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Natural phosphate and potassium fluoride doped natural phosphate: efficient catalysts for the construction of a carbon–nitrogen bond

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Abstract—The application of natural phosphates doped with potassium fluoride as heterogeneous catalysts for the Michael addition of aromatic and aliphatic amines to α,β-unsaturated carbonyl compounds is presented. The natural phosphate catalyst can be regenerated and reused without loss of activity, which makes it an attractive alternative to homogeneous basic reagents. Doping natural phosphate with potassium fluoride significantly enhances the rate and yield of the reaction.

Heterogeneous catalytic reactions are of interest[1] due to their well-documented advantages over homogeneous catalytic systems. Natural phosphates (NP)[2] have emerged as ideal basic and acidic heterogeneous catalysts as they are available from nature and are inexpensive. The surface of these phosphates presents multi-catalytic active sites (basic[3] and acidic[4]) and thus increases their utility in both types of catalytic applications. The positive features of NP also include high stability, ease of handling and regeneration, nontoxic and other environmental hazards. In recent years, we have developed several new applications of NP both alone and doped with mineral salts in heterogeneous catalytic reactions.[5]

The Michael condensation of an aliphatic or aromatic amine and an α,β-unsaturated carbonyl compound is a convenient route for the synthesis of β-amino carbonyl compounds. This condensation is normally carried out in the presence of a Lewis acid,[6] although, in some cases the reaction occurs with no special activation,[7] in others, stronger reaction conditions are required.[8]

Recently, Deshpande and co-workers[9] have shown that kaolinitic clay[10] or commercially available montmorillonite K10[11] are excellent catalysts for the addition of amines to α,β-ethylenic compounds. However, these catalysts are only suitable for activating aliphatic amines for addition towards α,β-ethylenic compounds and failed for less nucleophilic aromatic amines. This encouraged us to investigate the reaction with NP alone or doped with potassium fluoride. We have previously shown that various phosphate catalysts can promote Michael additions forming carbon–carbon[12] and carbon–sulfur[13] bonds. In this work we present the efficient construction of carbon–nitrogen bonds using natural phosphate and natural phosphate doped with potassium fluoride (KF/NP).

Several α,β-unsaturated carbonyl compounds such as chalcone, *p*-methoxychalcone, *p*-chlorochalcone, *p*-methylchalcone and ethyl acrylate as Michael acceptors were subjected to this reaction with NP or KF/NP as catalysts and aniline, *p*-methoxyaniline or benzylamine as the nucleophilic amine (Scheme 1). The reactions were carried out at room temperature.

Natural phosphate comes from an ore extracted in the region of Khouribga (it is available in raw form or treated form from CERPHOS Casablanca, Morocco).[2] Prior to use this material requires initial treatments such

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Keywords: Natural phosphate; Potassium fluoride; Heterogeneous catalysis; β-amino derivatives; Recyclable catalyst.

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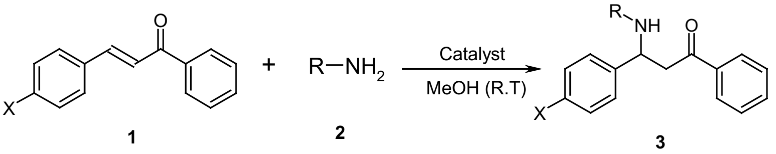


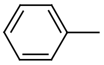
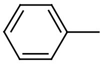
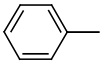
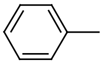
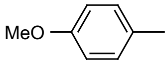
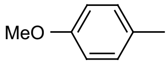
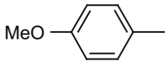
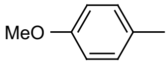
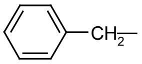
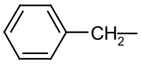
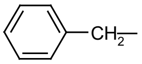
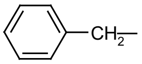
Scheme 1.

as crushing and washing. For use in organic synthesis, the NP is treated by techniques involving attrition, sifting, calcinations (900 °C), washing and recalcination. These treatments lead to a fraction between 100 and 400 μm, which is rich in phosphate. The structure of NP is similar to that of fluorapatite ($Ca_{10}(PO_4)_6F_2$), as shown by X-ray diffraction and chemical analysis.[3d,13a] The surface area of NP was measured at $1\,m^2\,g^{-1}$ (nitrogen adsorption) and the total pore volume was $0.005\,cm^3\,g^{-1}$. KF/NP was prepared by adding 8 g of NP to a 1 g aqueous KF solution. The mixture was stirred, evaporated to dryness and then further dried at 150 °C for 2 h. The catalyst KF/NP (weight ratio KF/NP:1/8)[5c,13a] is a grey powder, the colour of NP itself.

Aniline and chalcone (X = H, Scheme 1) were chosen as model substrates to determine suitable reaction conditions. The best weight ratio of KF/NP is 1/8.[3]

In the presence of KF/NP various solvents were tested. Thus, after 1 h the yields of product **3a** obtained were 95%, 87%, 63% and 11% in the presence of methanol, ethanol, *n*-butanol and *iso*-propanol, respectively. In the cases of acetone, dichloromethane, dimethylformamide, tetrahydrofuran, dioxane and hexane no product was observed, only the starting material was recovered. In the absence of solvent, only a 10% yield of **3a** was obtained. This behaviour indicates that some solvent is needed to facilitate contact between the reagents and the active site.

Table 1. Synthesis of products **3** by Michael addition using NP

Products	R	X	Yield/% (time/h)[a]	
			NP	KF/NP
3a		H	25 (2); 96 (8)	80 (0.75); 95 (1)
3b		Cl	71 (14)	66 (2), 95 (5)
3c		OMe	60 (6); 93 (14)	67 (2); 95 (3.5)
3d		Me	86 (14)	70 (2); 94 (4)
3e		H	75 (6), 90 (14)	79 (0.5), 92 (1)
3f		Cl	73 (14), 95 (19)	77 (3.5), 94 (5.5)
3g		OMe	77 (14), 95 (19)	76 (3.5), 90 (5.5)
3h		Me	87 (16)	80 (4), 93 (5)
3i		H	64 (24)	70 (5), 90 (24)
3j		Cl	75 (24)	92 (5)
3k		OMe	23 (24)	50 (4), 75 (24)
3l		Me	55 (24)	55 (6), 91 (24)

[a] Yields of pure products isolated by chromatography and recrystallized from *n*-hexane/ethyl acetate. The products were identified by ^1H, ^{13}C NMR, IR spectrometry and melting points.

The study of the influence of the volume of the solvent showed that 0.5–1.5 mL of methanol resulted in optimal yields. An increase in the volume of up to 2 mL slightly decreased the reaction yield (66%), and this was reduced further to 13% when a volume of 10 mL was used. The large solvent volume reduced the overall reaction concentration, which explains the decreased yield.

In general the use of NP alone as the heterogeneous catalyst in Michael additions has allowed the isolation of the 1,4-addition product in moderate to good yields (Table 1).[14] However, the rate of reaction was relatively slow. Moreover, the use of NP is particularly interesting since it can be regenerated by calcination at 500 °C over 15 min, and after seven successive recoveries, the product **3a** was obtained in the same yield.

Under the optimized conditions, the use of NP doped with KF, remarkably, increased the catalytic activity and decreased the reaction time of the Michael addition (Table 1 and Fig. 1). The yields were very high (91–95%; Table 1), except in one case, the reaction of benzylamine with a Michael acceptor bearing a methoxy (X = MeO) in the *para*-position, which afforded only a moderate yield (75%) of the 1,4-addition product.

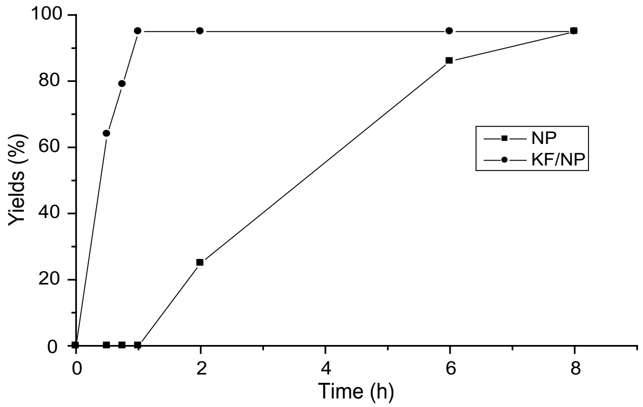


Figure 1. Time course of product **3a** synthesis in the presence of NP and KF/NP, respectively.

In the presence of 0.01 g of KF alone (the present quantity in the KF/NP:1/8 catalyst), no 1,4-addition product was observed under the reaction conditions, only the starting material was isolated. Products of undesirable side reactions resulting from 1,2-addition, polymerization and bis-addition were not observed. For the catalytic activity of KF/NP in this Michael addition we speculate that the reaction occurs at the surface rather than inside tunnels present in the catalyst. The acidic surface of NP[4] probably induced the polarization of the C=O bond and the basic sites[3] deprotonate RH_2N^+–C after addition to the C=C bond. The final product is obtained after protonation of the resulting enolate.

The reactions of benzylamine and acrylates were investigated separately to establish conditions for the selective preparation of mono and bis-addition products. Reaction of ethyl acrylate with an excess of benzylamine in the presence of KF/NP furnished **4** as the sole product (Scheme 2). The reaction of benzylamine with an excess of ethyl acrylate in the presence of KF/NP gave bis-addition product **5** in excellent yield. While compound **4** is a direct precursor of β-amino acids, **5** has been used as a starting material for the synthesis of heterocyclic compounds,[15] and derivatives of nipecotic acids.[16]

In summary, we have developed a practical and novel phosphate-catalyzed Michael-type addition reaction of aliphatic and aromatic amines with α,β-unsaturated carbonyl compounds at room temperature. The natural phosphate catalyst can be regenerated and reused without loss of activity, which makes it an attractive alternative to homogeneous basic reagents. The use of potassium fluoride doped natural phosphate enhances the rate and the yield of the reaction.

Acknowledgements

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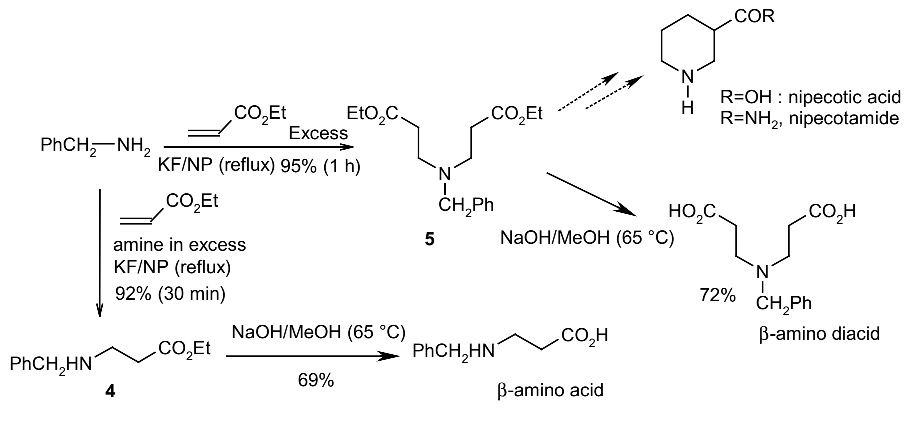

Scheme 2.

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14. The general procedure is as follows: To a flask containing an equimolar mixture (1.5 mmol) of amine **2** ($PhNH_2$ or p-CH_3O–C_6H_4–NH_2 or $PhCH_2NH_2$) and chalcone derivative **1** in methanol (1.5 mL), phosphate catalyst (NP or KF/NP) 0.1 g was added and the mixture was stirred at room temperature until completion of the reaction, as monitored by thin layer chromatography (TLC). The reaction mixture was filtered and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to chromatography or recrystallization (*n*-hexane/ethyl acetate) leading to the Michael adduct as a solid. The product structure was verified by ^{1}H, ^{13}C NMR and IR spectrometry.
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