Original Research Article

Synthesis of icosadeuterio-benzopinacol (Benzopinacol-d20)

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ARTICLE INFORMATION

ABSTRACT

This work reports on synthesis of high yield (92%) of isosadeuterio-benzopinacol (benzopinacol-d20) *via* photo-reductive dimerization of benzophenone-d10. The latter compound was obtained using an improved method to achieve a material with high isotopic purity (> 99%). This material can be served for calibration of mass spectrometric assays. In this study, it was also observed that benzophenone-d10 reacts faster than its natural abundance counterpart. However, elucidating the origin of this phenomenon will require additional work.

Graphical Abstract

Introduction

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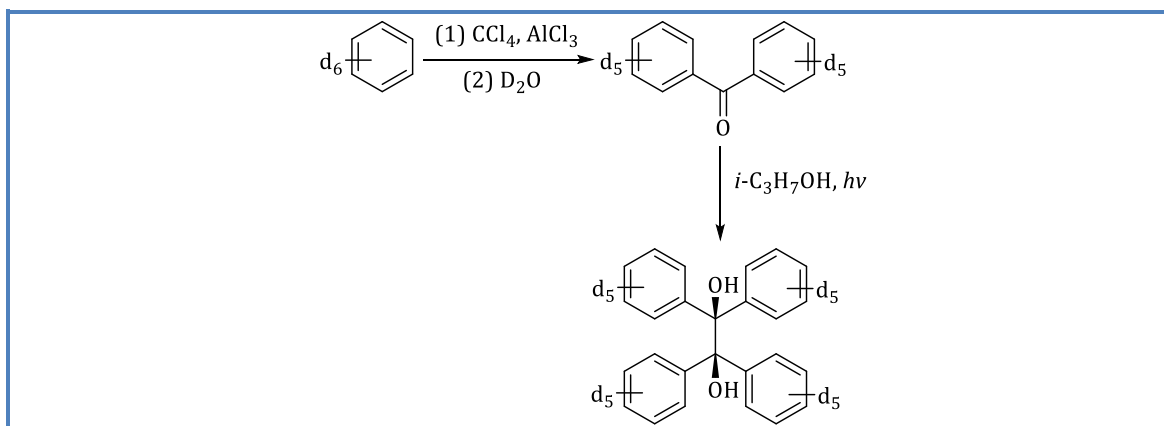
While photochemistry has found an importantly growing position in the realm of organic chemistry, photoreductive processes have been less exploited due to the cost of equipment and the poor selectivity of most reactions, which leads to multiple sub-products. An exception to this is the photoreduction of carbon dioxide, which becomes a critical actuality owing to stringent ecological problems in earth atmosphere [1].

The photochemical behavior of ketoprofen which is badly known for producing photo-induced skin burns in patients treating painful joint with a gel containing this active ingredient [2, 3]. In this regard, we undertook various experiments to explain the mechanisms underlying this exceptional photo-toxicity [4–7]. In short, upon exposure to natural-ambient sun light, the n-pi* band of the ketonic carbonyl (C=O) is excited and gives rise to a triplet state which readily reacts with triplet ground state dioxygen to generate reactive oxygen species (ROS) [8, 9]. In this context, we now want to report on the peculiar photochemical behavior of decadeuterio-benzophenone (BZP-d10). Along this line, we had first to synthesize icosadeuterio-benzopinacol (benzopinacol-d20) as a reference internal standard for calibrating the mass spectrometric assay of benzopinacol in order to study the kinetics of the photo-dimerization of benzophenone in different biological environments. In this research study, we report first the synthesis of benzophenone-d10 using an improved procedure to obtain a material endowed with high isotopic content starting from commercially available hexadeuteriobenzene (benzene-d6).

Experimental Section

General procedures

Melting points (uncorrected) determined in open capillary tubes using a Büchi SMP20 melting point apparatus. IR spectra were recorded using a fine dispersion of the product in anhydrous potassium bromide disks by means of a Perkin-Elmer Model 297 spectrometer. The 1H- and 13C-NMR spectra (Bruker AM400 spectrometer) reported in the delta scale were recorded under ambient conditions using tetramethylsilane (TMS) as internal standard reference. All compounds reported had IR, 1H- and 13C-NMR, MS, and elemental analysis data consistent with their structure. The experimental elemental analysis were found within 0.4% of the calculated values. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60F 254, E. Merck, Darmstadt, ref. 5735). All the compounds were found chromatographically homogenous in two standard solvents, i.e. acetone/toluene/cyclohexane (5:2:3, v/v/v) and methanol/chloroform equilibrated with traces of ammonia (1:9, v/v). All reagents were purchased from Sigma/Aldrich, excepted for aluminum trichloride from Merck.

Decadeuterio-benzophenone (BZP-d10)

In a flame-dried DCl-pretreated 250-mL two-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a separator funnel, a thermometer, and a reflux condenser connected with a trap for absorbing the hydrogen chloride evolved, are placed 45.5 g (340 mmol) of analytical grade anhydrous aluminum chloride (Merck) and 100 mL (1.02 mol) of analytical grade dry carbon tetrachloride (Aldrich). The flask is surrounded by an ice bath. The mechanical stirrer is started and when the temperature of the carbon tetrachloride has dropped to 10–15°, 15 mL of dry benzene-d6 (Aldrich) is added in one portion. The reaction begins immediately as indicated by evolution of hydrogen chloride vapors and rising temperature. As soon as the reaction has started, salt and little acetone are

added to the ice bath in order to get a more efficient cooling. As the temperature was under control, a mixture of 45 mL (amounting therefore a total of 0.67 mol) of benzene-d6 and 55 mL (for a total of 60 mL, i.e. 1.45 mol) of carbon tetrachloride is run in at such a rate that the temperature is maintained around 5-10°C. This addition was completed after 60 min. The stirring is continued for about 3 h after the benzene-carbon tetrachloride solution has been added, while the temperature is held around 10°. The stirring is then discontinued and the mixture is allowed to stand overnight over which time the mixture is allowed to come slowly to room temperature. The stirrer is then started and 100 mL of distilled water is slowly added. Some external cooling was used to be able to add water as rapidly as possible. The carbon tetrachloride was distilled and collected during this part of the procedure. The reaction mixture is then heated to remove entirely the excess of carbon tetrachloride and to hydrolyze the benzophenone dichloride to benzophenone. The carbon tetrachloride comes over in about 30 min; however, the steam distillation is continued for about 1 h to insure complete hydrolysis. The upper benzophenone layer was then separated from the aqueous layer by decantation of an ethyl acetate-added solution. The organic solution of benzophenone-d10 were transferred to a Claisen distillation flask and the product was distilled under reduced pressure. The yield was 59.5 g of a product slowly solidifying which upon trituration with n-pentane gave a white crystalline solid (Fus 52–54°C, yield = 92% based on benzene-d6). MS (direct introduction) m/z 192 (57%, molecular ion), 110 (100%, Phd5C=O), 82 (Phd5); IR (Kbr disk, cm-1) 1712 (stretching C=O), 1650, 1600, 760, 720, 690; UV (MeOH) 342 nm (C=O band III).

13C-NMR (CDCl3, 10 % m/v) 196.63 (C=O); 137.41 (ipso-carbon); 132.07 (para-carbon, J1 = 35 Hz); 129.66 (ortho-carbon, J1 = 35 Hz); 127.93 (meta-carbon, J1 = 35 Hz)

Icosadeuterio-benzopinacol (Benzopinacol-d20)

A mixture of 1.54 g (0.82 mmol) of benzophenone-d10, 30 µL of glacial acetic acid (syringe), and 10.0 mL of analytical grade of 2-propanol was prepared in a cylindrical flat-bottomed glass stoppered dry flask at room temperature. Warming up the flask was necessary to ensure the complete dissolution. The flask was filled up almost to the stopper by adding little 2-propanol and tightly closed. After 6 h of irradiation to bright sun light, crystals of benzopinacol-d20 begin to separate already within the first hour and sediment at the bottom of the flask; after 6 h of light exposure, the flask is filled with white thin crystals of benzopinacol-d20. Benzophenone-d10 is no longer detectable by TLC. The solution is chilled in a refrigerator overnight and the crystalline product is filtered with suction over a Buchner funnel, washed with a small amount of ice-cold 2-propanol, and allowed to dry in a ventilated oven thermostat at 90°C. The filtrate is preserved for subsequent eventual operations. The yield of an analytical pure grade of benzopinacol, m.p. 192–193°C, is 1.42 g (92% yield). On the basis of its TLC behavior and 1H- and 13C-NMR spectra, this product is judged pure enough for further applications. It may be recrystallized with some loss in absolute ethanol. After cooling in a refrigerator and filtering there is obtained 1.15 g of a nice crystalline analytical product. The melting point is not significantly affected by this additional recrystallization.

13C-NMR 143(ipso-carbon); 127.3 (ortho-carbon) ; 127.8 (meta-carbon) ; 124.8 (para-carbon) ; 99.1 (C-OH peri-carbon)

Results and Discussion

The most convergent three-component synthesis makes use of the twin-alkylation Friedel-Crafts reaction of hexadeuterio-benzene with carbon tetrachloride at the presence of the dry aluminum chloride powder (Figure 1) [10, 11].

Figure 1. Synthesis of Benzopinacol-d20**.**
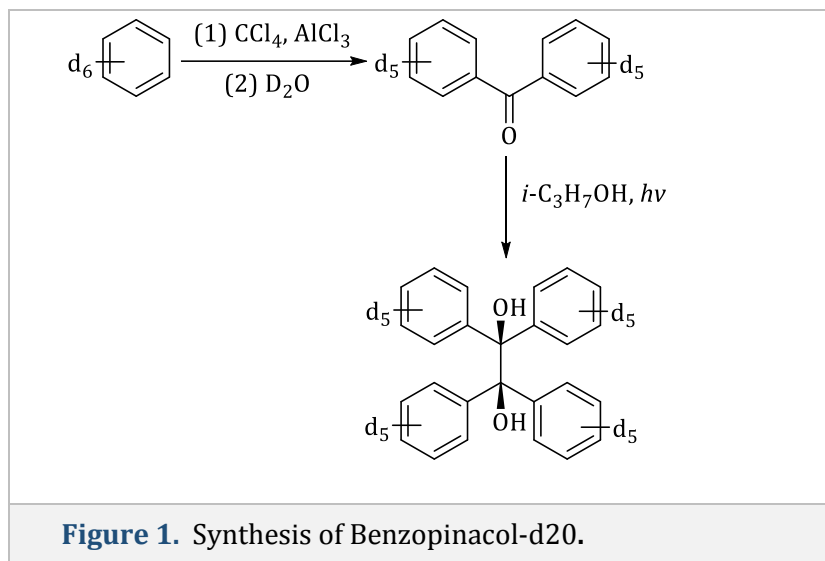
This reaction was selected among others because it is endowed with high atom-economy and proceeds in high yield (92%). After different trials and errors before finding the clue, we were disappointed by the deuterium enrichment found over the small scale syntheses (deuterium content around 91-94%). As a matter of fact, both principal reagents were found very dry by 1H-NMR and even after dried at 130°C for 24 h, the deuterium level remained sort of a disillusionment. By trapping the deuterio-hydrochloric acid (DCl) over our multiple initial trials in heavy water (D_2O), we obtained somehow gratis pro deo a D_2O-DCl solution (10%, w/w) which was used to give a thorough ultimate back-wash of the reaction glassware before the final drying [12]. This DCl pre-treatment of the glassware was found decisive in getting a satisfactory deuterium content and was therefore implemented for the large scale synthesis of decadeuterio-

benzophenone reported hereunder (see experimental section) [13]. In other words, the surface chemistry of glass is critical as it allows some sort of deuterium-protium isotopic scrambling. With high deuterium content in hands, we could proceed to the next step and synthesized the benzopinacol-d20.

Based on previous experience and relevant literature [14], we carried out the reductive dimerization of benzophenone-d10 in solution in 2-propanol under UV-VIS irradiation using natural-ambient sun light. The different reactions that reported hereunder were carried in Brussels, Belgium (Latitude: 50°51′01″ Nord, Longitude: 4°20′55″ East) in May 2018 during days of fair weather in the upper Northern Hemisphere. The light-catalyzed synthesis of icosabenzopinacol (benzopinacol-d20) is a classical example of photo-induced dismutation process in that benzophenone is reduced while 2-propanol is oxydized to acetone [15].

The reaction of benzophenone-d10 was carried out concomitantly in direct comparison with regular benzophenone TLC. To our pleasure and also astonishment, the reaction on the deuterated species (BZP-d10) was found in our hands by far much faster than the benzophenone of natural abundance. In effect, the reaction was complete with total disappearance of BZP-d10 in about 6 h while BZP required two sessions of 12 h (for a total thus of about 24 h). The higher susceptibility of benzophenone-d10 compared to its protio-counterpart is probably related to the fact that the carbonyl in the deuterated species is slightly more electron-rich as reflected by its downfield shielding in 13C-NMR (chemical shift difference 0.13 ppm). The resulting benzopinacol-d20 was found homogenous in TLC and conform with regard to MS, IR, and UV spectroscopic data.

As to the photochemical behavior of BZP-d10 [16], we investigated the origin of the acceleration of the coupling reaction. The results showed that, the morphological inspection of the UV-VIS spectrum of BZP-d10 did not reveal special features of the 340 nm n – pi* band III of the ketonic carbonyl [17]. Where there might be a difference is probably located in the 1Lb vibration bands situated in the 245-275 nm region but covered at least by other chromophores and therefore poorly readable. Molecular modeling studies (semi-empirical AM1 quantum mechanics) revealed a small but significant difference in the carbonyl-aromatic torsion angle (around 5°) which may affect the mesomeric effect transfer of electronic information from the aromatic rings to the carbonyl via poorer overlapping of the p orbitals. Altogether, at this level, these preliminary investigations were inconclusive which will require further close examination.

Conclusion

In this work, we reported the synthesis of high yield (92%) of icosadeuterio-benzopinacol (benzopinacol-d20) via photo-reductive dimerization of benzophenone-d10. The latter was synthesized using an improved method to obtain a material with high isotopic purity. This material can be served for the mass spectrometric assays. During this research, it was observed that, the benzophenone-d10 reacts faster than its natural abundance counterpart. Elucidating the origin of this phenomenon also may require additional evaluation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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