Synthesis of esters of *para*-hydroxy substituted α -trifluoromethylmandelic acids

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Methyl trifluoropiruvate in trifluoroacetic acid at 20 °C rapidly C-hydroxyalkylates various phenols at the *para*-positions to afford the corresponding esters of *para*-hydroxy substituted α -trifluoromethylmandelic acids.

Key words: methyl trifluoropiruvate, trifluoroacetic acid, phenol, 3-cresol, 2,3-xylenol, 2,5-xylenol, thymol, C-hydroxyalkylation.

The use of fluorine compounds in fine organic synthesis and, most of all, in the synthesis of medical preparations and pesticides, has been developed intensively in recent years.¹ In connection with this, the synthesis of fluorine-containing derivatives of mandelic acid presents interest, since this acid is a constituent of plant glycosides and plays a significant role in their ontogenesis. Previously we showed that the reaction of esters of trifluoropyruvic acid with phenols can be used for the synthesis of esters of substituted α trifluoromethylmandelic acids.^{2,3} At the same time, if the phenol used contains no substituent in the orthoposition, the *para*-selectivity of hydroxyalkylation is partly deteriorated, and the resulting product can only be isolated after hydrolysis as the corresponding acid.³ Furthermore, in the case when phenol contains a metasubstituent, whose steric constant is greater than that of Me, C-alkylation occurs at the *para*-position, rather than at the ortho-position. For example, the reaction of methyl trifluoropyruvate (1) and 2,3-xylenol results in the formation of the corresponding benzo b furanone.³ The previously described methods of C-alkylation of phenols with polyfluoroketones in the presence of acid catalysts (p-MeC₆H₄SO₃H, AlCl₃, BF₃·OEt₂) did not furnish the desired result in the case of methyl trifluoropyruvate.

We studied the reaction of pyruvate 1 with phenols catalyzed by trifluoroacetic acid (TFA). In order to exclude a solvent effect, the reaction was carried out in the minimum amount of TFA. It turned out that phenols are hydroxyalkylated with ketoester 1 in TFA at 20 °C at the *para*-position to give methyl esters of *para*-hydroxy substituted mandelic acids 2-4, 7, 8.

Electron-donating substituents in the *meta*-position facilitate hydroxyalkylation. For example, whereas the



reaction of 1 with phenol is completed over a period of 2 days, the processes involving 2,3-xylenol and 3-cresol occur over a period of 30 min. However, in these cases, along with *para*-hydroxyalkylation, *ortho*-hydroxyalkylation also occurs probably due to steric factors. The latter is accompanied by lactonization into the corresponding benzo[b]furanones 5 and 6, which have been described previously.^{5,6} In the case of 2,5-xylenol and thymol, the reaction is exothermic and is completed after 30 min to give only *para*-hydroxyalkylation products 7 and 8 in quantitative yields.

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Com- pound	Yield (%)	M.p./°C (solvent)	R _f	Found (%) Calculated			Molecular formula
				С	Н	F	
2	84.0	111-113 (pentane)	0.35	<u>47.97</u> 48.00	<u>3.52</u> 3.60	<u>22.51</u> 22.80	C ₁₀ H ₉ F ₃ O ₄
3	50.0	203—205 (CF ₃ COOH)	0.38	<u>51.34</u> 51.80	<u>4.82</u> 4.68	<u>20.09</u> 20.50	$C_{12}H_{13}F_{3}O_{4}$
4	42 .1	165—167 (CF ₃ COOH)	0.36	<u>49.80</u> 50.00	<u>4.04</u> 4.17	<u>21.54</u> 21.59	$C_{11}H_{14}F_{3}O_{4}$
7	97.0	108—110 (CCl ₄)	0.40	<u>51.87</u> 51.80	<u>4.72</u> 4.68	<u>20.35</u> 20.50	$C_{12}H_{13}F_{3}O_{4}$
8	99.0	93—95 (hexane)	0.50	<u>54.96</u> 54.90	<u>5.59</u> 5.56	<u>18.61</u> 18.63	$C_{14}H_{17}F_3O_4$

Table 1. Physicochemical characteristics of compounds 2-4, 7, and 8

Table 2. ¹H and ¹⁹F NMR spectra of compounds 2–4, 7, and 8 (δ , J/Hz)

Com- pound	^I H NMR								
	H(2)	H(3)	H(5)	H(6)	ОН	O-Me	C-Me	CF ₃	
2	7.45 d	$6.80 ext{ d}$ J = 8.5)	6.80 d (J = 8	7.45 d 8.5)	8.60 br.s 6.15 s	3.75 s	_	0.90 s	
3	_	_	$6.70 ext{ d}$ (J = 8)	7.70 br.d 3.5)	8.40 br.s 6.35 br.s	3.73 s	2.15 s 2.10 s		
4		6.67 br.s	6.70 d.d. (J = 9) (J = 2.5)	7.45 br.d 9.0))	8.50 br.d 6.67 br. s	3.76 s	2.20 s	-	
7	7.30 s	_	6.60 s	_	8.38 s 6.15 s	3.75 s	2.20 s 2.13 s	_	
8	7.40 s	_	6.60 s	_	_	3.75 s	2.20 d 2.15 s	*)	

* A signal at 3.25 ppm (CH).

Experimental

¹H and ¹⁹F NMR spectra were recorded on a Bruker-AC-200F spectrometer operating at 200.00 and 188.31 MHz, respectively. The ¹H chemical shifts were referred to TMS (the internal standard) and the ¹⁹F chemical shifts were referred to CF₃COOH (the external standard). The R_f values for the compounds obtained were determined on Silufol UV₂₅₄ plates (Cavalier) in an acetone/CCl₄ (1:3) system. The compounds were detected under UV irradiation. Physical and spectroscopic characteristics of compounds **2**–**4**, **7**, and **8** are presented in Tables 1 and 2.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxyphenyl)propionate (2). Phenol (0.94 g, 0.01 mol), CF_3COOH (2 mL), and ketoester 1 (1.7 g, 0.011 mol) were placed in a stoppered flask, and allowed to stand at 20 °C for 48 h. The solvent was evaporated and the residue was crystallized from pentane to give 2.1 g of white crystalline ester 2.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxy-2,3-dimethylphenyl)propionate (3) and 3-hydroxy-6,7-dimethyl-3trifluoromethylbenzo[b]furan-2(3H)-one (5). The reaction between 2,3-xylenol (1.22 g, 0.01 mol) and ketoester 1 (1.7 g, 0.011 mol) was carried out as described above for compound 2. After 30 min, the crystalline precipitate was filtered off and washed with hexane to give 1.4 g of chromatographically pure colorless ester 3. The solvent was evaporated from the mother liquor, and the residue was crystallized from hexane to give 1.2 g (48 %) of compound 5 as a white crystalline solid, m.p. 93-94 °C.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxy-2-methylphenyl)propionate (4) was prepared from 3-cresol (1.08 g, 0.01 mol) and ketoester 1 (1.7 g, 0.011 mol) in a way similar to that described for ester 3. According to the TLC and ¹⁹F NMR data, the mother liquor mostly contained 3-hydroxy-6-methyl-3-trifluoromethylbenzo[b]furan-2(3H)-one (6).

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxy-2,5-dimethylphenyl)propionate (7) was prepared from 2,5-xylenol (1.22 g, 0.01 mol) and ketoester 1 (1.7 g, 0.011 mol) in a way similar to that described for ester 3.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxy-5-isopropyl-2-methylphenyl)propionate (8) was prepared from thymol (1.5 g, 0.011 mol) and ketoester 1 (1.7 g, 0.0109 mol) in a way similar to that described for ester 3. The present study was carried out with the financial support of the Russian Foundation for Basic Research (Project code 93-03-22696).

References

- 1. Soedineniya ftora: sintez i primenenie [Fluorine Compounds: Synthesis and Application], Ed. N. Isikava, Mir, Moscow, 1990, 306 (Russ. Transl.).
- 2. V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin, Izv. Akad. Nauk SSSR, Ser. khim., 1987, 1080 [Bull. Acad. Sci.

USSR, Div. Chem. Sci., 1987, 36, 1080 (Engl. Transl.)].

- V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin, *Zh. Org. Khim.*, 1992, **29**, 1684 [*J. Org. Chem. USSR*, 1992, **29** (Engl. Transl.)].
- 4. B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and Jorn P. Sibilia, J. Org. Chem., 1965, 30, 1004.
- V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. khim.*, 1987, 2849 [Bull. Acad. Sci. USSR, Div. Chem. Sci., 1987, 36, 2646].
- V. I. Dyachenko, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. khim.*, 1987, 2511 [Bull. Acad. Sci. USSR, Div. Chem. Sci., 1987, 36, 2332].

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