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

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Abstract

Benzyl trifluoromethyl ketone and ethyl bromoacetate afforded ethyl 3-hydroxy-4-phenyl-3-(trifluoromethyl)butanoate in a Reformatsky-type reaction. This hydroxy ester, by successive stages of dehydration to a but-2-enoate, hydrogenation of the double bond, nitration, and conversion of the nitro group to amino, was converted into ethyl 4-(4′-aminophenyl)-3-(trifluoromethyl)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 trifluoromethyl group was then obtained after hydrolysis of the ester. With DAST, the hydroxy ester afforded the same but-2-enoate as that from the dehydration stage. © 1997 Elsevier Science S.A.

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1. Introduction

Since its original synthesis by Ross et al. [1], and introduction into clinical use shortly afterwards [2,3], the drug chlorambucil has had an important place in cancer chemotherapy, and many analogues have been made subsequently. Studies on its metabolism in vivo showed [4–6] that the major pathway involved in its degradation is oxidation at the β-position, as was confirmed by deuteration studies [7]. Derivatives of chlorambucil that have substituents at the β-position, capable of modifying this degradative attack, are therefore of obvious interest. Some years ago, our group carried out the successful preparation of 3,3-difluorochlorambucil [8], and some of its biological properties were described [9]. The synthesis of a derivative of chlorambucil carrying a trifluoromethyl substituent at the β-position was achieved soon afterwards and is now reported.

2. Results and discussion

Retrosynthetic considerations suggested that the desired carbon structure could be made from the known [10] benzyl trifluoromethyl ketone (**1**), by utilizing the widely-applicable and efficient [11,12] Reformatsky reaction, which is known to work well when applied to fluorinated carbonyl compounds [13,14]. The reported route [10] (condensation of benzyl cyanide with ethyl trifluoroacetate promoted by sodium ethoxide, followed by acidic hydrolysis of the intermediate keto-nitrile) was found to produce the proposed starting material (**1**) smoothly and in good yield.

The Reformatsky reaction of **1** with ethyl bromoacetate, promoted by zinc, was carried out in refluxing benzene, and was an efficient process, although a long reaction time was necessary. The product had the correct analytical and spectroscopic data for that expected, namely ethyl 3-hydroxy-4-phenyl-3-(trifluoromethyl)butanoate (**2**). When its hydroxyl group is adjacent to perfluoroalkyl, a secondary and even a tertiary alcohol is usually quite difficult to dehydrate, and compound **2** was no exception. This is despite the ready loss of water, with the formation of unsaturated acids, usually undergone by non-fluorinated β-hydroxy-carboxylic acids [11]. Several standard dehydrating agents (P_2O_5 in benzene, polyphosphoric acid, sulfuric acid) failed to generate a double bond, and most of the starting material (**2**) was recovered. Success was achieved using thionyl chloride in pyridine [15], which was effective with a related hydroxy acid bearing a trifluoromethyl group [16]. After 48 h at 75 °C, **2** was converted into an ethyl ester of a phenyl(trifluoromethyl)butenoic acid (**3**). Although two stereoisomers of each of two positional isomers could arise, the ^1H- and ^{19}F-

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NMR spectra strongly suggested that only one form was present. Using increments reported in Refs. [17,18] for ^1H peaks of the type $>C{=}C<_H$ and $>CH_2$ carrying substituents in the various positions, the best fit for the values shown by **3** was for the *E*-stereo-isomer of ethyl 4-phenyl-3-(trifluoromethyl)but-2-enoate. Thus, it appears that the dehydration of **2** is both regioselective and stereospecific.

Hydrogenation of butenoate **3** proceeded smoothly (palladized carbon catalyst) to give the saturated ester, ethyl 4-phenyl-3-(trifluoromethyl)butanoate (**4**). Nitration of the arene ring of this ester seemed likely to be a troublesome stage, because of the possible lack of dominant *para*-orientation. However, nitration using fuming nitric acid at low temperature [19] proved to give a preponderance of the desired isomer. Lower temperatures (−70 °C) than those recommended were used and the ratio of products *ortho*:*meta*:*para* was 4:1:24. Fractional distillation afforded the target product, ethyl 4-(4′-nitrophenyl)-3-(trifluoromethyl)butanoate (**5**). Hydrogenation of this (palladized carbon catalyst) yielded the relatively stable arylamine, ethyl 4-(4′-aminophenyl)-3-(trifluoromethyl)butanoate (**6**).

In the original synthesis of chlorambucil [1], hydroxyethylation of the aminophenyl group was effected by oxirane/aqueous acetic acid; our earlier work [8] utilized 16 M acid. Using the latter system for 72 h at room temperature with compound **6** afforded ethyl 4-[4′-bis(2″-hydroxyethyl)aminophenyl]-3-(trifluoromethyl)butanoate (**7**). Conversion of OH to Cl in **7** required a mild neutral reagent, and triphenylphosphine in carbon tetrachloride [20] worked well, giving a good yield of ethyl 4-[4′-bis(2″-chloroethyl)-aminophenyl]-3-(trifluoromethyl)butanoate (**8**). In this case, no morpholino by-product was detected (c.f. Ref. [8]).

The final stage in the synthesis was hydrolysis of the ester group, which was accomplished successfully with concentrated hydrochloric acid to give the target product, 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(trifluoromethyl)-butanoic acid (**9**) as a crystalline solid. Unfortunately, it appeared that the presence of the trifluoromethyl group in **9** increased the toxicity relative to that of the parent compound [21].

It seemed that hydroxy acid **2** could be the source of another analogue of chlorambucil, if it was possible to convert the OH group to F. This is often a difficult exchange in organofluorine chemistry, but diethylaminosulfur trifluoride (DAST) is one of the best reagents for conversions of this type [22]. A smooth reaction occurred with DAST in dry benzene at room temperature, but the product was ethyl 4-phenyl-3-(trifluoromethyl)but-2-*E*-enoate (**3**), and the yield was only slightly less than that obtained in the earlier dehydration stage. Obviously, in this case an elimination process prevails over fluorine exchange.

Structures of all the compounds made followed from their analytical data and their ^1H- and ^{19}F-NMR spectral characteristics. Infrared spectra did not provide conclusive structural information, but the peaks displayed were in accord with the groups present.

3. Experimental details

General procedures were as described previously [8]. Ether means diethyl ether.

3.1. Ethyl 3-hydroxy-4-phenyl-3-(trifluoromethyl)butanoate (2)

Benzyl trifluoromethyl ketone (**1**) [10] (150 g) in dry benzene (500 ml) was added slowly and with stirring onto zinc metal (Analar grade; purified by being washed with 2% hydrochloric acid, solvents, and dried [11]) (52.2 g) under an atmosphere of dry nitrogen. Ethyl bromoacetate (133.5 g) was added to the mixture, which was then refluxed for 48 h, a yellow solid being precipitated. To the cooled mixture, ammonium hydroxide solution (500 ml; sg. 0.880) was added, and the mixture was stirred for 1 h. Extraction with ether, followed by concentration, left a yellow liquid (191.6 g), which was distilled (15 cm Vigreux column; 0.5 mm Hg) to give: (i) ethyl bromoacetate (3.5 g), b.p. 30–70 °C; (ii) product (185 g), b.p. 86–92 °C. Fraction (ii) was compound **2**, b.p. 90–92 °C/0.5 mm Hg (Found: C, 56.3; H, 5.3; F, 21.0. $C_{13}H_{15}F_3O_3$ requires C, 56.5; H, 5.5; F, 20.6%).

3.2. Ethyl 4-phenyl-3-(trifluoromethyl)but-2-E-enoate (3)

A solution of compound **2** (180 g) in thionyl chloride (130 g) was added slowly and with stirring at 0 °C to pyridine (73 g) (both freshly distilled). When the exothermic reaction had subsided, the mixture was stirred at 75 °C for 48 h. The cooled mixture was poured into water (50 ml), and the product extracted into ether. The extracts were washed with aqueous sodium bicarbonate and water, dried and concentrated to leave an orange liquid (146.4 g). Distillation in vacuo afforded compound **3** as a bright yellow liquid (145.7 g), b.p. 56–58 °C/0.1 mm Hg (Found: C, 60.8; H, 5.1; F, 21.8. $C_{13}H_{13}F_3O_2$ requires C, 60.5; H, 5.1; F, 22.1%).

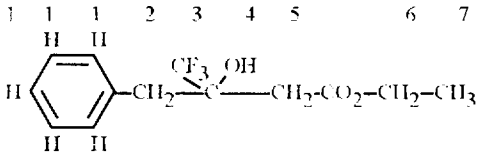
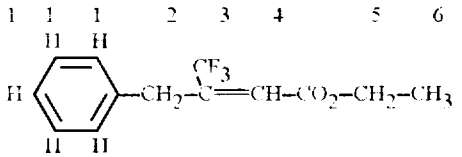
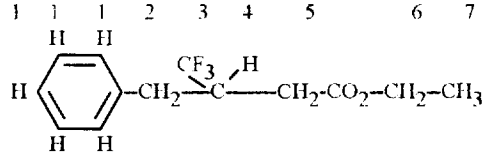
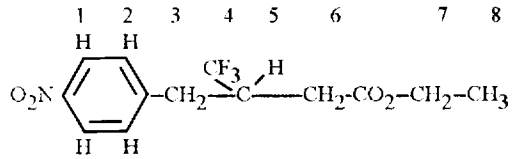
3.3. Ethyl 4-phenyl-3-(trifluoromethyl)butanoate (4)

A solution of compound **3** (70 g), in ethanol (300 ml), together with palladized carbon (10%; 1.5 g), 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, the colourless liquid obtained was distilled to give compound **4** (67.2 g), b.p. 70–74 °C/0.1 mm Hg (Found: C, 60.1; H, 5.9; F, 21.4. $C_{13}H_{15}F_3O_2$ requires C, 60.0; H, 5.8; F, 21.9%).

3.4. Ethyl 4-(4′-nitrophenyl)-3-(trifluoromethyl)butanoate (5)

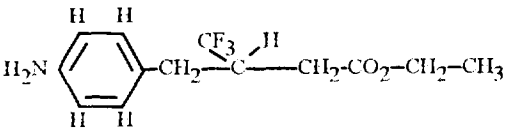
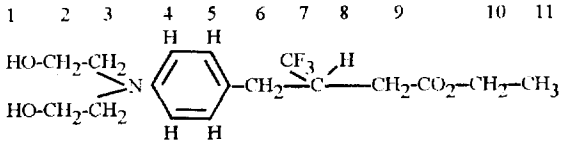
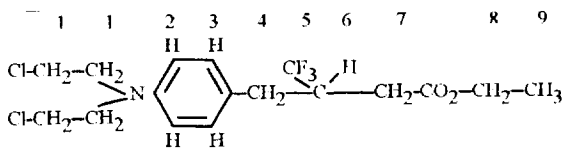
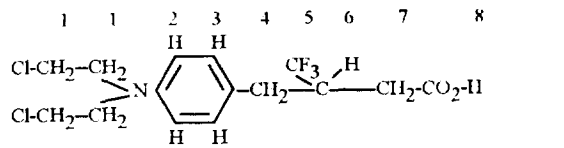
Compound (**4**) (60 g) was added slowly with stirring to fuming nitric acid (127 ml) cooled to −70 °C, and the mixture left to attain room temperature. It was stirred for 1 h

Table 1
Nuclear magnetic resonance data for compounds **2–9**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
 **(2)**				
^{1}H NMR				
1	s	5	7.26	
2	AB	2	$\delta_A - \delta_B = 24$ Hz $\delta_A = 189$ Hz	$J_{AB} = 14$
4	bs	1	5.15–5.35	
5	AB	2	$\delta_A - \delta_B = 15$ Hz $\delta_A = 155$ Hz $\delta_B = 140$ Hz	$J_{AB} = 14$
6	q	2	4.06	$J_{6,7} = 7$
7	t	3	1.17	
^{19}F NMR				
3	s	–	81.3	
 **(3)**				
^{1}H NMR				
1	s	5	7.26	
2	s	2	4.10	
4	s	1	6.50	
5	q	2	4.23	$J_{5,6} = 7$
6	t	3	1.25	
^{19}F NMR				
3	s	–	67.5	
 **(4)**				
^{1}H NMR				
1	bs	5	7.26	
2,4,5	cm	5	2.25–3.35	
6	q	2	4.00	$J_{6,7} = 7$
7	t	3	1.16	
^{19}F NMR				
3	d	–	71.8	
 **(5)**				
^{1}H NMR				
1	AA'BB'	2	8.22	$J_{1,2} = 8$
2	AA'BB'	2	7.47	
3,5,6	cm	5	2.13–3.63	
7	q	2	4.11	$J_{7,8} = 7$
8	t	3	1.23	
^{19}F NMR				
4	d	–	71.3	

(*continued*)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 2 3 4 5 6 7 8 9  **(6)**				
^{1}H NMR				
1	bs	2	3.63	
2	AA′BB′	2	6.99	$J_{2,3}=9$
3	AA′BB′	2	6.59	
4,6,7	cm	5	2.0–3.2	$J_{5,6}=3$
8	q	2	4.05	$J_{8,9}=7$
9	t	3	1.17	
^{19}F NMR				
5	d	–	72.25	
1 2 3 4 5 6 7 8 9 10 11  **(7)**				
^{1}H NMR				
1	bs	2	4.30	
2	m	4	3.74	
3	m	4	3.49	
4	AA′BB′	2	7.05	$J_{4,5}=9$
5	AA′BB′	2	6.63	
6,8,9	cm	5	2.2–3.3	
10	q	2	4.00	$J_{10,11}=7$
11	t	3	1.17	
^{19}F NMR				
7	d	–	71.7	
1 1 2 3 4 5 6 7 8 9  **(8)**				
^{1}H NMR				
1	cm	8	3.65	
2	AA′BB′	2	7.13	$J_{2,3}=9$
3	AA′BB′	2	6.64	
4,6,7	cm	5	2.0–3.55	$J_{5,6}=4$
8	q	2	4.02	$J_{8,9}=7$
9	t	3	1.17	
^{19}F NMR				
5	d	–	71.8	
1 1 2 3 4 5 6 7 8  **(9)**				
^{1}H NMR				
1	bcs	8	3.63	
2	AA′BB′	2	7.10	$J_{2,3}=9$
3	AA′BB′	2	6.60	
4,6,7	cm	5	2.3–3.3	
8	bs	1	10.8	
^{19}F NMR				
5	d	–	71.7	

further, and then poured carefully onto crushed ice (500 g). Ether extraction, followed by washing (water and aqueous sodium bicarbonate), concentration and distillation (15 cm Vigreux column; 0.15 mm Hg), afforded: (i) crude product (35.8 g), b.p. 130–136 °C; (ii) mixture (15.3 g), b.p. 138–144 °C. Compound **5** (32.8 g), b.p. 131 °C/0.1 mm Hg (Found: C, 51.2; H, 4.4; F, 19.1; N, 4.6. $C_{13}H_{14}F_3NO_4$ requires C, 51.1; H, 4.6; F, 18.7; N, 4.6%) was obtained by redistillation of fraction (i). Fraction (ii) contained **5** and its 2′-nitro-isomer.

3.5. Ethyl 4-(4′-aminophenyl)-3-(trifluoromethyl)butanoate (6)

Product **5** (30 g) in ethanol (300 ml) with palladized carbon (10%; 1.0 g) was hydrogenated as for compound **3** above. The crude dark blue amine was distilled in vacuo to give pure **6** (19.0 g), b.p. 124–126 °C/0.1 mm Hg (Found: C, 56.4; H, 6.0; F, 20.3; N, 5.1. $C_{13}H_{16}F_3NO_2$ requires C, 56.7; H, 5.9; F, 20.7; N, 5.1%) as a colourless liquid.

3.6. Ethyl 4-[4′-bis(2″-hydroxyethyl)aminophenyl]-3-(trifluoromethyl)butanoate (7)

Oxirane (10 ml) was added to a solution of compound **6** (18.5 g) in acetic acid (100 ml, 16 M) at 0 °C. After being allowed to attain 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** (17.7 g) as a red viscous liquid. A portion (2.5 g) was purified by adsorption chromatography (column 54 cm × 2.5 cm; eluted with ether:acetone, 9:1) to give: (i) unknown (0.3 g), Rf 0.72; (ii) a colourless viscous liquid (1.9 g), Rf 0.50; (iii) unknown (0.1 g), Rf 0.31. Fraction (ii) was compound **7** (Found: C, 56.2; H, 6.9; F, 16.1; N, 4.0. $C_{17}H_{24}F_3NO_4$ requires C, 56.2; H, 6.7; F, 15.7; N, 3.9%). The rest of the red crude product **7** was used to prepare compound **8**.

3.7. Ethyl 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(trifluoromethyl)butanoate (8)

Crude compound **7** (15.1 g), in dry carbon tetrachloride (75 ml) was added to a stirred solution of triphenylphosphine (26.7 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 (14.8 g). Part of this (7.0 g) was subjected to adsorption chromatography (column 66 cm × 3.5 cm; eluted with ether:benzene, 9:1) to give: (i) a liquid (5.9 g), Rf 0.84; (ii) triphenylphosphine oxide, Rf 0.04. Fraction (i), on short-path distillation (b.p. 148 °C/0.1 mm Hg), afforded a liquid which solidified on being kept. This was recrystallized from hexane to give compound **8** (4.5 g) as colourless plates, m.p. 63 °C (Found: C, 51.2; H. 5.5; Cl, 17.6; F, 14.5; N, 3.5. $C_{17}H_{22}Cl_2F_3NO_2$ requires C, 51.0; H, 5.5; Cl, 17.7; F, 14.2; N, 3.5%).

3.8. 4-[4′-bis(2″-chloroethyl)aminophenyl]-3-(trifluoromethyl)butanoic acid (9)

Compound **8** (3.0 g) and concentrated hydrochloric acid (60 ml) were stirred together at 60 °C for 7 h. The cooled solution was diluted with water (200 ml) and extracted with ether. Concentration of the dried extracts left a pale yellow liquid (1.99 g) which solidified when kept. Recrystallization from hexane gave acid **9** (1.5 g), m.p. 88 °C (Found: C, 48.1; H, 5.1; Cl, 19.4; F, 15.0; N, 3.5. $C_{15}H_{18}Cl_2F_3NO_2$ requires C, 48.4; H, 4.9; Cl, 19.1; F, 15.3; N, 3.8%).

3.9. Reaction of ethyl 3-hydroxy-4-phenyl-3-(trifluoromethyl)butanoate (2) with DAST

A solution of **2** (10.3 g) in dry benzene (30 ml) was added slowly, with stirring, at −70 °C, to a solution of DAST (4.8 ml) in dry benzene, under an atmosphere of dry nitrogen. The reaction mixture was allowed to attain room temperature and was then stirred for 1 h further. After work-up by pouring into water (50 ml), followed by extraction as usual, concentration left a yellow liquid (8.2 g), which was shown by its spectral properties to be ethyl 4-phenyl-3-(trifluoromethyl)but-2-*E*-enoate (**3**).

3.10. Spectroscopy

This was done as described previously [8].

Nuclear magnetic resonance spectra were measured on a Perkin–Elmer R12B machine (Table 1): ^1H chemical shifts (60 MHz) are quoted on the δ scale in parts per million downfield of tetramethylsilane, and ^{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.

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