Journal of Fluorine Chemistry, *46* (1990) 515–519

Received: April 12, 1989; accepted: July 17, 1989

THE ANGULAR TRIFLUOROMETHYL GROUP. PART 2. SYNTHESIS OF (+)2,3,7,7a-TETRAHYDRO-7a-TRIFLUOROMETHYL-1*H*-INDENE-1,5-(6*H*)-DIONE

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SUMMARY

Michael Condensation of 2-trifluoromethyl-cyclopentane-1,3-dione with methyl vinyl ketone, followed by amino-acid mediated cyclization of the resulting prochiral triketone, gives access to optically active (+) 2,3,7,7a - tetrahydro -7a- trifluoromethyl -1*H*- indene -1,5-(6*H*)- dione.

INTRODUCTION

The amino-acid catalysed aldol cyclization of prochiral triketones, leading to optically active tetrahydro-indanediones [1] or hexahydro-naphthalenediones [2] precursors of steroids or prostaglandins, have been standardized to a high level of reproducibility.

The availability of 2-trifluoromethyl-cyclopentane-1,3-dione **1** [3, 4] prompted us to extend this synthetic scheme to the case of trifluoromethylated compounds.

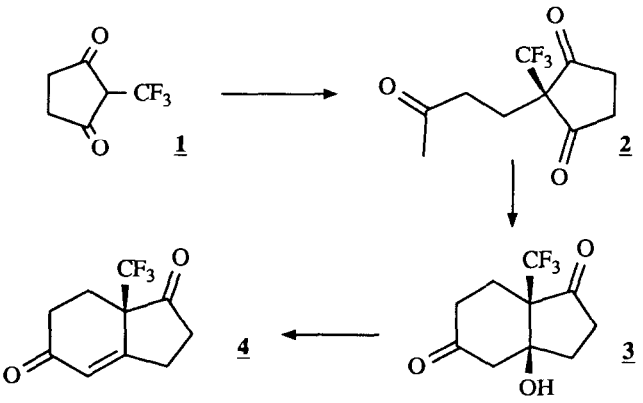
RESULTS AND DISCUSSION

Our own experience with the trifluoromethyl-dione **1** [5] has shown the lability of the fluorine atoms in this molecule. Transposition of well known reactions of its unfluorinated analogue, 2-methyl-cyclopentane -1,3-dione, is not always obvious.

0022-1139/90/$3.50

In fact, initial attempts to perform the Michael condensation with methyl vinyl ketone in water (which is usually the medium of choice for this particular reaction [6]), led to a progressive hydrolysis of the trifluoromethyl group with no recovery of fluorinated addition products.

However we find that the reaction proceeded smoothly in refluxing benzene in the presence of an excess of methyl vinyl ketone (ten molar equivalents). The oily triketone 2 was isolated by chromatography in a 53% yield. (Scheme).



For the next step we selected S(-)-proline as the chiral auxiliary, since this amino-acid has been shown to give the best chemical and optical yields in most cases [7]. Thus, cyclization of the prochiral ketone 2 in acetonitrile [8], in the presence of S(-)-proline for 27 hours gave the optically active ketol 3 (α_D^{25} +43.7°) in a 35 % yield after recrystallization from diethyl ether. Use of (±)-proline in the above reaction gave the racemic ketol in the same yield.

We assumed a cis ring junction for this compound on the basis of a less hindered nucleophilic attack on the opposite side of the bulky trifluoromethyl group [9], and previous evidence for related reactions [8].

The (+) ketol 3 was readily dehydrated with a catalytic amount of toluene-p-sulphonic acid in refluxing benzene [10] affording the (+) indanedione 4 (α_D^{22} +268.2) as a light and air sensitive oil in a 60 % yield. Unfortunately we could not estimate the optical purity of this compound or its predecessor by the use of chiral N.m.r. shift reagents.

In conclusion we have shown that the trifluoromethyl cyclopentanedione 1 could be engaged in Michael reactions and that the trifluoromethyl group does not suppress assymetric induction in amino-acid mediated cyclization. This behaviour is compatible with the initial

formation of an enamine by reaction of the amino group with the side chain carbonyl, without participation of the angular alkyl substituent [11, 12].

EXPERIMENTAL

M.p.s. were determined on a Mettler FP-61 apparatus. I.r. spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. ^{1}H N.m.r. spectra were taken on Bruker AC-200 E spectrometer. ^{13}C N.m.r. spectra were recorded on a Varian CFT-20 or Bruker AC-200 E instruments with $SiMe_4$ as internal reference. ^{19}F N.m.r. spectra were from a Varian EM-360 L apparatus with $CFCl_3$ as internal standard. All chemical shifts were reported downfield from the reference [13]. Optical rotations were determined on a Perkin Elmer 241 Polarimeter. Mass spectra were taken on AEI MS30 or RIBER MAG R-1010-C mass spectrometers. Silica gel refers to silica gel 60, 70-230 Mesh (Merck).

2-(3-Oxobutyl)-2-Trifluoromethyl-cyclopentane-1,3-dione

A mixture of 2-trifluoromethyl cyclopentane-1,3-dione **1** (1.0g, 6.06 mmol) and methyl vinyl ketone (4.1 g, 59 mmol) among with a trace of hydroquinone (*ca.* 5 mg) in benzene (60 ml) was refluxed for 23 h. After cooling unreacted cyclopentanedione was recovered by filtration and washed with benzene (10 ml); (220 mg, 22% recovery). The solvent and excess methyl vinyl ketone were removed under vacuum, and the residue was eluted on a column of silica gel (20% ether in benzene) to give the dione **2** (750 mg, 53%) as an oil. **Analysis:** Found: C, 51.0; H, 4.7; F, 24.4 $C_{10}H_{11}F_3O_3$ requires C, 50.9; H, 4.7; F,24.1%. $\upsilon_{max}(CCl_4)$ 1735 and 1710 cm^{-1}; $\delta_F(CDCl_3)$ -69.3 p.p.m; $\delta_H(CDCl_3)$ 2.09 (3H, s, *Me*), 2.17 and 2.68 (4H, *CH*$_2$*CH*$_2$*COMe*) 2.93 p.p.m. (4H, s, *ring-CH*$_2$); $\delta_C(CDCl_3)$ 209.1 (*COMe*), 205.8 (*ring CO*), 122.5 (*CF*$_3$, J_{CF} 284 Hz), 59.7 (*2-C*, J_{CF} 23 Hz), 36.2 (*CH*$_2$*COMe*), 36.5 (*ring-CH*$_2$), 30.0 (*CH*$_3$) and 21.6 p.p.m. (*MeCOCH*$_2$*CH*$_2$, J_{CF} 2 Hz); **m/z** 236 ($M^{+\cdot}$, 1%) and 43 (100%).

2,3,3a,4,7,7a-Hexahydro-3a(β)-hydroxy-7a-trifluoromethyl-*1H*-indene-1,5(6*H*)-dione

a: with (±) proline

A mixture of 2-(3-oxobutyl)-2-trifluoromethyl cyclopentane-1,3-dione **2** (700 mg, 2.9 mmol) and proline (340 mg,2.9mmol) in acetonitrile (5 ml) was stirred for 27 h under an inert atmosphere. The solvent was removed and the brown residue was chromatographed on

silica gel using 20% ether in methylene chloride as eluant to give 350 mg of yellow crystals which were recrystallized from ether to give the (±) ketol 3 as a white solid (250 mg, 35%), which had **m.p.** 132 - 133°C; **Analysis:** Found: C, 50.9; H, 4.7; F, 24.4 $C_{10}H_{11}F_3O_3$ requires C, 50.9; H, 4.7; F, 24.1%; $\upsilon_{max}(CHCl_3)$ 3590 (sharp), 3380(broad), 1755 and 1720cm^{-1}; $\delta_F(CDCl_3)$ -63.4 p.p.m.; $\delta_H(CDCl_3)$ 2.84 (1H, $H_{4\beta}$, $J_{4\alpha,4\beta}$ 15.1 Hz), 2.71 (1H, $H_{2\alpha}$, $J_{2\alpha,2\beta}$ 18.7, $J_{2\alpha,3\alpha}$ 9.3, $J_{2\alpha,3\beta}$ 10.1 Hz), 2.52 (1H), 2.36 (1H, *OH*), 2.34 (1H), 2.08 (1H, $H_{3\alpha}$, $J_{3\alpha,3\beta}$ 14.2 Hz), 1.95 (1H, $H_{3\beta}$) and 1.8 - 1.6 p.p.m. (2H) ; **m/z** 236 ($M^{+\cdot}$, 100%).

b: with S(-) proline

In the same way the (+) ketol 3 was obtained from S(-) proline and had **m.p.** 127 - 128°C (from ether); α_D^{25} +43.7° (c = 0.45, $CHCl_3$).

2,3,7,7a-Tetrahydro-7a-trifluoromethyl-*1H*-indene-1,5-(*6H*)-dione

a: from (±) ketol

A solution of the (±) ketol 3 (185 mg, 0.78 mmol) was refluxed in benzene (30 ml, preheated bath) containing toluene-p-sulphonic acid (5 mg). The progress of the reaction was followed by tlc. After 1 h, the solvent was removed, the residue was applied to a column of silica gel and eluted with 20% ether in methylene chloride. The semi-solid product thus obtained (140 mg) was sublimed (50°C, 0.15 kPa) to give the (±) unsaturated ketone 4 (100 mg, 60 %); **m.p.** 62 - 63°C; **Analysis:** Found: C, 55.0; H, 4.3 $C_{10}H_9F_3O_2$ requires C, 55.1; H, 4.2 %; $\upsilon_{max}(CHCl_3)$ 1760 and 1675 cm^{-1}; $\delta_F(CDCl_3)$ -67.3 p.p.m.; $\delta_H(C_6D_6)$ 5.77 p.p.m. (1H, *H-4*, $J_{3\alpha,4}$ 2.4 Hz), 2.3 - 1.7 (6H), 1.61 (1H, $H_{2\beta}$, $J_{2\alpha,2\beta}$ 18.4, $J_{2\beta,3\alpha}$ 9.2, $J_{2\beta,3\beta}$ 9.2 Hz), and 1.15 p.p.m. (1H); $\delta_C(CDCl_3)$ 207.2 (*C1*), 196.1 (*C5*), 157.2 (*C3a*), 128.6 (*C4*), 123.7 (*CF*$_3$, J_{CF} 286 Hz), 54.3 (*C7a*, J_{CF} 25 Hz), 36.7 (*C7*), 32.0 (*C2*, J_{CF} 1.2 Hz), 27.9 (*C3*), and 24.8 p.p.m. (*C7*, J_{CF} 1.7 Hz); **m/z** 218 ($M^{+\cdot}$, 100 %).

b: from (+) ketol

Dehydration of the (+) ketol 3 was conducted in the same manner as for the racemic counterpart. The optically active indenedione 4 was obtained as an oil which resisted crystallization and had α_D^{22} +268.2° (c = 0.51, $CHCl_3$).

ACKNOWLEDGMENTS

The author wishes to thank D^r. C. Wakselman for advice and interest in this work, and M^{rs}. R. Dorme for helpful technical assistance.

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