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Di[bis(4-methoxyphenyl)methyl]ether as dehydration product of 4,4'-dimethoxybenzhydrol under unusually mild conditions

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Summary – 4,4'-Dimethoxybenzhydrol **1b** was readily dehydrated by the isocyanate reagent **5** to furnish di[bis(4-methoxyphenyl)methyl] ether **4b**. This symmetrical ether was similarly obtained upon treatment of **1b** with diethylaminosulfur trifluoride (DAST).

diarylcarbinol / dehydration

Introduction

As part of a programme to develop new biomaterials from synthetic polymers, we investigated convenient routes to selectively functionalize the surface of poly(aryl ether ether ketone) (PEEK) in order to direct the interactions between the material and the biological environment. The reduced surface, PEEK-OH (fig 1), was obtained by treatment of polymer films with solutions of boron or aluminium hydrides [1, 2] and was considered as a versatile key intermediate for the design of derivatizations [2].

To define the proper conditions of the surface chemistry [3, 4], a model study was carried out using the commercially available 4,4'-dimethoxybenzhydrol **1b** as a representative substrate of the PEEK-OH repeated unit. This study led us to discover an unexpected dimerization reaction of the alcohol.

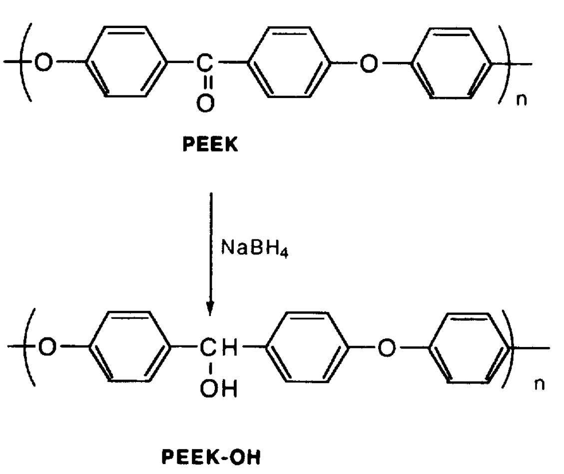

Fig 1. Reduction of PEEK film.

Results and Discussion

We were interested in the coupling of glycine to PEEK-OH in order to obtain a carboxylated surface. This could be formally realized in one step by using ethyl 2-isocyanatoacetate **2** as an electrophilic partner to react with the hydroxyl group of either the benzhydrol moiety of PEEK-OH or the model compounds **1** (fig 2).

The addition of isocyanates to alcohols has been extensively reviewed [5, 6]. This reaction readily produces stable urethanes and is usually catalyzed by tertiary amines or organometallic compounds like tin (IV) derivatives. We examined the reaction of 4,4'-dimethoxybenzhydrol **1b** under various experimental conditions in benzene or toluene solution; at room temperature or at 60°C; with one to three equivalents of reagent **2**; and without catalyst or in the presence of diaza[2.2.2]bicyclooctane (DABCO) or dibutyltin dilaurate (DBTDL) in the homogeneous phase. In all cases, the only isolated product was the symmetrical ether **4b**; the expected urethane **3b** could not be identified in the crude reaction mixtures. The dimer **4b** was fully characterized by standard spectroscopic methods (see *Experimental section*).

Thus, the cumulene **2** behaved as a mild dehydrating agent. This unexpected result led us to consider the reaction of benzhydrol **1a** under the same experimental conditions. In this case, the alcohol quantitatively added to the isocyanate **2** to give the stable urethane **3a** (fig 2).

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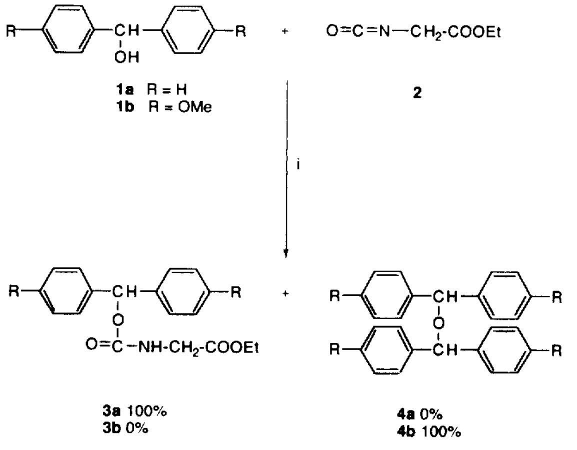


i = benzene, 20°C, 20 days; or toluene, 60°C, 10 days.

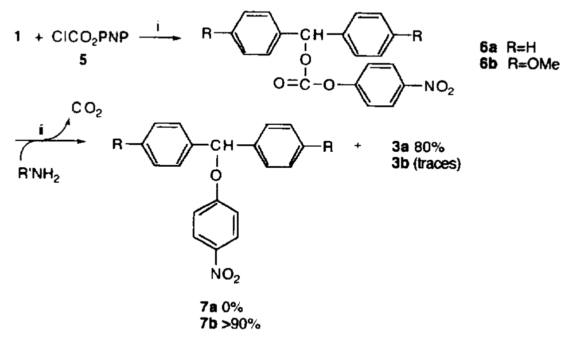
Fig 2. Reaction of diarylcarbinols with ethyl 2-isocyanatoacetate.

The reaction of **2** with the parent alcohol **1a** was a particularly slow process (several days), and so we assumed that the related reaction of **1b** also produced an adduct (**3b**) in a rate-limiting step. The transient species **3b** would then be used in a faster step involving the displacement of the carbamate substituent by unreacted alcohol. This nucleophilic substitution was favored by the presence of two electron-releasing groups (OMe) on the aromatic rings, which could stabilize a positive charge developing on the benzhydryl carbon atom of **3b**.

The formation of di[bis(4-methoxyphenyl)methyl] ether **4b** in rather modest yield was mentioned in the previous literature for the treatment of **1b** with large excesses of strong acids [7].

We envisaged an alternative two-step procedure for the coupling of glycine and other amine derivatives to PEEK-OH, *ie* the alcohol activation as (*p*-nitrophenyl)carbonate and the subsequent *p*-nitrophenoxide substitution by the appropriate NH_2-reagent. We were disappointed to find that the model carbonate **6b**, prepared by reaction of 4,4′-dimethoxybenzhydrol **1b** with *p*-nitrophenyl chloroformate **5** and pyridine in toluene, was highly unstable and decomposed in solution or in the pure phase, even at room temperature, to give carbon dioxide and [bis(4-methoxyphenyl)methyl] (4-nitrophenyl)ether **7b** (fig 3). The symmetrical ether **4b** could not be identified in the crude mixture; we concluded that *O*-acylation of **1b** with chloride **5** was much more rapid than nucleophilic substitution of intermediate **6b** by unreacted alcohol.

Once again, we observed that the presence of electron-releasing substituents on the benzhydryl moiety dramatically changed the reactivity of the alcohol derivatives. Indeed, the parent carbonate **6a** prepared in a similar manner was thermally stable and could be purified by column-chromatography. Moreover, **6a** reacted easily with amines to form a variety of carbamates (for instance, **3a**). In contrast, the treatment of a freshly

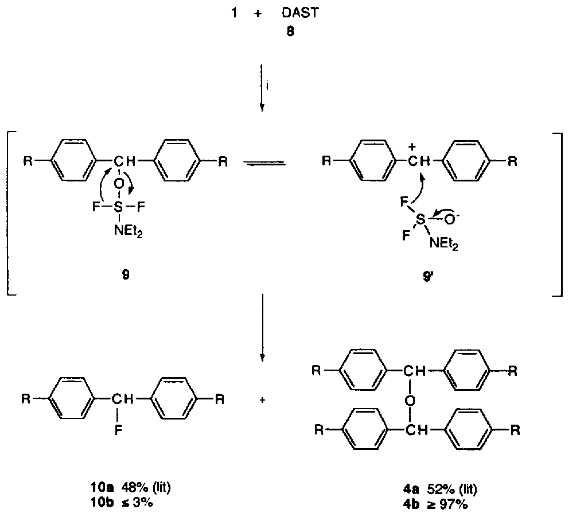


(i) toluene, pyridine, 20°C; (ii) toluene (or neat), 20°C

Fig 3. Reactions of (*p*-nitrophenyl)carbonates derived from diarylcarbinols.

prepared solution of **6b** with a series of amines (including ethyl glycinate) gave only traces of carbamates (**3b**), and the stable ether **7b** was always the major product.

Finally, we considered the possibility of PEEK-OH fluorination in order to produce a blood-repulsive hydrophobic surface. Diethylaminosulfur trifluoride (DAST) has been described as an excellent reagent for preparing fluorides from alcohols under mild conditions [8]. Treatment of 4,4′-dimethoxybenzhydrol **1b** with DAST in trichlorofluoromethane at low temperature gave the symmetrical ether **4b** as the main product and only traces (⩽ 3%) of the fluoride **10b** (identified by TLC and ^1H NMR spectroscopy of the crude mixture). The reactive intermediate **9** (fig 4) probably did not undergo internal collapse [9] to fluoride **10b**, but rapidly reacted with the starting alcohol **1b** (or decomposed into **9′** which was trapped by unreacted alcohol **1b**). The reaction of the parent alcohol **1a** with DAST was previously described by Johnson, who recovered an equimolar mixture of diphenylmethyl fluoride **10a** and bis(diphenylmethyl)ether **4a** [10].



(i) CCl_3F, - 60 °C to 20°C

Fig 4. Reaction of diarylcarbinols with DAST.

Conclusion

Our model study has shown the limitation of reactions involving electrophilic attack on the hydroxyl group of 4,4′-dimethoxybenzhydrol. Stable substitution products could not be obtained since the intermediates appeared to be highly sensitive towards nucleophilic displacement by unreacted alcohol. Thus, the net result was the quantitative formation of di[bis (4-methoxyphenyl)methyl]ether as an intermolecular dehydration product. This dimerization occurred under very mild conditions. Therefore, attempts to modify the polymer surface PEEK-OH by reaction with ethyl 2-isocyanatoacetate or with DAST would probably lead to some crosslinking of the macromolecular chains by ether bond formation. However, for steric reasons, the expected derivatizations of PEEK-OH could be competitive with crosslinking since the reactions occur at the solid interface. This assumption is currently under investigation.

Experimental section

Reagents (analytical grade) were supplied by Janssen Chimica or Aldrich, and used as received. The solvents were dried as follows and then distilled : benzene and toluene were dried over sodium; cyclohexane, ethyl acetate and dichloromethane were dried over phosphorus pentoxide. Trichlorofluoromethane was distilled under argon atmosphere. Merck silica gel 60 (70-230 mesh ASTM) was used for the column chromatography; the R_f values were determined on Merck silica-gel 60 TLC plates (F254, 0.2 mm; UV and I_2 detection). Melting points were uncorrected (electrothermal microscope). The IR spectra were taken with a Perkin-Elmer 1710 instrument fourier transform (infrared) spectrometer and calibrated with polystyrene (1 601 cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer in chloroform-d_3 with tetramethylsilane as internal standard. The mass spectra were obtained on a Varian MAT 44 instrument. The microanalyses were performed at the University College of London (Dr Alan Stones).

Di[bis(4-methoxyphenyl)methyl]ether, **4b** *(method A)*

A solution of 4,4′-dimethoxybenzhydrol **1b** (0.5 g, 2.04 mmol) and ethyl 2-isocyanatoacetate **2** (0.690 mL, 6.1 mmol) in toluene (15 mL) was heated at 60°C for 10 days, under an argon atmosphere. Concentration under vacuum and column chromatography on silica gel (CH_2Cl_2/hexane, 70:30) gave pure ether **4b**; yield 450 mg (94%).

R_f (CH_2Cl_2/EtOAc, 95:5) = 0.73.

Mp = 79-81°C.

IR (KBr) ν 3 004, 2 820, 1 531, 1 587 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 12H), 5.29 (s, 2H, C*H*-O), 6.84 (d, 8H, J = 8.7 Hz), 7.25 (d, 8H, J = 8.7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ 55.25, 78.86, 113.70, 128.45, 134.79, 158.8.

MS (EI) m/z (%) : 470 (M^+, 10), 243 (24), 227 (100), 135 (36).

Anal calc for $C_{30}H_{30}O_5$: C, 76.57%; H, 6.43%. Found : C, 76.72%; H, 6.50%.

Di[bis(4-methoxyphenyl)methyl]ether, **4b** *(method B)*

A solution of 4,4′-dimethoxybenzhydrol **1b** (1.22 g, 5 mmol) in $CFCl_3$ (15 mL) was cooled at −60°C (dry ice/acetone bath) and treated with DAST (0.92 mL, 7 mmol) in $CFCl_3$ (5 mL) under an argon atmosphere. The mixture was allowed to warm slowly to room temperature and stirred for 1 h at 20°C. Washing with 5% $NaHCO_3$ and then brine, drying over $MgSO_4$, concentration and column chromatography on silica gel yielded pure **4b**.

Ethyl N-[(diphenylmethoxy)carbonyl]glycinate **3a**

A solution of benzhydrol **1a** (0.664 g, 2.72 mmol) and ethyl 2-isocyanatoacetate **2** (0.967 mL, 8.85 mmol) in toluene (20 mL) was heated at 60°C during 7 days, under an argon atmosphere. Concentration under vacuum and column chromatography on silica gel (CH_2Cl_2/cyclohexane, 50:50) gave pure carbamate **3a**; yield 0.665 g (78%).

R_f (CH_2Cl_2) = 0.44.

IR (KBr) ν 3 336, 1 755, 1 698, 1 539 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 3.96 (d, 2H, J = 5.4 Hz, NH-C*H*$_2$), 4.20 (q, 2H, J = 7.1 Hz), 5.39 (t, 1H, J = 5.4 Hz, N*H*-CH$_2$), 6.80 (s, 1H, C*H*-O), 7.30 (br s, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 13.95, 42.70, 61.32, 77.77, 126.96, 127.74, 128.35, 140.28, 155.49, 169.82.

MS (EI) m/z 313 (M^+).

Anal calc for $C_{18}H_{19}NO_4$: C, 68.99%; H, 6.11%; N, 4.47%. Found : C, 69.00%; H, 6.17%; N, 4.37%.

[Bis(4-methoxyphenyl)methyl](4-nitrophenyl)ether **7b**

A solution of 4,4′-dimethoxybenzhydrol **1b** (0.5 g, 2.04 mmol) and pyridine (0.194 mL, 2.4 mmol) in toluene (10 mL) was treated with nitrophenyl chloroformate **5** (0.51 g, 2.4 mmol) in toluene (5 mL) for 2 h at 20°C. Filtration of pyridinium hydrochloride gave a solution of carbonate **6b** (IR ν 1 783 cm^{-1}). Concentration under vacuum (1 h, 30°C) led to decarboxylation. The 4-nitrophenyl ether **7b** could be purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 97.5:2.5).

R_f (CH_2Cl_2) = 0.13.

IR (CH_2Cl_2) ν 2 837, 1 609, 1 592, 1 513, 1 511, 1 493, 1 463, 1 442, 1 341, 1 301, 1 247, 1 174 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.82 (s, 6H), 6.27 (s, 1H, C*H*-O), 6.91 (d, 4H, J = 9.1 Hz), 7.02 (d, 2H, J = 9.3 Hz), 7.31 (d, 4H, J = 9.1 Hz), 8.15 (d, 2H, J = 9.3 Hz).

MS (EI) m/e (%) : 365 (M^+, 1), 272 (40), 227 (100), 139 (40).

Benzhydryl 4-nitrophenyl carbonate **6a**

A solution of benzhydrol **1a** (0.368 g, 2 mmol) and pyridine (0.194 mL, 2.4 mmol) in toluene (10 mL) was treated with nitrophenyl chloroformate **5** (0.51 g, 2.4 mmol) in toluene (5 mL) for 2 h at 20°C. Filtration, concentration and column chromatography on silica gel (CH_2Cl_2/cyclohexane, 50:50) gave pure carbonate **6a**; yield 0.615 g (88%).

R_f (CH_2Cl_2) = 0.26.

IR (CH_2Cl_2) ν 1 765, 1 617, 1 594, 1 525, 1 494, 1 455, 1 347, 1 325, 1 252, 1 217, 1 187 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.80 (s, 1H, C*H*-O), 7.30 (d, 2H, J = 9.3 Hz), 7.33 (br s, 10H), 8.25 (d, 2H, J = 9.3 Hz).

MS (EI) m/z (%) : 349 (M^+, 2), 305 (M-CO_2, 10), 212 (40), 184 (63), 167 (Ph_2CH, 100).

Acknowledgments

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3 Our final objective is the PEEK-OH surface modification by wet-chemistry, *ie* by carrying out heterogeneous reactions at the interface between the solid polymer and a solvent containing the appropriate reagents. In this unusual organic chemistry, the role of the solvent appears to be crucial [4]. The solvent must not dissolve (or swell) the polymer but, obviously, must totally dissolve the reagents. Moreover, to facilitate the reaction, the liquid phase in contact with the polymer film sample must wet the surface efficiently without inducing a reorganization of the macromolecular chains or crystallization. The selected solvents in the model study are therefore specific for PEEK and PEEK-OH.

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