Synthesis and NMR Characterization of 4-[(2-Tetrahydropyranyloxy)methyl]piperidine and Intermediates

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4-(Hydroxymethyl)piperidine was selectively protected with tetrahydropyranyl group in several steps to give the title compound. Use of ^1H and ^{19}F nmr spectra in structure determination is discussed.

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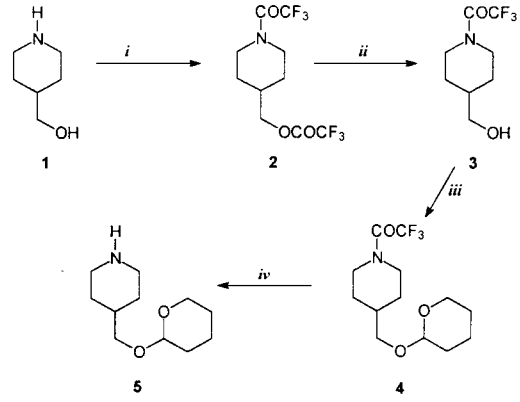
In the course of our work on the synthesis of novel fluorescent dyes [2] we needed 4-hydroxymethylpiperidine (**1**) only protected in the primary alcohol. The requirement was for the protecting group to be resistant towards organometallic reagents, easy to introduce, and later removable under the mildest reaction conditions possible. The tetrahydropyranyl (THP) group met these requirements. Literature search on compounds containing the 4-oxymethylpiperidinyl structural elemental revealed large interest in this field. In most of the reported work, however, authors obtained the target derivative by, first protecting the more reactive amine site, followed by reaction on the less reactive oxygen site [3,4]. One possibility for the synthesis of *O*-protected 4-(hydroxymethyl)piperidine is based on the findings that, when the benzyl group is used to protect the amino functionality, it is possible to remove it by treatment with methyl chloroformate followed by potassium hydroxide in methanol [4]. So, one would first prepare *N*-benzyl-4-(hydroxymethyl)piperidine, then suitably protect the OH group, and finally remove the benzyl group. We could not use this method because hydrogen chloride which is evolved during methyl chloroformate treatment would cause the removal of the acid-labile THP group.

We design the synthesis of 4-[(2-tetrahydropyranyloxy)-methyl]piperidine (**5**) by temporarily protecting the reactive sites in **1** by a trifluoroacetyl group followed by its selective removal, and further reaction with dihydropyran at the primary alcohol site, as depicted in the Scheme. The starting 4-(hydroxymethyl)piperidine (**1**) reacted at room temperature with trifluoroacetic acid anhydride to give a yellow oil. Despite the reported high reactivity of trifluoroacetates towards acid hydrolysis [5], washing of an ethyl acetate solution with 1 *N* hydrochloric acid, did not result in the expected *N*-trifluoroacetyl-4-(hydroxymethyl)piperidine (**3**). The ^{19}F nmr spectrum of the crude product contained two signals of approximately equal intensity suggesting the presence of two magnetically different fluorine-containing functional groups. Analysis (gc/ms) showed that the crude sample contained two compounds: a major component with molecular mass of 307 and a minor component (approximately 10%) with molecular mass of 211. On the basis of nmr and mass spectra, structure **2** for the major component and structure **3** for the minor component of the mixture were assigned. In order to find the conditions for complete hydrolysis of the ester group we ran a test reaction in a nmr tube as follows: to a solution of the crude product (15 mg) in 0.7 ml of deuteriochloroform concentrated aqueous ammonia (0.2 ml) was added and changes in ^{19}F spectra were recorded in time. We found that the signal at −75.35 ppm disappeared, the signal at −69.37 ppm remained unchanged, and that a new signal at −76.57 ppm appeared. The first signal was assigned to the trifluoroacetate group, the second to the *N*-trifluoroacetyl group, and the third to trifluoroacetamide. At 5 minutes the ratio of the signals at −75.35 ppm and −76.57 ppm was 3:2, after 10 minutes it was 1:6 and after 30 minutes there were only traces of **2** left. In a preparative run on a larger scale as described in the experimental section, a methylene chloride solution was shaken with concentrated aqueous ammonia for thirty minutes, washed with water, and 1 *N* hydrochloric acid. We found that this acid wash is essential for the removal of traces of ammonia from the product. Ammonia, depending on the quantity present, slow down or completely prevent the transformation **3** to **4**, the next step in the reaction. Amberlyst H was proposed as a strongly acidic catalyst in the protection of alcohols with 3,4-dihydropyran [6]. We chose it over *p*-tolu-



Reagents: *i*: TFAA, R.T.; *ii*: aqueous ammonia, R.T.; *iii*: 3,4-dihydropyran, Amberlyst H; *iv*: sodium borohydride, EtOH.

enesulfonic acid [7] or pyridinium *p*-toluensulfonate [8] for the simplicity of the workup and the absence of water which might promote unwanted hydrolysis of the *N*-trifluoroacetyl group. After bulb-to-bulb distillation we isolated *N*-trifluoroacetyl-4-[(2-tetrahydropyranyloxy)methyl]piperidine (**4**) in 86% yield. Attempts to remove the *N*-trifluoroacetyl group by treatment of **4** with concentrated ammonia in methanol [9] gave unsatisfactory results. In several attempts, reactions yielded mixtures of starting material and product in variable proportions. Finally we succeeded in achieving the removal of the trifluoroacetyl protecting group by treating **4** with sodium borohydride in anhydrous ethanol [10]. Compound **5** was obtained in 80% yield as a colorless oil. After prolonged standing at room temperature the oil crystallized. When the solid was dried at room temperature *in vacuo* for 24 hours, a colorless oil was obtained again, which suggested that the solid is a hydrate. The structure of compound **5** was confirmed also by ^{1}H nmr, ^{19}F nmr, gc/ms and hrms.

Because literature data are scarce and incomplete, properly assigned nmr was essential in the determination of structures. We used single frequency homonuclear decoupling to determine the coupling patterns in the ^{1}H nmr spectra of the starting 4-(hydroxymethyl)piperidine (**1**) (Figure 1, spectrum **a**). Except for the signal for 4a-H all other signals integrate equally (for 2 protons). From this fact, the symmetry of the molecule, and from the decoupling experiments we concluded that this molecule exists in chloroform solution at room temperature almost exclusively in the conformation where the 4-hydroxymethyl group is in an equatorial position. We also assigned signals to all pairs of axial and equatorial protons. The recorded splitting and relative intensities of respective signals resulting from short range couplings is in agreement with predicted first order coupling pattern (inset in Figure 1, spectrum **a**).

In addition to already described changes in the ^{19}F nmr spectra, going from starting 4-(hydroxymethyl)piperidine

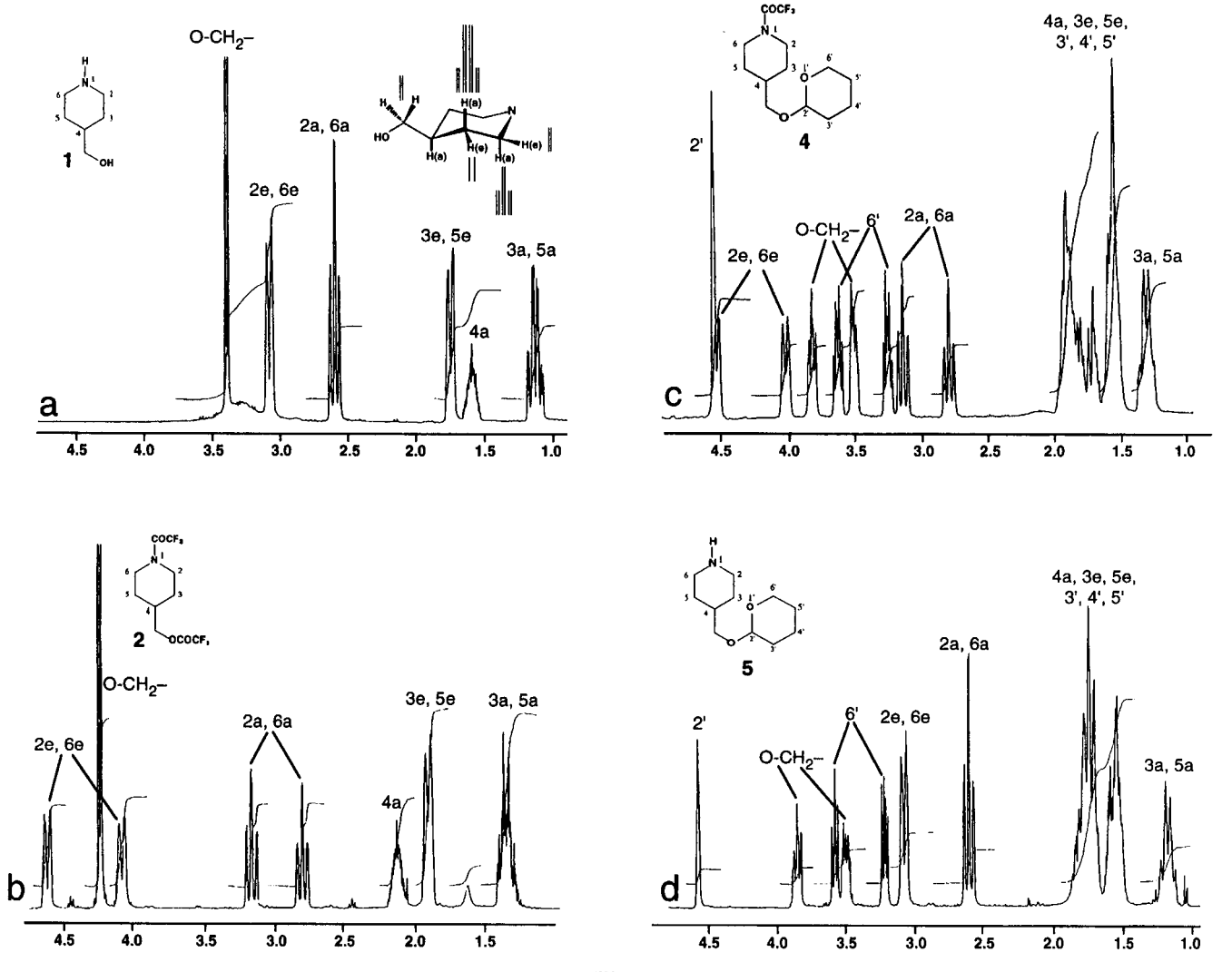


Figure 1.

(**1**) to the bistrifluoroacetylated intermediate **2**, significant changes occurred also in the ^1H nmr spectrum (Figure 1, spectrum **b**). Besides the expected downfield shift of the signals, corresponding to protons in the vicinity of the newly introduced trifluoroacetyl group (*e.g.* oxymethyl group signals shifted downfield by approximately 0.8 ppm), the most notable changes were recorded for protons on C-2 and C-6. Two effects, namely the effect of the *N*-acyl group (as the *N,N*-dimethylformamide where we observe two signals for the dimethylamino group) and the effect of the ring chair conformation (as has been described above for compound **1**) rendered these four protons magnetically nonequivalent resulting in appearance of four groups of signals: two tm at 2.78 and 3.14 ppm (for 2a-H and 6a-H) and two dm at 4.05 and 4.75 ppm (for 2e-H and 6e-H), each integrating for 1 proton. For compound **3** we found that removal of the trifluoroacetate group resulted in changes in the nmr spectrum mainly as the upfield shift of signals for the 4-hydroxymethyl group and 4a-H, while the rest of the spectrum remained essentially unchanged. For compound **4**, where as consequence of the presence of a chiral center (C-2′), protons in nearby methylene groups are in diastereotopic magnetic environment, we observed major changes in the nmr spectrum (Figure 1, spectrum **c**). The effect can be distinctly observed for the 4-oxymethyl- and H-6′ groups, while signals for 5′-H and 4′-H overlap with others thus making the observation difficult. We observed two multiplets at 3.51 and 3.83 ppm, each integrating for 1 proton, corresponding to the 4-oxymethyl group. Two multiplets at 3.25 and 3.65 ppm, also integrating for 1 proton each, correspond to the 6′-H. As shown for compound **5** in Figure 1 (spectrum **d**), removal of the *N*-trifluoroacetyl group results in simplification of the spectrum, namely, the four multiplets, corresponding to 2a-H, 2e-H, 6a-H, and 6e-H shifted upfield and collapsed into two sets of signals: a tm at 2.62 ppm (2a-H and 6a-H) and a dm at 3.09 ppm (2e-H and 6e-H).

EXPERIMENTAL

The nmr spectra were obtained on a Bruker AM360WB Spectrometer. The ^1H chemical shifts are reported in ppm downfield from TMS as the internal standard, ^{19}F chemical shifts are referenced to external fluorotrichloromethane. Melting points were determined on a Electrothermal Melting Point Apparatus and are uncorrected. Analyses gc/ms were performed by loading samples onto a dropping needle gc injector connected to a medium polarity bonded phase fused silica capillary column (DB5, 13 meters x 0.25 mm i.d., 25 micron film thickness, J & W Associates, Rancho Cordova, CA) the end of which was inserted directly into the ion source of a quadropole mass spectrometer (modified HP 5985B gc/ms). The gc injector port and gc/ms transfer line was held at 250°, and the gc oven was held at 100° for the first minute following injection, following which it was increased linearly at a rate of 5°/minute to a plateau of 250°. Electron ionization mass spectra were obtained with 70 eV electron energy. Chemical ionization mass spectra were obtained using methane as the reagent gas which was introduced into the mass spectrometer ion source coaxially with the gc column at a rate which maintained an indicated pressure in the ion source of 0.5 mm Hg. Solvents and reagents were from Fisher, Aldrich or Fluka and were used as received unless noted otherwise.

4-(Hydroxymethyl)piperidine (**1**).

Compound **1** was prepared according to the literature procedure [11] from ethyl isonipecotate in 75-83% yield. After recrystallization from ethyl acetate it melted at 56-61° (lit 56-62 [12] or 58-60° [13]); ^1H nmr (deuteriochloroform): δ 1.13 (dq, 2H, J = 12.3, 3.8 Hz, 3a-H and 5a-H), 1.62 (m, 1H, 4a-H), 1.72 (bd, 2H, J = 12.5 Hz, 3e-H and 5e-H), 2.61 (dt, 2H, J = 12.2, 2.1 Hz, 2a-H and 6a-H), 3.09 (dm, 2H, J = 12.2 Hz, 2e-H and 6e-H), 3.3 (b, 1H, OH or NH), 3.48 (d, 2H, J = 6.2 Hz, O-CH_2-).

N-Trifluoroacetyl-4-(trifluoroacetoxymethyl)piperidine (**2**) and *N*-Trifluoroacetyl-4-(hydroxymethyl)piperidine (**3**).

In a round bottom flask 2.1 g (18 mmoles) of 4-(hydroxymethyl)-piperidine was cooled in an ice-water bath and 15 ml of trifluoroacetic acid anhydride (TFAA) were slowly added. After stirring at room temperature for 3 hours the excess of TFAA was removed *in vacuo* and the residue was dissolved in 100 ml of ethyl acetate. The solution was successively washed with 1 *N* hydrochloric acid, brine, and saturated sodium bicarbonate solution (35 ml each), dried and evaporated to leave 3.5 g (62%) of a yellow oil. ^1H nmr (deuteriochloroform): δ 1.35-1.42 (m, 2H, 3a-H, 5a-H), 1.89 (dm, 2H, J = 13.3 Hz, 3e-H, 5e-H), 2.1 (m, 1H, 4a-H), 2.80 and 3.16 (tm, 2H, J = 12.9 Hz, 2a-H and 6a-H), 4.08 and 4.62 (dm, 2H, J = 12.9 Hz, 2e-H and 6e-H), 4.24 (d, 2H, J = 6.2 Hz, C-CH_2O); ^{19}F nmr (deuteriochloroform): δ −69.37 (N-$COCF_3$), −75.35 (O-$COCF_3$); ms: Calcd. for $C_{10}H_{11}NO_3F_6$: 307.19. Found: 307.

The above raw *N*-trifluoroacetyl-4-(trifluoroacetoxymethyl)piperidine (**2**, 3.5 g) was dissolved in 100 ml of methylene chloride and was shaken with 50 ml of concentrated aqueous ammonia for 30 minutes. The organic layer was then thoroughly washed with water, 1 *N* hydrochloric acid and water (100 ml each) and dried. After drying and removal of the solvent 2.15 g (89%) of a colorless oil was obtained; ^1H nmr (deuteriochloroform): δ 1.20-1.46 (m, 2H, 3a-H, 5a-H), 1.70-1.95 (m, 3H, 3e-H, 5e-H, 4a-H), 2.78 and 3.14 (tm, 2, J = 13.2 Hz, 2a-H and 6a-H), 3.54 (d, 2H, J = 5.1 Hz, C-CH_2-O), 4.05 and 4.57 (dm, 2H, J = 13.2 Hz, 2e-H and 6e-H); ^{19}F nmr (deuteriochloroform): δ −69.30 (N-$COCF_3$).

Anal. Calcd. for $C_8H_{12}F_3NO_2$: C, 45.50; H, 5.73; N, 6.63. Found: C, 45.51; H, 5.96; N, 6.64.

N-Trifluoroacetyl-4-[(2-tetrahydropyranyloxy)methyl]piperidine (**4**) and 4-[(2-Tetrahydropyranyloxy)methyl]piperidine (**5**).

A mixture of 2.9 g (13.8 mmoles) of *N*-trifluoroacetyl-4-(hydroxymethyl)piperidine (**3**), 1.39 g (16.6 mmoles, 1.2 equivalents) of 3,4-dihydropyran, and 300 mg of Amberlyst H in 30 ml of benzene was stirred at room temperature for 3 days. Solid particles were filtered off and the filtrate was concentrated *in vacuo* to leave 3.8 g of colorless oil. It was bulb-to-bulb distilled at 145°/0.7 mm Hg to collect *N*-trifluoroacetyl-4-[(2-tetrahydropyranyloxy)methyl]piperidine **4** (3.5 g, 86%) as a colorless oil; ^1H nmr (deuteriochloroform): δ 1.2-1.4 and 1.49-2.0 (m, 11H, 3a-H, 4a-H, 5a-H, 3e-H, 5e-H, 3′-H, 4′-H, 5′-H), 2.79 and 3.14 (tm, 2H, J = 12.5 Hz, 2a-H and 6a-H), 3.25 and 3.65 (m, 2H, 6′-H), 3.51 and

3.83 (m, 2H, C-CH_2-O), 4.03 and 4.55 (dm, 2H, J = 12.5 Hz, 2e-H and 6e-H), 4.57 (bs, 1H, 2'-H); ^{19}F nmr (deuteriochloroform): δ −69.3 (N-$COCF_3$).

A solution of 1 g (3.4 mmoles) of *N*-trifluoroacetyl-4-[(2-tetrahydropyranyloxy)methyl]piperidine (**4**) in 17 ml of freshly distilled anhydrous ethanol [14] was cooled to 0° and 512 mg (13.5 mmoles) of sodium borohydride was added. The mixture was stirred at room temperature under nitrogen overnight and then it was cooled to 0° again. Acetone (3 ml) was slowly added and after the reaction has subsided the solution was distributed between saturated solution of potassium carbonate (50 ml) and methylene chloride (100 ml). The organic layer (top) was dried and concentrated *in vacuo*. The oily residue (800 mg) was bulb-to-bulb distilled at 90°/0.75 mm Hg to give 540 mg (80%) of 4-[(2-tetrahydropyranyloxy)methyl]piperidine (**5**). After prolonged standing in a vial at room temperature the compound crystallized. It melted at 65-72°; ^{1}H nmr (deuteriochloroform): δ 1.1-1.18 and 1.48-2.93 (m, 11H, 3a-H, 4a-H, 5a-H, 3e-H, 5e-H, 3'-H, 4'-H, 5'-H), 2.62 (tm, 2H, J = 11.8 Hz, 2a-H and 6a-H), 3.09 (dm, 2H, J = 11.8 Hz, 2e-H and 6e-H), 3.21 and 3.57 (m, 2H, 6'-H), 3.50 and 3.85 (m, 2H, C-CH_2-O), 4.56 (m, 1H, 2'-H); gc/ms analysis shows the presence of a single compound; hrms Calcd. for $C_{11}H_{21}NO_2$: (M^+) 199.1572. Found: 199.1566. Calcd. for $C_6H_{12}NO$ (M^+ -tetrahydropyranyl group): 114.0919. Found: 114.0913.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62; N, 7.03. Found: C, 65.96; H, 10.54; N, 6.95.

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