Natural phosphate and potassium fluoride doped natural phosphate as new catalysts for the Vilsmeier–Haack type reaction

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The catalytic activity of the inexpensive natural- or potassium fluoride doped phosphates as bases was evaluated in a Vilsmeier–Haack type reaction. High efficiency, in term of chemical yields and reaction rates was found in the preparation of 2-chlor-3-cyanopyridines starting from 2-propylidene-malonitriles.

Keywords: natural phosphate, potassium fluoride, heterogeneous catalysis, Vilsmeier–Haack reaction, recyclable catalyst

Reactions that are facilitated on various solid inorganic surfaces are receiving increasing attention.[1] The advantage of these methods over conventional homogeneous reactions is that they provide greater selectivity, enhanced rates, clean products and manipulative simplicity. In this kind of process the use of environmentally friendly reagents and recoverable heterogeneous catalysts is a key goal.

We previously reported that natural phosphate (NP) can be used as a heterogeneous catalyst for several reactions such as Michael addition,[2] Knoevenagel reaction,[3] 1,3-dipolar cycloaddition,[4] acyclonucleosides synthesis[5] and other reactions.[6] We have also demonstrated that doping with potassium fluoride increases the activity of natural phosphate.[2, 3]

2-Chloro-3-cyanopyridine is an important substructure for the construction of some biologically relevant compounds.[7] The Vilsmeier–Haack reaction[8] is one of the useful general methods employed for the synthesis of substituted 2-chloro-3-cyanopyridines. However, this reaction has been accomplished, in general with low yields. In continuation of our ongoing program in the field of heterogeneous catalysis, we describe the use of the NP alone or KF/NP as new efficient solids catalyst in the Vilsmeier–Haack reaction between phosphorus oxytrichloride ($POCl_3$), N,N-dimethylformamide and *gem*-dicyanoalkenes **1** (Scheme 1).

Four 2-propylidene-malonitriles **1a–d** were selected for this study. Under usual the Vilsmeier–Haack conditions ($POCl_3$/DMF at 70–80 °C) the expected pyridine derivatives were isolated in low to moderate yields (Table 1).

Addition of catalytic amounts of natural phosphate (NP) to the usual mixture of Vilsmeier–Haack reaction leads to remarkable improvement of yields which increase from 12–56 to 62–80% (Table 1). Moreover, use of NP is particularly interesting since it is regenerated by calcinations at 500 °C during 15 min, and after seven successive recoveries, products **3a** are obtained with the same yields.

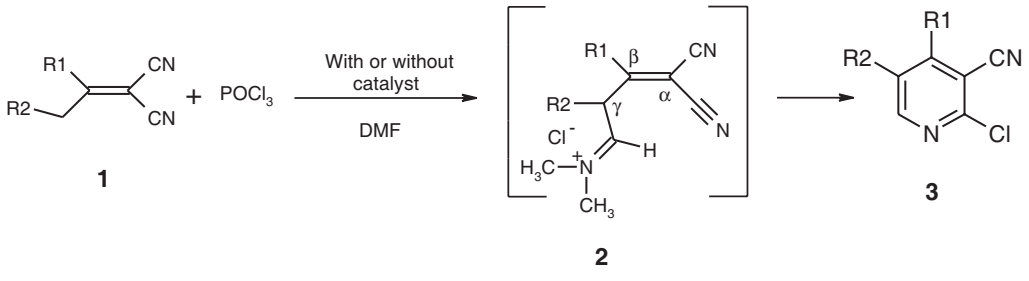
On the other hand, doping natural phosphate with potassium fluoride resulted in a yield improvement of *ca* 10% compared to similar reactions catalysed with natural phosphates (Table 1). The basic character of the KF/NP surface probably enhances the necessary polarisation of the C_γ–H bond of alkenes **1** prior to reaction with the Vilsmeier iminium intermediate. Consequently, the carbon-carbon bond formation is facilitated and the intermediate alkene **2** is obtained by transfer of a proton followed by dehydration. In a second step, addition of chloride to the *cis*-cyano-group promotes the latter's nitrogen addition onto the iminium moiety and subsequent aromatisation, by elimination of dimethylamine, finally leads to substituted 2-chloro-3-cyanopyridines **3**.

In summary, we have developed novel catalysts for the synthesis of substituted 2-chloro-3-cyanopyridines by a one-pot Vilsmeier–Haack reaction. These catalysts (NP or KF/NP) bring advantages such as high catalytic activity under very mild liquid phase conditions, easy separation of the catalyst, use of simple filtration, possible recycling of the catalyst, use of non-toxic and inexpensive catalysts.

Experimental

^{1}H spectra were recorded at 400 MHZ on a Bruker DRX-400 spectrometer in $CDCl_3$, using $CDCl_3$ as internal standard. The chemical shifts (δ) are expressed in ppm relative to $CDCl_3$ and coupling constants (*J*) in Hertz. IR spectra were obtained on a FTIR (ATI Mattson-Genesis Series) and reported in wavenumbers (cm^{-1}). Surface area and pore size analysis were carried out at 77 K on a Micromeritics ASAP2010 instrument using nitrogen as adsorbent. X-ray diffraction patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu–K_α radiation and SEM images were taken on a Hitac hi S-2400 microscope. Melting points were determined with a "Thomas Hoover" melting (capillary method) apparatus and are uncorrected. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM).

All reactions were carried out under atmospheric air. Solvents and starting materials (Aldrich) were used without further purification.



Scheme 1

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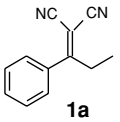
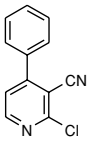
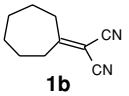
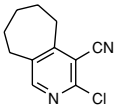
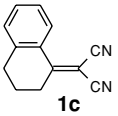
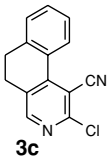
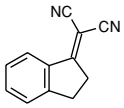
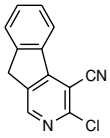
Table 1 Synthesis of substituted 2-chloro-3-cyanopyridines by the Vilsmeier–Haack reaction with or without catalyst (NP and KF/NP)

Alkene	Product	Yields/% (time: 3 h)[a]		
		Without catalyst	NP (0.1 g)	KF/NP (0.1 g)
 **1a**	 **3a**	08	80	91
 **1b**	 **3b**	12	75	87
 **1c**	 **3c**	15	62	83
 **1d**	 **3d**	56	70	85

[a]Yields in pure products isolated by chromatography, recrystallised with *n*-hexane/ethyl acetate and identified by ^{1}H NMR and IR spectrometry.

Preparation of the catalysts and structural characteristics

Natural phosphate comes from Khouribga (it is readily available raw or treated from CERPHOC Casablanca, Morocco).[9] The fraction of 100–400 μm grain size was washed with water, calcined at 900 °C for 2h, washed again, calcined at 900 °C for 0.5 h and ground (63–125 μm). The structure of NP is similar to that of fluorapatite $Ca_{10}(PO_4)_3F_2$, as shown by X-ray diffraction pattern and chemical analysis.[6a]

The KF/NP catalyst was prepared by addition of NP (8 g) to a solution of KF (1 g) in water.[2] The mixture was stirred for 1 h, evaporated to dryness and dried at 150 °C for 2h. The catalyst KF/NP (weight ratio KF/NP : 1/8) was a grey powder, the colour of NP itself. The surface area and pore volume of the NP were increased by doping with KF. Thus, the results obtained are 8.9 $m^2\ g^{-1}$ and 0.128 $cm^3 g^{-1}$ for KF/NP and 1 $m^2\ g^{-1}$ and 0.005 $cm^3\ g^{-1}$ for NP respectively. These results are in contradiction with that reported in typically supported metal salts on solids.[9] X-ray diffraction of KF/NP gives a diffraction pattern almost identical to that of NP itself. Peak positions and intensities are essentially unaltered, except for a minor reduction in intensity. This result indicates that the crystalline structure of the support remains essentially unaltered in the catalyst, and also indicates that no demixing crystalline KF phase is present. We showed in our previous work[2b,6c] that supporting KF on NP causes the formation of a more open structure which incorporates KF in such a way that crystalline KF is not formed in significant quantities. However, it appears that the basic structure of the NP is not destroyed, indicating a less profound interaction of KF with NP than is the case with alumina.[10]

General procedure for the syntheses of substituted 2-chloro-3-cyanopyridines (**3a–d**)

To a flask containing 10 mmol of alkene 1 and 20 mmol (3.0 g) of $POCl_3$ in DMF (10 ml), phosphate catalyst (NP or KF/NP, 0.1 g) was added and the mixture was stirred at room temperature for 30 min and the bath temperature slowly raised to 70–80 °C. The reaction mixture was heated during 3 h and, then washed with water. The solid was filtered and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to chromatography or recrystallisation (*n*-hexane/ethyl acetate) leading to the Vilsmeier–Haack adduct as a solid. The product was characterised by ^{1}H NMR, IR spectrometry and melting point.

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