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Synthesis of 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoic acid [3-(difluoromethyl)chlorambucil]

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Abstract

Benzyl chlorodifluoromethyl ketone, ethyl bromoacetate and zinc afforded ethyl 3-(chlorodifluoromethyl)-3-hydroxy-4-phenylbutanoate in a Reformatsky-type reaction. By successive stages of dehydration to a mixture of but-2- and -3-enoates; simultaneous hydrogenation of the double bond and replacement of Cl by H nitration; and conversion of the nitro-group to amino; this hydroxy-ester was converted into ethyl 4-(4′-aminophenyl)-3-(difluoromethyl)butanoate. Treatment of this with oxirane gave the bis(2″-hydroxyethyl)-amino-derivative, from which the bis(chloroethyl)-analogue was made using Ph_3P/CCl_4. The target chlorambucil, bearing a difluoromethyl group at position 3, was then obtained after hydrolysis of the ester.

Keywords: 4-[4′-Bis(2″-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoic acid; 3-(Difluoromethyl)-chlorambucil synthesis

1. Introduction

We have already reported the synthesis of the 3,3-difluoro- [1], 3,3,4,4-tetrafluoro- [2] and 3-trifluoromethyl- [3] derivatives of the important anti-cancer drug chlorambucil [4], and of the 4,4-difluoro-derivative of its *meta*-isomer [5]. These fluorinated substituents in the alkyl chain are capable of modifying the mode of degradative attack on chlorambucil [6]. As an extension of this fluorine-containing series, the synthesis of a derivative of chlorambucil carrying a difluoromethyl substituent at the β-position of the carboxylic acid chain is now described.

2. Results and discussion

The synthetic route used was based on that established earlier for the trifluoromethyl analogue [3]. Since it appeared that replacement of Cl by H at a later stage, probably by hydrogenation, should be achieved fairly readily, the starting material chosen was the readily available chlorodifluoroacetic acid. However, the first intermediate in the sequence, benzyl chlorodifluoromethyl ketone (**1**), could not be made via reaction between ethyl chlorodifluoroacetate and benzyl cyanide promoted by sodium ethoxide (cf. Refs. [3,7]). The primary product, the keto-nitrile, was formed, but was quite resistant to hydrolytic cleavage. Another well-established route to ketones [8,9], reaction of fluoro-acids with Grignard reagents, was therefore utilized, and ketone (**1**), was generated by treatment of the precursor acid with benzyl magnesium bromide.

The next stage used the convenient Reformatsky reaction [10,11], which usually succeeds with fluorinated carbonyl compounds [12,13]. The reaction of (**1**) with ethyl bromoacetate, promoted by metallic zinc, proceeded efficiently, though slowly, in refluxing benzene. The product had correct analytical and spectroscopic data for the expected structure, ethyl 3-(chlorodifluoromethyl)-3-hydroxy-4-phenylbutanoate (**2**).

Double bonds are quite difficult to generate by elimination of water from tertiary alcohols of the type $R_2C(OH)Rf$, even for compounds such as (**2**), where an unsaturated acid is formed. As with the trifluoromethyl analogue [3], however, dehydration of (**2**) occurred using thionyl chloride in pyridine [14], and, after 72 h at 90°C, a product which was analyzed as an ethyl ester of a (chlorodifluoromethyl)phenylbutenoic acid (**3**) had been formed. For this structure, two positional isomers exist, each in two stereoisomeric forms, and the reaction was not selective. The ^1H and ^{19}F NMR spectra strongly suggested that all four butenoic

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ester isomers were present in compound (**3**). This contrasts with the trifluoromethyl analogue [3], where one form predominated.

Hydrogenation of butenoate (**3**) proceeded smoothly (palladized carbon catalyst). All isomers gave the same saturated ester, which was ethyl 3-(difluoromethyl)-4-phenylbutanoate ((**4**), all forms having undergone not only saturation of the >C=C< bond, but also replacement of Cl by H, to give the required fluoroalkyl group.

The subsequent stages in the synthetic sequence parallelled those described before for 3-(trifluoromethyl)chlorambucil [3]. Nitration of the arene ring of ester (**4**) using fuming nitric acid at low temperature (−70°C) gave a mixture of *ortho* and *para* isomers. The latter predominated, and it was obtained pure by fractional distillation; its structure was confirmed as ethyl 3-(difluoromethyl)-4-(4′-nitrophenyl)-butanoate (**5**). Hydrogenation of (**5**) over a palladized carbon catalyst yielded the reasonably stable arylamine, ethyl 4-(4′-aminophenyl)-3-(difluoromethyl)butanoate (**6**).

Hydroxyethylation of the aminophenyl group of (**6**) was effected by use of oxirane/16 M acetic acid, affording ethyl 3-(difluoromethyl)-4-[4′-bis(2″-hydroxyethyl)aminophenyl]-butanoate (**7**). Conversion of OH to Cl in (**7**) was carried out with a mild neutral reagent, triphenylphosphine in carbon tetrachloride [15,16], giving ethyl 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoate (**8**). Hydrolysis of the ester group was the final stage in the synthesis and was accomplished with concentrated hydrochloric acid to give the target product, 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoic acid (**9**) as a crystalline solid.

Analytical data and ^{1}H and ^{19}F NMR spectral characteristics confirmed the structures of all the compounds synthesized. Infrared spectra did not provide conclusive structural evidence, but the peaks shown corresponded with the groups present.

3. Experimental details

General procedures were as described previously [1,3]. Ether means diethyl ether.

3.1. Benzyl chlorodifluoromethyl ketone (1)

Benzyl magnesium bromide was prepared under an atmosphere of dry nitrogen from benzyl bromide (385 g) and dry magnesium turnings (60.75 g) in dry ether (1250 ml). After being refluxed for 2 h, the system was cooled to 0°C, and chlorodifluoroacetic acid (97.5 g) in ether (150 ml) added slowly and with stirring at 0°C during 1 h. After being stirred for 30 min at 0°C, and 1 h at 17°C, the system was cautiously poured onto a mixture of crushed ice (2500 g) and conc. hydrochloric acid (250 ml). The ether layer and ether extracts of the aqueous layer were combined, washed with saturated aq sodium bicarbonate, then with water, and dried. Concentration left a pale yellow liquid, which was distilled at 0.2 mmHg to give two fractions: (i), (100 g), b.p. 55–60°C; (ii), b.p. 90–106°C, which solidified and was 1,2-diphenylethane. Fraction (i) was compound (**1**), b.p. 58°C/0.2 mmHg (Found: C, 53.0; H, 3.7; Cl, 17.1; F, 18.3. $C_9H_7ClF_2O$ requires C, 52.8; H, 3.4; Cl, 17.3; F, 18.6%).

3.2. Ethyl 3-(chlorodifluoromethyl)-3-hydroxy-4-phenylbutanoate (2)

Ketone (**1**) (96 g) in dry benzene (300 ml) was added slowly and with stirring onto zinc metal (Analar grade; purified by being washed with 2% hydrochloric acid, solvents, and dried [10]) (30.7 g) under an atmosphere of dry nitrogen. Ethyl bromoacetate (78.8 g) was added to the mixture, which was then refluxed for 48 h, a red colour developing. To the cooled mixture, ammonium hydroxide solution (300 ml; sg. 0.880) was added, and the mixture was stirred for 1 h, a white precipitate being formed. Extraction with ether, followed by concentration and drying, left a red liquid (108.7 g), which was distilled (15 cm Vigreux column; 0.2 mmHg) to give: (i), recovered **1**, (1.2 g), b.p. 30–60°C; (ii), (106.5 g), b.p. 110–124°C. Fraction (ii) was compound (**2**), b.p. 124°C/0.2 mmHg (Found: C, 53.6; H, 5.1; F, 13.0. $C_{13}H_{15}ClF_2O_3$ requires C, 53.3; H, 5.2; F, 13.0%).

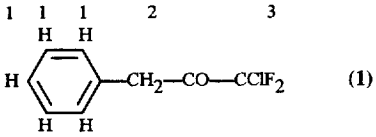
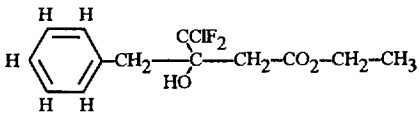
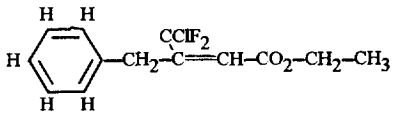
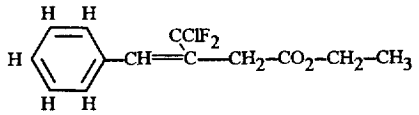
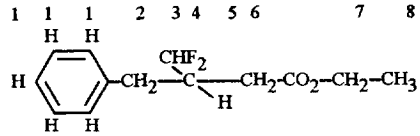
3.3. Dehydration of ethyl 3-(chlorodifluoromethyl)-3-hydroxy-4-phenylbutanoate (2)

Compound (**2**) (104 g) in thionyl chloride (71 g) was added slowly and with stirring at 0°C to pyridine (39 g) (both freshly-distilled). The exothermic reaction subsided, and the mixture was stirred at 90°C for 72 h. It was then cooled and poured into water (400 ml), and the product extracted into ether. The extracts were washed (aq sodium bicarbonate; then H_2O), dried and concentrated to a red liquid (83 g). Distillation in vacuo afforded mixture (**3**) as a pale yellow liquid, b.p. 98°C/0.1 mmHg (Found: C, 57.1; H, 5.0; Cl, 12.8; F, 13.8. $C_{13}H_{13}ClF_2O_2$ requires C, 56.8; H, 4.8; Cl, 12.9; F, 13.8%). NMR spectra (Table 1) showed the presence in (**3**) of ethyl 3-(chlorodifluoromethyl)-4-phenyl-but-2-enoate and -3-enoate in a ratio of approximately 3:1, each in two stereoisomeric forms (the 2-*E*-enoate was formed exclusively from the trifluoromethyl analogue [3]).

3.4. Ethyl 3-(difluoromethyl)-4-phenylbutanoate (4)

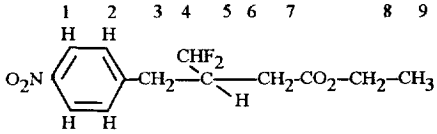
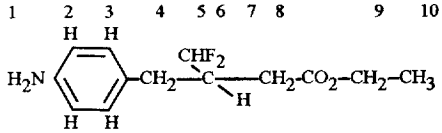
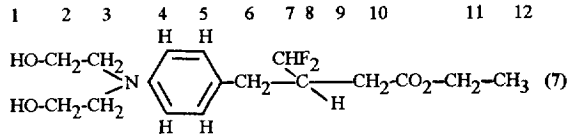
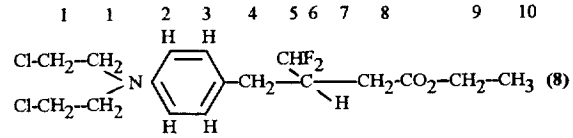
A solution of compound (**3**) (80 g), in ethanol (350 ml), with palladized carbon (10%; 2.5 g) in suspension, was shaken in a hydrogen atmosphere at 20°C. When the uptake had reached the calculated value, the filtered solution was concentrated. Water (100 ml) was added, and, following ether extraction, and concentration, an orange-coloured liq-

Table 1
Nuclear magnetic resonance data for compounds **1-9**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 1 1 2 3  **(1)**				
^{1}H NMR				
1	cm	5	7.03-7.53	
2	s	2	3.98	
^{19}F NMR				
3	s	-	67.8	
1 1 1 2 3 4 5 6 7  **(2)**				
^{1}H NMR				
1	s	5	7.24	
2	AB	2	δ_A-δ_B = 26.5 Hz δ_A = 193.25 Hz	J_{AB} = 14
3	s	1	5.48	
5	AB	2	δ_A-δ_B = 15 1 Hz δ_A = 157.55 Hz	J_{AB} = 16
6	q	2	4.03	$J_{6,7}$ = 7
7	t	3	1.17	
^{19}F NMR				
4	s	-	64.9	
1 1 1 2 3 4 5 6  **(3a)**				
1 1 1 7 8 9 5 6  **(3b)**				
^{1}H NMR				
1	cm	5	7.04-7.54	
2	s	1.4	4.17	
4	bs	0.8	6.49	
5	q	2	4.20	
6	t	3	1.25	
7	s	0.2	7.40	
9	s	0.6	3.43	
^{19}F NMR				
3,8	4×s	-	51.1; 51.9; 52.9; 53.9	
1 1 1 2 3 4 5 6 7 8  **(4)**				
^{1}H NMR				
1	bs	5	7.04-7.54	
2,5,6	cm	5	2.24-3.04	$J_{3,5}$ = 2
3	dt	1	C5.81	$J_{3,4}$ = 58
7	q	2	4.09	$J_{7,8}$ = 7
8	t	3	1.21	

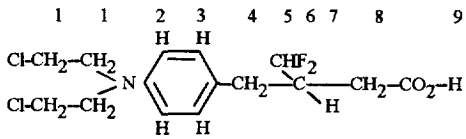
(*continued*)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
^{19}F NMR				
4	dd	-	126.2	
1 2 3 4 5 6 7 8 9  (5)				
^{1}H NMR				
1	AA′BB′	2	8.21	$J_{1,2}=9$
2	AA′BB′	2	7.46	
3,6,7	cm	5	2.13-3.63	$J_{4,6}=2$
4	dt	1	5.89	$J_{4,5}=58$
8	q	2	4.13	$J_{8,9}=7$
9	t	3	1.24	
^{19}F NMR				
5	dd	-	125.1	
1 2 3 4 5 6 7 8 9 10  (6)				
^{1}H NMR				
1	bs	2	3.70	
2	AA′BB′	2	6.97	$J_{2,3}=9$
3	AA′BB′	2	6.59	
4,7,8	cm	5	2.03-3.03	$J_{5,7}=2$
5	dt	1	5.79	$J_{5,6}=58$
9	q	2	4.08	$J_{9,10}=7$
10	t	3	1.20	
^{19}F NMR				
6	cm	-	126.3	
1 2 3 4 5 6 7 8 9 10 11 12  (7)				
^{1}H NMR				
1	bs	2	4.53	
2	m	4	3.69	
3	m	4	3.48	
4	AA′BB′	2	7.40	$J_{4,5}=9$
5	AA′BB′	2	6.60	
6,9,10	cm	5	2.2-2.8	$J_{7,9}=2$
7	dt	1	C5.77	$J_{7,8}=56$
11	q	2	4.08	$J_{11,12}=7$
12	t	3	1.21	
^{19}F NMR				
8	cm	-	C125.9	
1 1 2 3 4 5 6 7 8 9 10  (8)				
^{1}H NMR				
1	cm	8	C3.64	
2	AA′BB′	2	7.10	$J_{2,3}=9$
3	AA′BB′	2	6.63	
4,7,8	cm	5	2.2-3.1	$J_{5,7}=2$
5	dt	1	C5.80	$J_{5,6}=57$

(continued)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
9	q	2	4.09	$J_{9,10}=7$
10	t	3	1.22	
^{19}F NMR				
6	cm	-	C125.7	
1 1 2 3 4 5 6 7 8 9  (9)				
^{1}H NMR				
1	col. m	8	C3.63	
2	AA'BB'	2	7.09	$J_{2,3}=9$
3	AA'BB'	2	6.64	
4,7,8	cm	5	2.0–3.0	$J_{5,7}=2$
5	dt	1	C5.8	$J_{5,6}=57$
9	bs	1	9.3	
^{19}F NMR				
6	cm	–	C126.3	

uid was obtained. Distillation gave compound (**4**) (52.7 g), b.p. 89°C/0.1 mmHg (Found: C, 64.3; H, 6.6; F, 15.3. $C_{13}H_{16}F_2O_2$ requires C, 64.4; H, 6.7; F, 15.7%).

3.5. Ethyl 3-(difluoromethyl)-4-(4'-nitrophenyl)butanoate (5)

Compound (**4**) (40 g) was added slowly with stirring to fuming nitric acid (86 ml) cooled to −70°C, and the mixture left to reach room temperature. It was stirred for 1 h further, and then poured carefully onto crushed ice (500 g). Ether extraction, followed by washing (H_2O then aq $NaHCO_3$) and concentration, left a yellow liquid (33.5 g). Distillation (12 cm Vigreux column; 0.01 mmHg), afforded: (i), (2.3 g), b.p. 138–146°C; (ii), (5.5 g), b.p. 146–156°C; (iii), (14.5 g), b.p. 156–160°C. NMR spectra indicated that the fractions contained the isomers: (i) mainly *ortho*; (ii) largely *para* with a little *ortho*; (iii), mainly *para*. Fractions (ii) and (iii) were combined and redistilled at 0.01 mmHg to give: (iv), (1.95 g) b.p. 138–150°C; (v), (16.1 g) b.p. 152–160°C. Fraction (iv) was impure *ortho*-isomer, and fraction (v) the *para*-isomer (**5**), b.p. 160°C/0.1 mmHg (Found: C, 53.1; H, 5.2; F, 12.8; N, 5.0. $C_{13}H_{15}F_2NO_4$ requires C, 54.3; H, 5.3; F, 13.2; N, 4.9%).

3.6. Ethyl 4-(4'-aminophenyl)-3-(difluoromethyl)butanoate (6)

Product (**5**) (15.6 g) in ethanol (300 ml) with palladized carbon (10%; 1.5 g) was hydrogenated as for compound (**3**) above. The crude amine was distilled in vacuo to give pure (**6**), a colourless liquid, (11.4 g), b.p. 140°C/0.05 mmHg (Found: C, 60.2; H, 6.7; F, 14.9; N, 5.7. $C_{13}H_{17}F_2NO_2$ requires C, 60.7; H, 6.7; F, 14.8; N, 5.4%).

3.7. Ethyl 3-(difluoromethyl)-4-[4'-bis(2"-hydroxyethyl)-aminophenyl]butanoate (7)

Oxirane (5 ml) was added to a solution of compound (**6**) (9.6 g) in acetic acid (100 ml, 16 M) at 0°C. After being allowed to reach room temperature, the solution was stirred for 72 h further. It was then concentrated, washed, and extracted with ether. The extracts were washed and concentrated to leave crude (**7**) (8.7 g) as a viscous yellow liquid. A portion (2.0 g) was purified by adsorption chromatography (column 54×2.5 cm, eluted with ether: acetone-9:1) to give: (i), unknown (0.16 g), Rf 0.47; (ii), a colourless viscous liquid (1.4 g); Rf 0.30; (iii), unknown (0.07 g), Rf 0.125. Fraction (ii) was compound (**7**) (Found: C, 57.8; H, 7.5; F, 11.3; N, 4.1. $C_{17}H_{25}F_2NO_4$ requires C, 59.1; H, 7.3; F, 11.0; N, 4.1%). The rest of the crude product (**7**) was used to make (**8**).

3.8. Ethyl 4-[4'-bis(2"-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoate (8)

Crude compound (**7**) (6.7 g), in dry carbon tetrachloride (75 ml) was added to a stirred solution of triphenylphosphine (13.1 g) in carbon tetrachloride (75 ml) in an atmosphere of dry nitrogen. After being refluxed gently for 3 h, a light brown precipitate had deposited. The mixture was filtered hot, and the precipitate washed with ether (2×75 ml). The combined organic solutions were concentrated, and the solid residue was extracted with refluxing ether (3×100 ml). The combined extracts were cooled, filtered, and concentrated to half volume. After being refluxed, then cooled and filtered again, the solution was concentrated to leave a viscous oil (5.9 g). This was purified by adsorption chromatography (column 66×3.5 cm, eluted with carbon tetrachloride: chloroform-3:2) to give: (i), a liquid (4.1 g), Rf 0.72; (ii),

unknown, (0.06 g), Rf 0.5; (iii), triphenyl-phosphine oxide, Rf 0.43. Fraction (i), on short-path distillation (b.p. 170°C/0.05 mmHg), afforded a yellow liquid, compound (**8**), (2.8 g) (Found: C, 53.3; H.6.3; Cl, 18.9; F, 10.0; N, 3.7. $C_{17}H_{23}Cl_2F_2NO_2$ requires C, 53.4; H, 6.1; Cl, 18.6; F, 9.9; N, 3.7%).

3.9. 4-[4'-bis(2"-chloroethyl)aminophenyl]-3-(difluoromethyl)butanoic acid (9)

Ester (**8**) (1.7 g) and concentrated hydrochloric acid (40 ml) were stirred together at 60°C for 8 h. The cooled solution was diluted with water (100 ml) and extracted with ether. Concentration of the dried extracts left a cream-coloured liquid (0.82 g), which solidified when kept. Recrystallization from hexane gave acid (**9**) as a white solid (0.33 g), m.p. 47 ± 1°C (Found: C, 51.1; H, 5.7; Cl, 20.3; F, 11.2; N, 4.2. $C_{15}H_{19}Cl_2F_2NO_2$ requires C, 50.9; H, 5.4; Cl, 20.0; F, 10.7; N, 4.0%).

3.10. Spectroscopy

NMR spectra were measured as described previously [1,3] on a Perkin Elmer R12B machine: ^1H chemical shifts (60 MHz) are quoted on the δ scale in parts per million downfield of tetramethylsilane; ^{19}F (56.4 MHz) in p.p.m. upfield of trichlorofluoromethane, both internal standards. The solvent used was deuterochloroform.

Signals are designated by: s (singlet), d (doublet), t (triplet), q (quartet), AB, AA'BB', m (incompletely resolved multiplet), b (broad), c (complex).

When a coupling is recorded for a peak, the corresponding coupling was present also in the other designated peak. Where a chemical shift value is preceded by C, the centre of a complex multiplet is indicated.

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