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NOTES

Synthesis of 3-[D_7]isopropylbenzo-2-thia-1,3-diazinon-(4)-2,2-dioxide ([D_7]-bentazone)

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Summary

[D_7]bentazone (95 atom% D) was synthesized from methyl antranilate and [D_7]isopropylsulfamoyl chloride. [D_7]isopropylsulfamoyl chloride was prepared by treatment of [D_7]isopropyl amine with chlorosulfonic acid and phosphorous pentachloride. The overall yield from [D_7]isopropyl amine was 7%.

Introduction

Bentazone is a frequently used herbicide which is not easily biodegradable. Bentazone is one of the herbicides that was recently found in rainwater (1). Bentazone also occurs in drinking water (2). In order to monitor drinking water for the presence of bentazone a reliable and quantitative method had to be developed. For this purposes isotope-dilution gas chromatography-mass spectrometry (ID-GC-MS) is the method of choice. This method requires an isotopically labelled internal standard. In this paper the synthesis of such a standard is reported.

Key words: [D_7]bentazone, [D_7]isopropylsulfamoyl chloride

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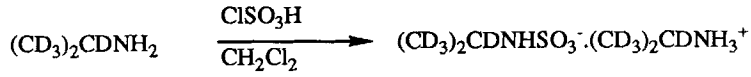
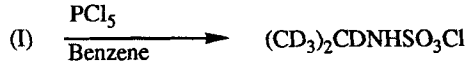
Results and discussion

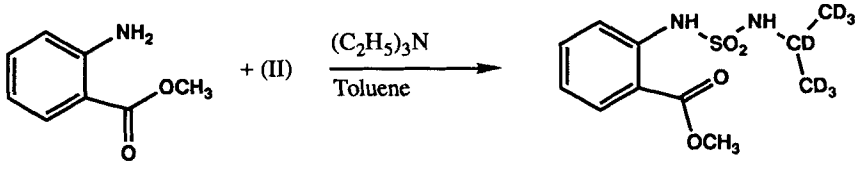
Bentazone-[D_7] (IV) was prepared according to the following scheme:



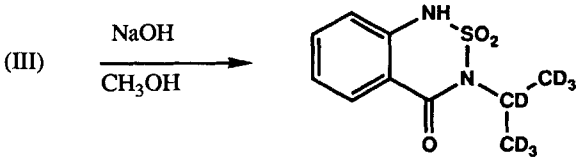
(I)



(II)



(III)



Bentazone-D_7 (IV)

Isopropyl[D_7]sulfamoyl chloride (II) was prepared according to Kloek and Leschinsky (3). In our hands the isopropyl[D_7]ammonium salt of isopropyl[D_7]sulfamic acid (I) did not precipitate from the dichloromethane solution.The crude product obtained after evaporating the solution was used as such in the subsequent preparation of the corresponding isopropyl[D_7]sulfamoyl chloride(II). The procedure to prepare [D_7]bentazone is an adaptation of the method described by Mangold *et al* (4) : after treatment of methyl anthranilate with sulfamoyl chloride (II), the intermediate sulfonamide product (III) was isolated, and treated with sodium hydroxide in methanol at 40 °C . After removal of the solvent, [D_7]bentazone precipitated upon acidification. Pure [D_7]bentazone was obtained by recrystallisation from aqueous ethanol. The product was characterised by its melting point, chromatographic (TLC) and spectroscopic (IR, NMR, MS) methods. From MS measurements the isotopic purity was estimated to be 95 atom%. This labelled material will be used as an internal standard in an ID-GC-MS method to quantify bentazone in various water samples.

Experimental

IR spectra were taken using a Bruker FTIR type IFS 85. NMR spectra were recorded on a JEOL GSX 270 instrument in $CDCl_3$ using tetramethyl silane (TMS) as an internal standard (δ=0.0 ppm). Melting points were determined on a Mettler FP62 using a heating rate of 1° per minute. GC-MS experiments using pentafluorbenzylated bentazone and [D_7]bentazone were performed on a Finnigan 4500 GC-MS instrument in Negative Chemical Ionisation (NCI) (CH_4) mode (column: DB1701 30m*0.262mm*df=0.25µm, injection temp. 250°C, column temp.70°C (1 min.)-20°C/min.-280°C, carrier gas helium). [D_7]isopropyl amine was obtained from MSD Isotopes Division of Merck Frosst Canada inc..

[D_7]Isopropylsulfamoyl chloride (II)

To a cooled (0 °C) solution of [D_7]isopropyl amine (5 g, 0.076 moles) in dry dichloromethane (100 ml) a solution of chlorosulfonic acid (3.16 g, 0.027 moles) in dry dichloromethane (50 ml) was cautiously added. After the addition was complete the resulting solution was stirred for 48 hours and concentrated *in vacuo* using a rotary evaporator. The residue was purified by bulb to bulb distillation to afford [D_7]isopropylsulfamoyl chloride (2.1 g, 40%) as a colourless liquid.

[D_7]Bentazone

To a stirred solution of methyl antranilate (2.1 g, 0.016 moles) and triethyl amine (1.4 g, 0.014 moles) in toluene (10 ml) was added [D_7]isopropylsulfamoyl chloride (2.1 g, 0.013 moles) while keeping the temperature of the reaction mixture at 20-40 °C using an ice/water bath. The mixture was stirred for an additional hour at 60 °C. The solvent was removed by distillation under reduced pressure to give the intermediate sulfonamide (III) as a white solid (IR (KBr, cm^{-1}) 3300,3202 (N-H), 2840 (O-CH_3), 2250 (C-D) 1680 (C=O), 1316 (SO_2), 1266 (SO_2, C-O); ^{1}H-NMR ($CDCl_3$) δ10.5 (s, 1H), 7.05-8.07 (m, 4H), 3.95 ppm (s,3H)). The crude product was dissolved in a solution of sodium hydroxide (2.1 g, 0.03 moles) in methanol (50 ml). The resulting mixture was stirred for 48 hours at 40 °C. Methanol was removed using a rotary evaporator, water (80 ml) was added, and the solution acidified with concentrated sulfuric acid to pH 1. The solid that precipitated was filtered off, and dissolved in ethanol. After the addition of a little charcoal the mixture was refluxed for 15 minutes. The suspension was filtered to give a colourless solution. Addition of water and cooling at 6 °C overnight gave white crystals. Washing with cold water and drying *in vacuo* afforded pure [D_7]bentazone (1.3 g, 7% overall yield from [D_7]isopropyl amine, m.p. 140-140.6 °C). IR (KBr, cm^{-1}) 3183 (N-H), 2250 (C-D), 1642 (C=O, amide 1), 1360, 1318 (SO_2), 750 (C-H ar).

^{1}H-NMR ($CDCl_3$) δ8.17 (m, 1H), 7.4 (m, 2H), 7.2 (bs, 1H), 7.09 (m, 1H), no absorptions at 5.0 and 1.59 ppm).
MS(NCI) spectra of the PFB drivatives of bentazone and [D_7]bentazone showed very intense peaks at fragment ion [M-181]$^-$. These fragments at m/z 239 and 246, respectively, occur by electron captive dissociation of the ionised molecule with splitting off of the $C_6F_5CH_2$ part. From the spectrum a 95atom% deuteration grade was calculated.

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References

1 Richards, R.P., Kramer, J.W., Baker, J.W., and Krieger, K.A., Nature 327 129 (1987)
2 Smeenk, J.G.M.M., Lindhout, R.C., Snoek, O.I., H_2O 21 : 183 (1988)
3 Kloek, J.A., Leschinsky, K.L., J.Org.Chem., 41 : 4028 (1976)
4 Mangold, D., Konig, K., Hamprecht, G, Ger.Offen., 2,357,063 (1975)