14.49 15.04	$C_{16}H_{20}F_3NO$
8	81.7	140—142 (heptane)	0.60	61.91 62.13	5.42 5.45	3.42 3.81	—	$C_{19}H_{20}F_3NO$
9	90.2	128—130 (hexane)	0.50	57.20 57.14	5.10 5.01	3.42 3.51	14.04 14.29	$C_{19}H_{20}F_3NO_2$

* M.p. 120 °C (3 Torr).

Table 2. ^1H and ^{19}F NMR spectra of compounds **3—9** (in $(CD_3)_2CO$)

Compound	δ ^1H (*J*/Hz)							δ ^{19}F
	H-2, H-6	H-3, H-5	Me	OMe	OH	—NH	Other substituents	(s, CF_3)
3	—	7.09 (s), 6.90 (s)	1.82 (s), 1.71 (s)	3.72 (s)	—	—	—	−24.00
4	—	6.49 (s), 6.40 (s)	—	3.85 (s), 3.75 (s), 3.70 (s)	—	—	—	−24.40
5	7.46 (s)	—	2.19 (s)	3.88 (s)	7.84 (s)	2.60 (s)	—	—
6	7.35 (s)	—	—	3.75 (s)	7.73 (s)	—	3.60 (m, 4 H, 2 CH_2O); 2.75 (m, 4 H, 2 CH_2N)	−15.68
7	6.70 (s)	—	—	3.85 (s (1)), 3.70 (s (2))	7.65 (s)	—	3.55 (m, 4 H, 2 CH_2O); 2.70 (m, 4 H, 2 CH_2N)	—
8	7.30 (s)	—	2.40 (s (1)), 2.20 (s (2))	3.85 (s)	7.70 (s)	5.65 (s)	6.90 (d, 2 H, H-3′, H-5′); 6.60 (d, 2 H, H-2′, H-6′, $J_{H,H}$ = 7.8)	—
9	6.75 (s)	—	2.15 (s)	3.65 (s (2)), 3.63 (s (1))	7.50 (s)	5.60 (s)	6.68 (d, 2 H, H-3′, H-5′); 6.45 (d, 2 H, H-2′, H-6′, $J_{H,H}$ = 7.8)	—

After 10 min more benzene (15 mL) was added, and the reaction mixture was heated until the complete dissolution of the solid that had precipitated. The hot solution was then passed through a layer of silica gel (l = 5 mm, d = 15 mm). After removal of the solvent, the solid residue was crystallized from hexane to give 1.61 g of compound **6**.

***N*-[1-(4-Hydroxy-3,5-dimethoxyphenyl)-1-methoxycarbonyl-2,2,2-trifluoroethyl]morpholine** (**7**) was obtained from methylenequinone **4** and morpholine similarly to compound **6** (duration of the reaction was 2 h).

***N*-(4-Tolyl)-α-(4-hydroxy-3,5-dimethylphenyl)-β,β,β-trifluoro-α-alanine methyl ester (8)**. A solution of compound **3** (1.3 g, 0.005 mol) in benzene (1.5 mL) was added to a solution of *p*-toluidine (0.54 g, 0.005 mol) in benzene (1 mL). After 30 min more benzene (20 mL) was added, and the reaction mixture was refluxed for 5 min. The hot solution was passed through a layer of silica gel (l = 5 mm, d = 15 mm). Removal of the solvent afforded 1.5 g of chromatographically pure ester **8** as white crystals.

***N*-(4-Tolyl)-α-(4-hydroxy-3,5-dimethoxyphenyl)-β,β,β-trifluoro-α-alanine methyl ester (9)** was obtained from methylenequinone **4** analogously to ester **8** (duration of the reaction was 12 h).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 93-03-22696).

References

1. *Soedineniya ftora: sintez i primenenie* [*Fluorine Compounds: Synthesis and Application*], Mir, Moscow, 1990 (in Russian).
2. F. Veigand and V. Otmayer, *Usp. Khim.*, 1970, **39**, 622 [*Russ. Chem. Rev.*, 1970, **39** (Engl. Transl.)].
3. V. P. Kukhar', Yu. L. Yagupol'skii, and V. A. Soloshonok, *Usp. Khim.*, 1990, **59**, 149 [*Russ. Chem. Rev.*, 1990, **59** (Engl. Transl.)].
4. V. P. Kukhar', Yu. L. Yagupol'skii, I. I. Gerus, and M. T. Kolycheva, *Usp. Khim.*, 1991, **60**, 2047 [*Russ. Chem. Rev.*, 1991, **60** (Engl. Transl.)].
5. C. D. Cook and B. E. Noreross, *J. Am. Chem. Soc.*, 1956, **78**, 3797.
6. A. Hubele, H. Suhr, and U. Heilmann, *Chem. Ber.*, 1962, **95**, 639.
7. H. H. Takimoto, G. C. Denault, and L. O. Krnechek, *J. Org. Chem.*, 1964, **29**, 1899.
8. W. A. Sheppard, *J. Org. Chem.*, 1968, **33**, 3297.
9. A. A. Volod'kin and V. V. Ershov, *Usp. Khim.*, 1988, **57**, 595 [*Russ. Chem. Rev.*, 1988, **57** (Engl. Transl.)].
10. V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin, *Zh. Org. Khim.*, 1992, **29**, 1684 [*J. Org. Chem.*, 1992, **29** (Engl. Transl.)].
11. *Weygand-Hilgetag Organisch-Chemische Experimentierkunst*, Johann Ambrosius Barth Verlag, Leipzig, 1964.

Received April 13, 1994