Journal of Fluorine Chemistry, 10 (1977) 447 – 454

Received: April 28, 1977

AROMATIC POLYFLUORO-COMPOUNDS - PART LVI [1]

THE SYNTHESIS OF POLYFLUORO-BENZHYDROLS AND-BENZOPHENONES

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ABSTRACT

The synthesis of some polyfluoro-benzhydrols and -benzophenones is described and their anti-fungal and anti-bacterial activity mentioned.

RESULTS AND DISCUSSION

It has been known for some time that decafluorobenzhydrol exhibits strong herbicidal activity against American crab grass [2]. During the course of our work on the synthesis of polyfluoroacridones [3] (involving the electrochemical oxidation of aminopolyfluorobenzophenones) we observed, during routine screening for biological activity using staphylococcus pyogenes, streptococcus faecelis, penicillium chrysogenum, mucor haemelis, aspergillus niger and saccharomyces cerevesiae, that both polyfluoro-benzhydrols and -benzophenones possessed *in vitro* anti-bacterial and anti-fungal properties. Further, the results suggested that incorporation of an electronegative group into one or both of the aromatic rings might usefully increase this activity. Thus while benzophenone and 2-aminononafluorobenzophenone were inactive, 2H-nonafluorobenzophenone, octafluorobenzophenone and 2-nitrononafluorobenzophenone were all active against various of the organisms listed above. We therefore decided to attempt the synthesis of fluorinated benzhydrols and benzophenones with trifluoromethyl- and carboxy-groups substituted in the ring.

The starting point of the syntheses was 4H-heptafluorotoluene [4], which was converted to the perfluorotolyl magnesium bromide by reaction with ethyl magnesium bromide in ether/tetrahydrofuran (THF). Treatment of this with ethyl formate (0.5 mole/mole) afforded (after purification), 4,4'-bis(trifluoromethyl)octafluorobenzhydrol (I) *(identified by chemical analysis and the usual spectroscopic techniques). Reaction* of the perfluorotolyl magnesium bromide with pentafluorobenzaldehyde in the customary way gave 4-trifluoromethylnonafluorobenzhydrol (II), and with benzaldehyde itself the grignard reagent formed 4-trifluoromethyl-2,3,5,6-tetrafluorobenzhydrol (III). The structures of both of these were confirmed by the usual methods.

The benzhydrols were then oxidized with chromium trioxide in glacial acetic acid to afford in high yield the corresponding polyfluorobenzophenones, viz:- 4,4'-bis(trifluoromethyl)octafluoro-, 4-trifluoromethylnonafluoro- and 4-trifluoromethyl-2,3,5,6-tetrafluoro-benzophenone (IV, V and VI respectively). All of these had correct chemical analyses and consistent u.v., i.r., and n.m.r. spectra.

Finally, 4,4'-bis(trifluoromethyl)octafluoro- and 4-trifluoromethylnonafluorobenzophenone (IV and V) were heated with oleum as previously described [5] to hydrolyse the trifluoromethyl- to carboxy- groups. The 4-trifluoromethyl-2,3,5,6-tetrafluorobenzophenone was not reacted in this way in view of the likelihood of sulphonation of the non-fluorinated aromatic ring. Thus, from (IV) was obtained 4,4'-dicarboxyoctafluorobenzophenone (VII) and from (V), 4-carboxynonafluorobenzophenone (VIII), both in high yield, the structures being confirmed by the usual methods.

In vitro testing of these compounds using both bacterial and fungal organisms confirmed the anticipated higher activity expected of trifluoromethyl-substituted compounds, particularly the benzhydrols, although the carboxy-fluorobenzophenones were inactive. Compounds (I) and (II) in particular were active against a range of fungal organisms *in vitro*: unfortunately *in vivo* testing showed that the activity was not maintained.

EXPERIMENTAL

4,4'-Bis(trifluoromethyl)octafluorobenzhydrol (I)

4H-Heptafluorotoluene [4] (8.8 g), ether (10 cm^3) and dry THF (10 cm^3) were stirred at 0° and a solution of ethyl magnesium bromide in ether, prepared from ethyl bromide (6.58 g) and magnesium (1.46 g), added slowly. When ethane evolution ceased the solution was warmed to room temperature, ethyl formate (1.6 g) in ether (10 cm^3) added, and the mixture stirred for 36 h. The mixture was acidified (4N HCl, 50 cm^3), the ether layer separated and the aqueous residue ether extracted (50 cm^3). The combined ether solutions were dried ($MgSO_4$) and evaporated to a residue (8.35 g) which solidified on standing. The solid was sublimed at 125 - 130° (19 mm Hg) to a crystalline solid (6.55 g), a portion (1.0 g) of which was resublimed 105 - 110° (19 mm Hg) to afford 4,4'-bis(trifluoromethyl)octafluorobenzhydrol (I), (nc) (0.8 g) m.p. 75 - 76° (Found: C, 38.5; H, 0.8; F, 57.5. $C_{15}H_2F_{14}O$

requires: C, 38.8; H, 0.4; F, 57.3%); λ_{max} 280 nm (ϵ_{max} 5.05 x 10^3); ν_{max} (nujol) 3380 (OH) and 1490 cm^{-1} (fluoroaromatic ring); ϕ 57.5 (3F, tr J 21.9 Hz, CF_3-) 139.5 (2F, m, F-3,5) and 142.3 (2F, m, F-2,6); δ 3.43 (1H, s, -OH) and 6.59 (1H, s, > C$\underline{H}$OH).

4-Trifluoromethylnonafluorobenzhydrol (II)

4H-Heptafluorotoluene (5.5 g) was transmetallated as described above and on completion of the reaction pentafluorobenzaldehyde (4.9 g) in ether (10 cm^3) added and the mixture stirred for 14 h. The reaction mixture was then worked up as described above and evaporated to a residue (8.53 g) which was distilled (0.5 mm Hg) to give (i) a mixture of THF and pentafluorobenzaldehyde (1.6 g) and (ii) an oil (6.88 g) which solidified on standing. A portion (2.0 g) of the solid was decolourized with charcoal and recrystallized from petroleum (b.p. 60 - 80°) to afford 4-trifluoromethylnonafluorobenzhydrol (II) (nc), (0.82 g) m.p. 56 - 57° (Found: C, 40.7; H, 0.7; F, 55.6. $C_{14}H_2F_{12}O$ requires C, 40.6; H, 0.5; F, 55.1%); λ_{max} 247.5 nm (ϵ_{max} 2.92 x 10^3); ν_{max} (nujol) 3420 (OH) and 1490 cm^{-1} (fluoroaromatic ring); ϕ56.5 (3F, tr J 21.9, CF_3-), 140.8 (2F, m, F-3,5), 142.8 (4F, m, F-2,6,2',6'), 155.9 (1F, tr J 20.2 Hz, F-4') and 163.8 (2F, m, F-3',5'); δ 6.09 (1H, brs, -OH) and 6.73 (1H, s, > C$\underline{H}$OH).

4-Trifluoromethyl-2,3,5,6-tetrafluorobenzhydrol (III)

4H-Heptafluorotoluene (5.5 g) was transmetallated as above and freshly distilled benzaldehyde (2.70 g) in ether (20 cm^3) added slowly (30 mins) and stirred for 14 h. The product was worked up as above to afford a residue (8.5 g) which crystallized on standing. A portion (1.5 g) of the solid (7.5 g) was recrystallized from petroleum (b.p. 60 - 80°) to give 4-trifluoromethyl-2,3,5,6-tetrafluorobenzhydrol (III) (nc) (0.65) m.p. 88° (Found: C, 52.4; H, 2.5; F, 40.6. $C_{14}H_7F_7O$ requires: C, 51.9; H, 2.2; F, 41.0%); λ_{max} 277 nm (ϵ_{max} 2.54 x 10^3); ν_{max} 3250 (OH) and 1490 cm^{-1} (fluoroaromatic ring); ϕ 57.2 (3F, tr J 22.6 Hz, CF_3-) and 141.6 (4F, m, aryl F); δ 4.71 (1H, brs, OH), 6.25 (1H, s, > C<u>H</u>OH) and 7.32 (5H, m, aryl H).

4,4'-Bis(trifluoromethyl)octafluorobenzophenone (IV)

To chromium trioxide (10.0 g) in glacial acetic acid (40 cm^3) was added 4,4'-bis(trifluoromethyl)octafluorobenzhydrol (I) (2.32 g) and the mixture refluxed for 10 min. The mixture was then poured into ice-water (500 cm^3) and filtered to afford a solid (1.84 g) a portion (1.5 g) of which was recrystallized from perfluoro-p-dimethylcyclohexane to give 4,4'-bis(trifluoromethyl)octafluorobenzophenone (IV) (nc) (0.97 g), m.p. 125 - 126° (Found: C, 39.1; F, 57.4. $C_{15}F_{14}O$ requires C, 39.0; F, 57.6%); λ_{max} 234.5 nm (ϵ_{max} 1.28 x 10^4); ν_{max} (nujol) 1705 (> C = O) and 1490 cm^{-1} (fluoroaromatic ring); ϕ 56.9 (3F, tr J 21.9 Hz, CF_3-), 138.8 - 141.0 (4F, m, F-2,3,5,6).

4-Trifluoromethylnonafluorobenzophenone (V)

Chromium trioxide (12.0 g), glacial acetic acid (40 cm^3) and 4-trifluoromethylnonafluorobenzhydrol (II) (3.15 g) were refluxed for 15 mins and the reaction mixture worked up as described above to afford a solid product (2.16 g). A portion (1.6 g) of this was recrystallized from perfluoro-p-dimethylcyclohexane to give 4-trifluoromethylnonafluorobenzophenone (V), (nc) (0.79 g) m.p. 86 - 87° (Found: C, 40.9; F, 55.3. $C_{14}F_{12}O$ requires C, 40.8; F, 55.3%); λ_{max} 243.5

(ϵ_{max} 1.28 x 10^{4}) and 290 nm (ϵ_{max} 3.42 x 10^{3}): ν_{max} (nujol) 1695 (>C = O) and 1495 cm^{-1} (fluoroaromatic ring); ϕ 56.9 (3F, tr J 20.8 Hz, CF_3-), 139.6 (2F, m, F-3,5), 141.4 (4F, m, F-2,6,2',6'), 146.7 (1F, tr J 19.5 Hz, F-4') and 161.2 (2F, m, F-3',5').

4-Trifluoromethyl-2,3,5,6-tetrafluorobenzophenone(VI)

Chromium trioxide (12.0 g), glacial acetic acid (40 cm^{3}) and 4-trifluoromethyl-2,3,5,6-tetrafluorobenzhydrol(III)(3.24 g)were refluxed for 15 min. The reaction mixture was worked up as previously described to give a product (2.1 g). A portion (1.5 g) was decolourized with charcoal and recrystallized from perfluoro-*p*-dimethylcyclohexane to afford 4-trifluoromethyl-2,3,5,6-tetrafluorobenzophenone (VI) (nc) (1.0 g) m.p. 31.5 - 32.5° (Found: C, 52.7; F, 41.6. $C_{14}H_{5}F_{7}O$ requires C, 52.2; F, 41.3%); λ_{max} 260 nm (ϵ_{max} = 1.84 x 10^{4}); ν_{max} (nujol) 1685 (>C = O) and 1485 cm^{-1} (fluoroaromatic ring); ϕ 56.5 (3F, tr J 22.0 Hz, CF_3-) and 140.3 (4F, m, aryl F); δ 7.93 (m, aryl H).

4,4'-Dicarboxyoctafluorobenzophenone(VII)

A mixture of fuming sulphuric acid (30% SO_3, 10 cm^{3}) and 4,4'-bis(trifluoromethyl)octafluorobenzophenone(IV) (2.4 g) was heated at 100° in a sealed tube for 20 h. The reaction mixture was then poured into ice-water (250 cm^{3}), the solution ether extracted (5 x 100 cm^{3}), the combined extracts dried ($Mg\ SO_4$) and evaporated to a residue (2.4 g). A portion (1.6 g) of the residue was recrystallized from ethanol-water to afford 4,4'-dicarboxyoctafluorobenzophenone(VII) (nc) (0.9 g) m.p. (with decomp) 290-295° (Found: C, 43.1, H, 0.8; F, 37.1. $C_{15}H_{2}F_{8}O_{5}$ requires C, 43.5; H, 0.5; F, 36.7%); λ_{max} 250 nm (ϵ_{max} 1.49 x

10^4); ν_{max} (nujol) 3300 - 2500 (OH), 1705 ($>C = O$) and 1480 cm^{-1} (fluoroaromatic ring); ϕ 139.9 (m, F-3,5) and 142.4 (m, F-2,6) of equal intensity; δ 2.09 (s, -COO<u>H</u>).

4-Carboxynonafluorobenzophenone(VIII)

Fuming sulphuric acid (30% SO_3, 10 cm^3) and 4-trifluoromethylnonafluorobenzophenone(V) (1.70 g) were treated as described above and worked up as for (VII) to give a solid (1.6 g), a portion (1.3 g) of which was recrystallized from ethanol-water to afford 4-carboxynonafluorobenzophenone(VIII), (nc) (1.1 g) (Found: C, 43.3; H, 0.6; F, 43.7. $C_{14}HF_9O_3$ requires: C, 43.3; H, 0.3; F, 44.1%); λ_{max} 254 nm (ϵ_{max} 1.34 x 10^4); ν_{max} 3300 - 2300 (OH), 1720 ($>C = O$) and 1490 cm^{-1} (fluoroaromatic ring); ϕ 139.5 (2F, m, F-3,5), 142.1 (4F, m, F-2,6,2',6'), 146.8 (1F, tr of tr J 18.8 and 5.2 Hz, F-4') and 161.0 (2F, m, F-3',5'); δ 5.34 (s, -COO<u>H</u>).

ACKNOWLEDGEMENTS

Thanks are due to Dr. J. Burdon for n.m.r. spectroscopy, to Mr. E.T.J. Chelton and I.C.I. (Plant Protection) for biological screening tests and to Imperial Smelting Corporation for a maintenance grant (G.E.D.).

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