Pergamon

Tetrahedron Letters 44 (2003) 5617–5619

TETRAHEDRON
LETTERS

COCHO-modified oxides nanoparticles by using phosphonic acid as grafting agent

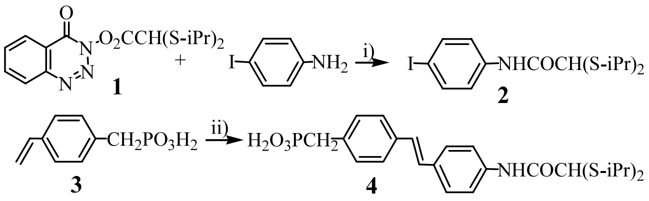
Samiran Kar,[a] Jean-Olivier Durand,[a,]* Michel Granier,[a] Pascal Joly[b] and Oleg Melnyk[b,]*

[a]*Chimie Moléculaire et Organisation du Solide UMR 5637, case courrier 007, Université Montpellier 2, place Eugène Bataillon, F-34095 Montpellier cedex 05, France*
[b]*Institut Pasteur de Lille, 1, rue du Professeur Calmette, F-59021 Lille cedex, France*

Received 12 March 2003; revised 2 June 2003; accepted 2 June 2003

Abstract—The synthesis of phosphonic acid **4** possessing a protected COCHO group, by using the Heck reaction is described. After grafting of the phosphonic acid **4** on metal oxides Al_2O_3, TiO_2 or SnO_2, the cleavage of the dithiane group was successful. The reactivity of the supported-COCHO group was examined by using model reactions with hydroxylamine and hydrazine derivatives.

The use of phosphonic acids for the preparation or modification of metal oxide-based materials has grown a lot in the last decades.[1] In particular, the grafting of functionalized phosphonic acids[1a,b] onto metal oxides particles has been described in fields such as modified electrodes,[1c] electron-transfert devices,[1d] catalysis,[1e] and biomaterials.[1f] In this context, we were interested in the preparation of a phosphonic acid possessing a protected α-oxoaldehyde (COCHO) function, to anchor the COCHO function onto oxide nanoparticles. Indeed, the reactivity of this function is specific and stable α-oxo-hydrazone or α-oxo-oximes bonds are formed by fast reaction with hydrazine or hydroxylamine groups, respectively.[2] Sophisticated macromolecules such as peptide dendrimers have been synthesized in solution by using this ligation procedure.[2b] However, despite important studies of the COCHO function related in solution, solid supports with the COCHO function have only been scarcely elaborated.[3] We present here the synthesis of COCHO functionalized oxide nanoparticles and the investigation of the reactivity at the surface of the particles.



Scheme 1. Synthesis of functionalized phosphonic acid **4**. *Reagents and conditions*: (i) Et_3N, CH_2Cl_2, rt, 4 h; (ii) a. **2**, $Pd(OAc)_2$ (6 mol%), 6 equiv. Et_3N, CH_3CN, 115°C, 24 h. Sealed tube; b. Dowex, $MeOH/H_2O$.

For the synthesis of phosphonic acid **4**, we have chosen the methodology developed by Badet,[4] with the COCHO function protected as a thioacetal group. Reaction of diisopropylthioacetic acid 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl-ester with *para* iodoaniline led to intermediate **2** which was cross-coupled with phosphonic acid **3**[5] in quantitative conversion by using Heck's reaction[6] with $Pd(OAc)_2$ as catalyst (Scheme 1). Diacid **4** was obtained[9] after cationic exchange with Dowex resin, but this exchange was not necessary for the next step.

We thus performed the grafting reaction of the triethylammonium disalt of phosphonic acid **4** on the surface of metal oxides, in order to investigate the properties of the new hybrid organic–inorganic materials thus prepared. We used three types of particle oxides: TiO_2 P25 Degussa (particle size 21 nm), SnO_2 Merck (particle size 20 nm), Al_2O_3 C Degussa (particle size 13 nm) (Scheme 2).

The particles were refluxed with the triethylammonium disalt of phosphonic acid **4** in MeCN for 3 days, filtered and thoroughly washed with MeCN, then dried at 100°C for 8 h. An excess of acid was used to ensure total coverage of the particle surfaces. The solids

---

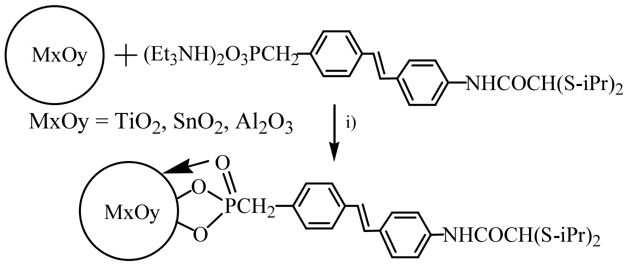
* Corresponding authors. Fax: 33-4-67-14-38-52; e-mail: durand@univ-montp2.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01367-4

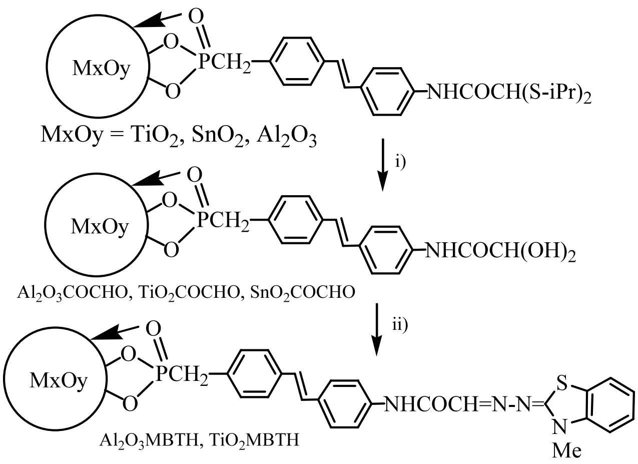
obtained were analyzed using elemental analysis, energy dispersive X-rays analysis (EDX), FTIR, solid-state ^{13}C and ^{31}P NMR spectroscopy. EDX showed the presence of P and S in all the samples indicating the presence of the molecule at the surface of the particles. No variation of the P/M_xO_y ratio was observed from one experiment to another on the same sample, which showed that the solids were homogeneous at a micrometric scale. Microanalysis showed P/M_xO_y ratio of 3.1%, 2.2%, 1% for Al_2O_3, TiO_2, SnO_2, respectively. These ratios are characteristic of a monolayer coverage of **4** at the surface of the oxide particles.[1a–c] Solid-state HPDECMAS ^{31}P NMR showed one signal centered at 16.3, 21.5 and 20.1 ppm respectively. The peaks at half maximum have been enlarged to 15 ppm. These data indicate that the phosphonic group has reacted at the surface of the oxide with formation of P–O–metal bonds.[1a–c] The phosphorus atom has different environments on the surface of the oxide because of different coordination modes; one two or three P–O–metal bonds are likely to be involved in the anchoring at the surface. CPMAS ^{13}C NMR, showed signals centered at 168 ppm (C=O), 128 ppm (Ar and C=C), 52 ppm (S–CH–S), 35 ppm (S–CH) and (CH_2P), 23 ppm (Me). Note that (C=O) and (S–CH–S) were difficult to detect. FT IR showed signals at 3450 (ν M–OH), 2964–2954 (ν CH), 2920–2910 (ν CH), 1661–1654 (ν C=O) 1597–1594 (δ NH) 1517–1515 (ν C=C). These data confirmed the presence of the carbon chain (Scheme 3).

The cleavage of the dithiane function was next examined. The materials were treated with *N*-bromosuccinimide in aqueous CH_3CN. No modification of the HPDECMAS ^{31}P NMR signals were observed indicating that the phosphonic acid was still grafted at the surface of the oxide. CPMAS ^{13}C NMR showed signals at 129 ppm (Ar and C=C), and 35 ppm (CH_2P). Signals of the dithiane function were not present any more. IRFT showed an important diminution of the signals at 2960–2910 cm^{-1}, signals at 1654 cm^{-1} and 1600 cm^{-1} were enlarged and overlapped each other. These data confirmed that the cleavage of the dithiane function was efficient.

The reactivity of the supported-COCHO function was then tested with NH_2OH and 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH), a reagent known to give a detectable adduct with aldehydes.[7] Unfortunately, IRFT and NMR techniques in the solid state were not sensitive enough to definitively confirm the formation of the imine bond, due to the low content of the COCHO function on the solid. We then turned to fluorescence spectroscopy to detect the adduct of MBTH with Al_2O_3COCHO and TiO_2COCHO (Fig. 1).



Scheme 2. Grafting of functionalized phosphonic acid **4**. *Reagents and conditions*: (i) CH_3CN, 80°C.



Scheme 3. Reactivity of the COCHO function at the surface. *Reagents and conditions:* (i) NBS, CH_3CN, H_2O, rt; (ii) MBTH, Phosphate buffer pH = 7, EtOH.

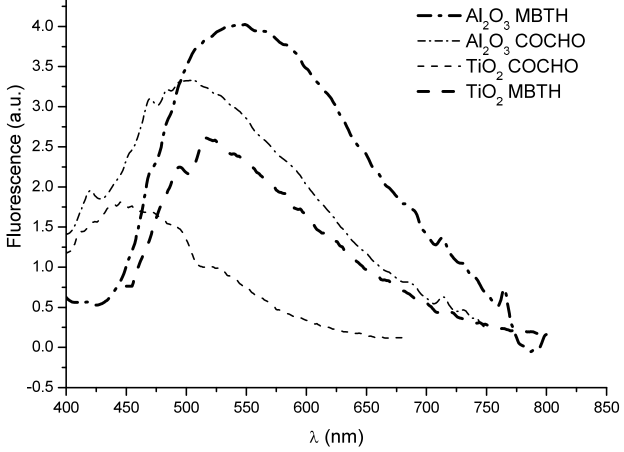


Figure 1. Fluorescence of Al_2O_3COCHO, Al_2O_3MBTH, TiO_2COCHO, TiO_2MBTH.

Fluorescence was easier to performed on Al_2O_3 than TiO_2, due to partial quenching of the fluorescence by TiO_2.[8] The stilbene unit of TiO_2COCHO was difficult to observe. Nevertheless, after reaction with MBTH, the fluorescence signal was enhanced and shifted to the red for both oxides (Fig. 1). This fluorescence behavior suggests the presence of a new conjugated chromophore and thus, the covalent attachment of MBTH at the surface of the materials through the formation of α-oxohydrazone bond.

In conclusion, we have shown that the Heck reaction is efficient in the synthesis of compound **4**, which possesses a phosphonic acid and a dithioacetal-protected COCHO groups. Compound **4** has formed an organic monolayer at the surface of metal oxides, and the

COCHO group was successfully deprotected. Its reactivity was investigated. Further developments of these compounds particularly in the field of biomaterials are in progress.

Acknowledgements

We thank the Degussa society for a gift of TiO_2 P25.

References

1. (a) Guerrero, G.; Mutin, P. H.; Vioux, A. *Chem. Mater.* **2001**, *13*, 4367–4373; (b) Pawsey, S.; Kimberly, Y.; Reven, L. *Langmuir* **2002**, *18*, 5205–5212; (c) Frantz, R.; Durand, J.-O.; Lanneau, G. F.; Jumas, J.-C.; Olivier-Fourcade, J.; Crétin, M.; Persin, M. *Eur. J. Inorg. Chem.* **2002**, 1088–1093; (d) Bonhote, P.; Moser, J.-E.; Humphry-Baker, R.; Vlachopoulos, N.; Zakeeruddin, S. M.; Walder, L.; Grätzel, M. *J. Am. Chem. Soc.* **1999**, *121*, 1321–1336; (e) Maillet, C.; Janvier, P.; Pipelier, M.; Praveen, T.; Andres, Y.; Bujoli, B. *Chem. Mater.* **2001**, *13*, 2879–2884; (f) Protet, D.; Denisot, B.; Rump, E.; Lejeune, J. J.; Jallet, P. *J. Coll. Inter. Science* **2001**, *238*, 37–42.
2. (a) Melnyk, O.; Fehrentz, J. A.; Martinez, J.; Gras-Masse, H. *Biopolymers (Peptide Science)* **2000**, *55*, 165–186; (b) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3893–3899.
3. (a) Falsey, J. R.; Renil, M.; Park, S.; Li, S.; Lam, K. S. *Bioconjugate Chem.* **2001**, *12*, 346–353; (b) Xu, Q.; Lam, K. S. *Tetrahedron Lett.* **2002**, *43*, 4435–4439; (c) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 5147–5151; (d) Schleibler, L.; Dumy, P.; Boncheva, M.; Leufgen, K.; Mathieu, H. J.; Mutter, M.; Vogel, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 696–699.
4. (a) Qasmi, D.; René, L.; Badet, B. *Tetrahedron Lett.* **1994**, *35*, 4343; (b) Qasmi, D.; De Rosny, E.; Rene, L.; Badet, B.; Vergely, I.; Boggetto, N.; Reboud-Ravaux, M. *Bioorg. Med. Chem.* **1997**, *5*, 707–714.
5. Frantz, R.; Durand, J. O.; Carré, F.; Lanneau, G. F.; Le Bideau, J.; Alonso, B.; Massiot, D. *Chem. Eur. J.* **2003**, *9*, 770–775.
6. (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; (b) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; (c) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411; (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
7. Mikolajczyk, S. D.; Meyer, D. L.; Starling, J. J.; Law, K. L.; Rose, K.; Dufour, B.; Offord, R. E. *Bioconjugate Chem.* **1994**, *5*, 636–646.
8. Wang, C.; Liu, C.; Wang, Y.; Shen, T. *J. Coll. Inter. Science* **1998**, *197*, 126–132.
9. *Synthesis of acid* ***4***: In a sealed tube, were placed para-vinylbenzylphosphonic acid **3** (396 mg, 2 mmol), aryl iodide **2** (818 mg, 2 mmol), palladium diacetate (27 mg, 0.12 mmol), triethylamine (2 mL) and the mixture was diluted in acetonitrile (25 mL). The reaction mixture was heated at 115°C under magnetic stirring for 24 h. The solution was allowed to cool to room temperature and then was filtered through celite, and solvent was evaporated. The triethyl ammonium disalt of **4** was obtained in 95% yield. It was purified by chromatography with ion exchange resin Dowex 50w (eluent MeOH–H_2O, 1:1). ^1H NMR (200 MHz, DMSO, 293 K): δ 1.29 (d, $^3J_{HH}=6.70$ Hz, 12H, CH_3); 3.00 (d, $^2J_{HP}=21.5$ Hz, 2H, CH_2–P); 3.20 (m, $^3J_{HH}=6.7$, 2H, -CH–S); 4.45 (sBr, 2H, PO_3H_2); 4.74 (s, 1H, S–CH–S); 7.25 (m, 5H); 7.53 (m, 5H), 10.28 (s, 1H, NH). ^{31}P NMR (81 MHz, DMSO, 293 K): δ 22.5. IR: 3431.2, 3296.2, 2958.6, 2913.6, 1669.2, 1584.8, 1517.3, 1404.7, 1309.1, 1259.5, 1095.3, 988.4, 797.1, 735.2, 598.9. HRMS (FAB$^+$, GT): 479.5996 (calc. for M$^+$); 479.6009 (obs.).