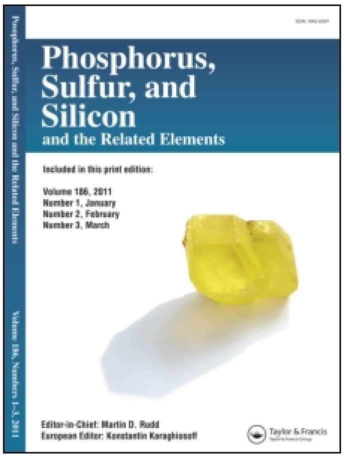

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Natural Phosphate Modified with Lithium Nitrate: A New Efficient Catalyst for the Construction of Carbon-Carbon, Carbon-Sulfur, and Carbon-Nitrogen Bonds

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Natural Phosphate Modified with Lithium Nitrate: A New Efficient Catalyst for the Construction of Carbon–Carbon, Carbon–Sulfur, and Carbon–Nitrogen Bonds

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Maroc

*The addition of small amounts of lithium nitrate to natural phosphate followed by calcination gives a new catalyst Li/NP (weight ratio $LiNO_3$/NP = 1/15). This material showed catalytic activity in the Michael addition of amines, mercaptans, and active methylene compounds to chalcone derivatives with high yields under mild reaction conditions. Li/NP is used as the catalyst for a facile synthesis of β-amino acids, β-sulfur acids, and 4*H*-chromenes under heterogeneous conditions. The usual, undesirable byproducts from the Michael condensation such as 1,2-addition, bis-addition, and polymerization compounds are not observed with this method. The work-up procedure is simplified by simple filtration with the use of Li/NP.*

Keywords 4*H*-chromene; β-amino acid; β-sulfur acid; heterogeneous catalysis; lithium nitrate; Michael addition; natural phosphate

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INTRODUCTION

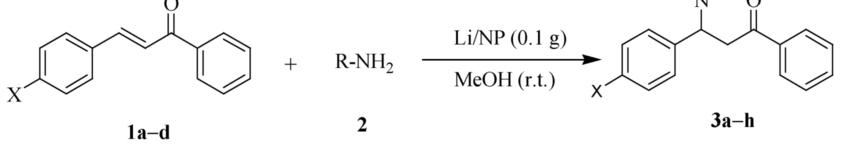
The use of environmentally benign reaction media is very important in the view of today's environmentally conscious attitude. The generation of wastes is dramatically important in the case of the synthesis of fine chemicals and pharmaceuticals, and they consist primarily of inorganic salts formed in the reaction or in subsequent neutralization steps. In this sense, heterogeneous catalysts[1] under solvent-free conditions at r.t. play an important role.

Various solid catalysts have been found useful in heterogeneous media, including Mg-Al-hydrotalcite,[2] zeolite,[3] aluminium oxide,[4] montmorillonite/$NiBr_2$,[5] synthetic phosphate $Na_2CaP_2O_7$,[6] fluoroapatite,[7] and hydroxyapatite,[8] and other solid catalysts were used with more or less success.[9] We previously reported that Natural Phosphate (NP) alone is capable of catalyzing the Michael addition.[10] We have also shown that doping with potassium fluoride[10a] and sodium nitrate[10b] increases the activity of natural phosphate.

The pharmaceutical industry requires the development of useful carbon–nitrogen bond-forming reactions exhibiting high yield and selectivity, low cost, safety, operational simplicity, mild reaction conditions, and reduced environmental problems.

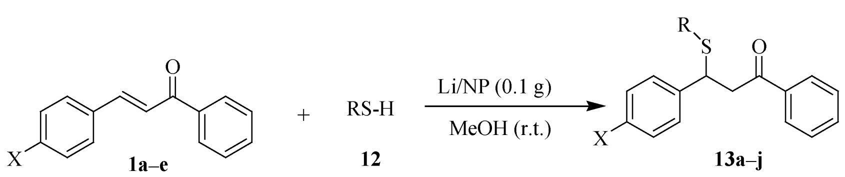
Recently, Shaikh and coworkers[11] have shown that kaolinitic clay[12] or commercially available montmorillonite K10[13] are excellent catalysts for the addition of amines to α,β-unsaturated carbonyl compounds. However, these catalysts are only suitable for activating aliphatic amines toward addition to α,β-unsaturated carbonyl compounds and they failed for the less nucleophilic aromatic amines. This encouraged us to investigate the reaction with natural phosphate doped by lithium nitrate.

In this work, we present a practical and novel phosphate-catalyzed Michael-type addition reaction of aliphatic and aromatic amines, thiols and active methylene compounds, with α,β-unsaturated carbonyl compounds at r.t. (Schemes 1, 2, and 3).



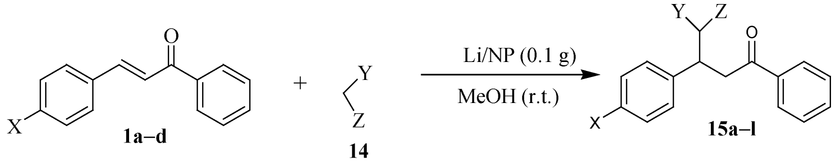
R = Ph and $PhCH_2$
X = H, Cl, Me and OMe

SCHEME 1



R = Ph and -2-$NH_2C_6H_4$
X = H, Cl, Me, OMe and NO_2

SCHEME 2



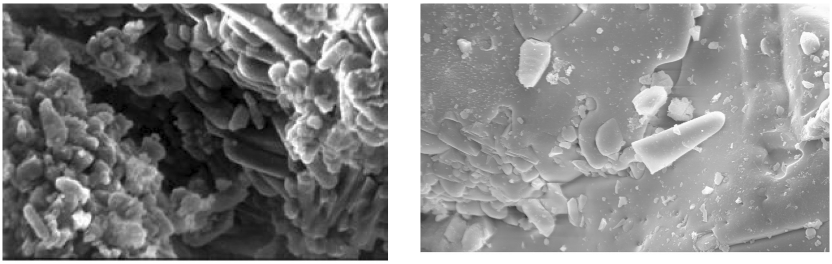
Y = CN and H, Z = CN, NO_2 and CO_2Me
X = H, Cl, Me and OMe

SCHEME 3

EXPERIMENTAL

Preparation of the Catalyst and Structural Characteristics

NP used in this work was obtained in the Khouribga region (it is available in raw form or treated form from CERPHOS Casablanca, Morocco).[14] Prior to use, this material requires initial treatments such as crushing and washing. For use in organic synthesis, 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 that is rich in phosphate and has the chemical composition P_2O_5 (34.24%), CaO (54.12%), F^- (3.37%), SiO_2 (2.42%), SO_3 (2.21%), CO_2 (1.13%), Na_2O (0.92%), MgO (0.68%), Al_2O_3 (0.46%), Fe_2O_3 (0.36%), K_2O (0.04%) and several metals (Zn, Cu, Cd, V, U, and Cr) in the ppm range. The structure of the material is similar to that of fluoroapatite ($Ca_{10}(PO_4)_6F_2$),[15] as shown by X-ray diffraction pattern and chemical analysis.[15] In sedimentary rocks, phosphates are formed from compounds derived from apatite by partial isomorphic substitution: Ca^{2+} ions by Na^+, Mg^{2+}, $Co^{2^{\circ}}$, $Fe^{3^{\circ}}$, or $Al^{3^{\circ}}$, PO_4^{3-} ions by VO_4^{3-}, SO_4^{2-}, CO_3^{2-} or MnO^{4-}; and F^- by ^-OH or Cl^-. These different substitutions cause distortions of the structure which depends on the nature and the radii of the ions involved. This solid presented a very



(a) (b)

FIGURE 1 SEM images of (a) NP and (b) Li/NP.

low surface area Brunauer, Emmett and Teller (BET) at ca. 1 m^2 g^{-1}, and the total pore volume was 0.005 cm^3 g^{-1}.

Li/NP has been prepared by adding 10 g of NP to an aqueous solution of 0.667 g (9.7 mmol) of lithium nitrate. The mixture was stirred for 1 h at r.t. evaporated to dryness, and dried at 100°C for 2 h. The solid obtained was calcined at 900°C for 1 h to give the catalyst Li/NP (weight ratio $LiNO_3$/NP = 1/15). The X-ray diffraction pattern of this catalyst is similar to that of NP. The mercury porosimetry data showed the pore diameter range 0.0035–400 μm. The total surface area and the total intruded volume are 0.24 m^2 g^{-1}, and 0.0831 cm^3 g^{-1}, and 0.14 m^2 g^{-1}, and 0.728 cm^3 g^{-1} for $LiNO_3$/NP non-calcined and $LiNO_3$/NP calcined at 900°C, respectively.

The morphology of the solids surface was observed in Scanning Electron Micrograph (SEM) images of Li/NP in comparison with NP (Figure 1). It clearly appears that some modifications have taken place at the surface of the catalyst.

Typical Experimental Procedure

To a flask containing an equimolar mixture (1.5 mmol) of nucleophile **2**,**12**, or **14** (Schemes 1, 2 and 3) and chalcone derivative **1** in methanol (1.5 mL), phosphate catalyst (Li/NP, 0.1 g) was added, and the mixture was stirred at r.t. until completion of the reaction, as monitored by TLC. The reaction mixture was filtered, and the catalyst was washed with dichloromethane (15 mL). After concentration of the filtrate under reduced pressure, the residue was subjected to chromatography or recrystallization (hexane/ethyl acetate = 9/1) leading to the Michael adduct product, whose structure was verified by ^{1}H-,and ^{13}C NMR, IR spectroscopies, and melting points.

RESULTS AND DISCUSSION

Construction of a Carbon–Nitrogen Bond in the Presence of Li/NP

Aniline and chalcone (X = H, Scheme 1) were chosen as model substrates to determine suitable reaction conditions. First, we proceeded to study the solvent effect in the synthesis of product **3a** using the Li/NP (0.1 g) catalyst.

In the cases of hexane, tetrahydrofuran, and dioxane, no product formation was observed. The use of 2-propanol, ethanol, and methanol gave, after 3 h of the reaction, 37%, 58%, and 92% yield of **3a**, respectively. It can be concluded that methanol is the best solvent for this reaction. A similar solvent effect has been observed in the use of the natural phosphate catalyst.[10a] In the absence of the solvent, no product was observed but only the starting material was recovered. This behavior indicates that some solvent is needed to facilitate the contact between the reagents and active sites.

The analysis of the amount of solvent utilized showed that with 0.5–1.5 mL of methanol, the best yield was obtained. An increase in the volume up to 2 mL slightly decreases the reaction yield (79%), and this dropped further to 44% when a volume of 5 mL was used (Figure 2). A large solvent volume reduced the concentration, which explains the yield lowering.

Next, the role of calcination temperature was examined. We have found that $LiNO_3$/NP calcined at 900°C gave the best yields of **3a**, while only a 48% yield of this product was obtained with $LiNO_3$/NP calcined at 500°C. The uncalcined catalyst or those calcined at 150°C or 300°C are inactive in this reaction. The calcination procedure possibly produces

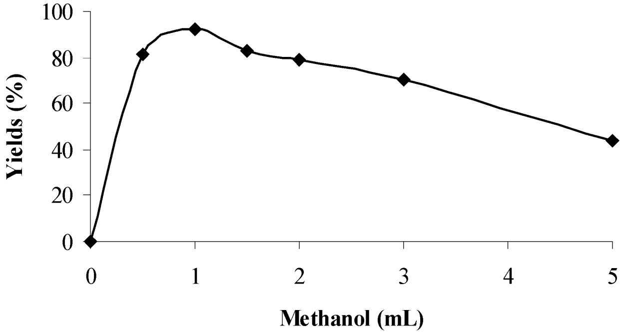


FIGURE 2 Influence of methanol as a solvent in the synthesis **3a**.

the decomposition of supported $LiNO_3$ into Li_2O, generating the basic sites of the new catalyst Li/NP.

The use of combinations of natural phosphate and lithium hydroxide as a catalyst gave to product **3a** with a moderate yield (70%, 3 h). with the presence of NP alone the yield in **3a** was 32% (3 h).

As it is reported that Li_2O in the presence of moisture regenerates lithium hydroxide as a strong basic compound and when in contacts with methanol it yields a basic solution, we suspected that the activation of reagents could be promoted by basic methanolic solution. To this end we carried out the same reaction in the basic solution obtained after filtration of a stirred suspension of $LiNO_3$/NP calcined at 900°C, and no formation of compound **3a** was observed; only the starting material was isolated, confirming the important role of the catalyst surface in the activation of the reagents. In the presence of 0.0063 g of $LiNO_3$ alone (the present quantity in $LiNO_3$/NP: 1/15 catalyst), no 1,4-addition product was observed under the reaction conditions, and only the starting material was isolated.

To determine the scope and limitation of this reaction, the optimum conditions were applied to other substrates as shown in Table I (Scheme 1). All products were isolated and identified by ^{1}H-, ^{13}C-NMR, and IR spectroscopies, and melting points.

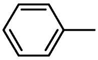
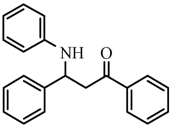
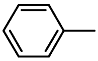
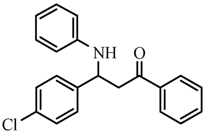
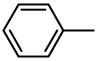
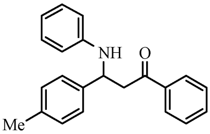
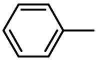
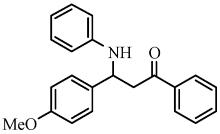
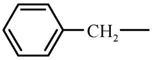
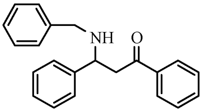
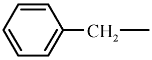
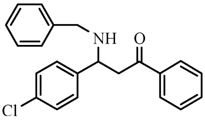
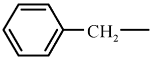
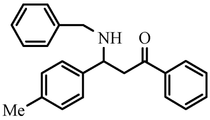
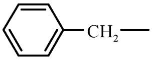
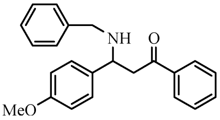
In all cases, the use of a low amount of Li/NP calcined remarkably increased the catalytic activity and decreased the reaction time in the construction of a carbon–nitrogen bond (Table I). The yields were good to excellent (70% to 97%, Table I) except in the case of the reaction of benzylamine with Michael acceptor bearing a methoxy group (X = MeO) in the *para* position, which afforded a moderate yield (60%) of the 1,4-addition product. Products of undesirable side reactions resulting from 1,2-addition, polymerization, and bis-addition were not observed.

Synthesis of β-Amino Acid and β-Sulfur Acid

Naturally occurring β-amino acids are compounds with an interesting pharmacological profile.[16] They are also found as components in a wide variety of biologically active compounds[17] including peptides such as bestatin[18] and pepstatin.[19] The β-amino acids are also useful precursors in the synthesis of β-lactams.[20]

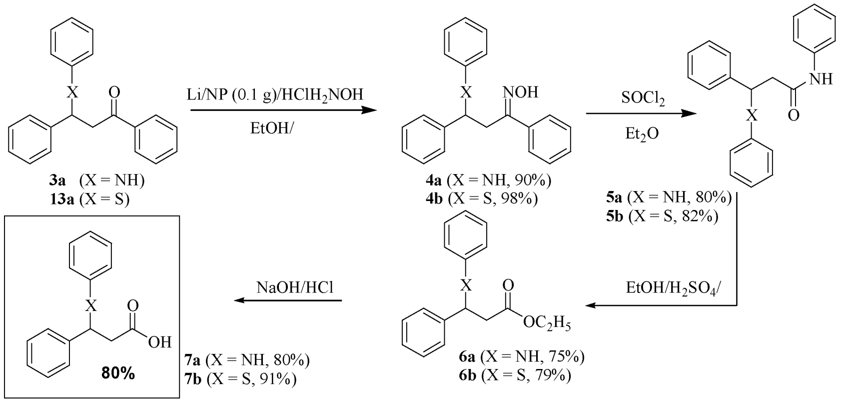
The β-amino carbonyl compound **3a** is a direct precursor to β-amino acids. Schemes 4 and 5 illustrate our approach wherein the starting materials is 1,4-adduct **3**. β-amino carbonyl **3a** is converted to oxime **4a**, in the presence of Li/NP catalyst in an excellent yield (90%). The oxime **4a** was subjected to the reaction induced by thionyl chloride, and the chemoselective Beckmann rearrangement gave anilide **5a**.

TABLE I Construction of a Carbon–Nitrogen Bond by Michael Addition Using NP and Li/NP as Catalysts

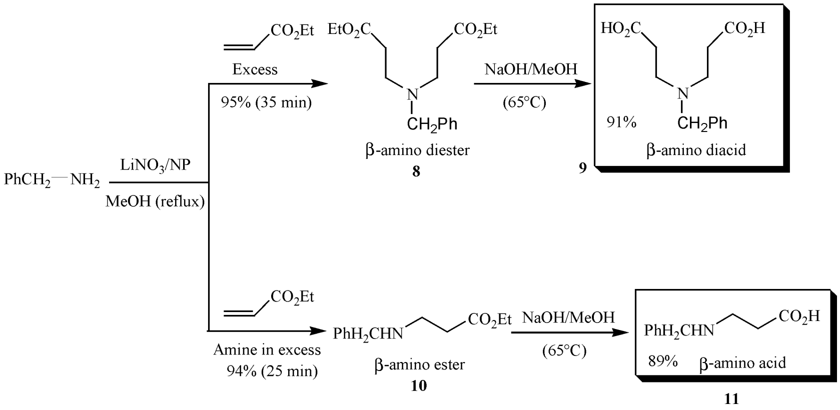
R	X	Products	Yield (%) (Time [h])[a]	
			NP[b]	Li/NP
	H **3a**		86 (6)	90 (3)
	Cl **3b**		71 (14)	90 (14)
	Me **3c**		76 (24)	95 (8)
	OMe **3d**		85 (20)	97 (12)
	H **3e**		64 (24)	82 (20)
	Cl **3f**		75 (24)	76 (8)
	Me **3g**		18 (24)	70 (24)
	OMe **3h**		23 (24)	60 (24)

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

[b] Reference 10b.



SCHEME 4



SCHEME 5

Finally, after two steps, β-amino acid **7a** was obtained in a good yield (Scheme 4).

On the other hand, the reaction of ethyl acrylate with an excess of benzylamine in the presence of Li/NP furnished β-amino ester **10** as the sole product due to a mono addition reaction (Scheme 5). The reaction of benzylamine with an excess of ethyl acrylate in the presence of Li/NP gave bis-addition product **8** in an excellent yield. β-amino diester **8** is a direct precursor of β-amino diacid **9**, which has been used as starting material for the synthesis of heterocyclic compounds[21] and derivatives of nicopecotic acids.[22]

Construction of Carbon–Sulfur Bond in the Presence of Li/NP

Recently, conjugate addition of mercaptans to enones has attracted considerable interest[6–9] as it leads to the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[23] Thus, a number of procedures either based on the activation of thiol by a base or activation of acceptor olefins with Lewis acids have been developed.[9,24] The optimized conditions for construction of a carbon–nitrogen bond are efficiently applied to the construction of a carbon–sulfur bond. Several α,β-unsaturated carbonyl compounds such as chalcone, *p*-methoxychalcone, *p*-chlorochalcone, and *p*-methylchalcone as acceptors were subjected to this reaction with Li/NP as a catalyst and thiophenol, *m*-aminothiophenol or ethyl thioglycolate as the nucleophile thiol (Scheme 2, Table II). In all cases the use of natural phosphate modified by lithium nitrate (Li/NP) as a heterogeneous catalyst in the construction of a carbon–sulfur bond allowed the isolation of products **13** rapidly (1–8 min) and with excellent yields (90–96%; Table II).

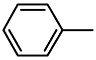
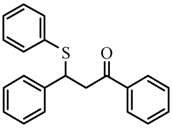
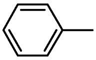
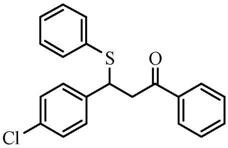
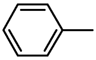
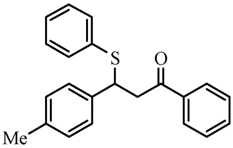
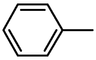
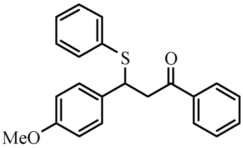
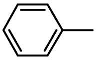
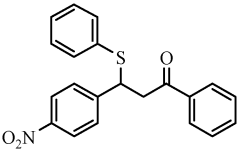
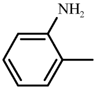
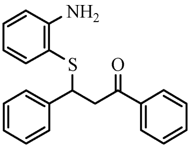
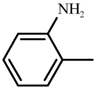
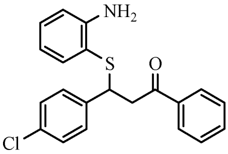
Except in one case, all combinations led to the selectivity of the corresponding expected 1,4-adducts. No byproducts resulting from the undesirable 1,2-addition and/or bis-addition side reactions (observed under classical conditions in some cases) were observed. However, a reaction of 2-aminothiophenol with Michael acceptor bearing in the *para* position a nitro group ($X = NO_2$, Table II, entry 10) gave an 85/15 mixture of 1,4- and 1,3-addition products. The product **13a** (X = H, R = Ph, Scheme 2) was converted to β-sulfur acid (anilide of 3-phenyl-3-sulfinylpropanoic acid) **7b** by different steps (Scheme 4).

Construction of a Carbon–Carbon Bond in the Presence of Li/NP

Under the best conditions for the previously discussed reactions, the use of NP doped by lithium nitrate increases remarkably the catalytic activity and decreases the reaction time in the formation of a carbon–carbon bond (Scheme 3; Table III).

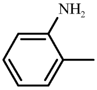
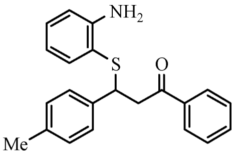
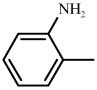
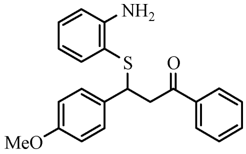
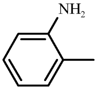
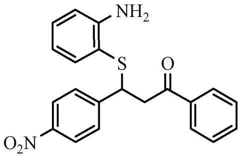
In all cases, the use of Li/NP as a heterogeneous catalyst in the Michael addition allowed the isolation of products **15** rapidly and with excellent yields (88–94%; Table III), except in the case where the nucleophile is nitromethane. In the presence of 0.0063 g of $LiNO_3$ alone (the present quantity in the $LiNO_3$/NP: 1/15 catalyst), no 1,4-addition product was observed under the reaction conditions, and only the starting material was isolated. No by-product resulting from the undesirable 1,2-addition and/or bis-addition side reactions (observed under classical conditions in some cases) were observed. However, a reaction of

TABLE II Construction of a Carbon–Sulfur Bond by Michael Addition Using NP and Li/NP as a Catalyst

			Yield (%) (Time [h])[a]	
R	X	Products	NP[b]	Li/NP
	H **13a**		95 (15)	90 (3)
	Cl **13b**		96 (15)	93 (3)
	Me **13c**		95 (20)	96 (6)
	OMe **13d**		92 (35)	94 (8)
	NO_2 **13e**		91 (07)	92 (1)
	H **13f**		97 (10)	93 (1)
	Cl **13g**		96 (10)	95 (1)

(Continued on next page)

TABLE II Construction of a Carbon–Sulfur Bond by Michael Addition Using NP and Li/NP as a Catalyst *(Continued)*

R	X	Products	Yield (%) (Time [h])[a]	
			NP[b]	Li/NP
	Me **13h**		91 (10)	92 (2)
	OMe **13i**		90 (10)	90 (2)
	NO_2 **13j**		90 (04)[c]	90 (<1)[c]

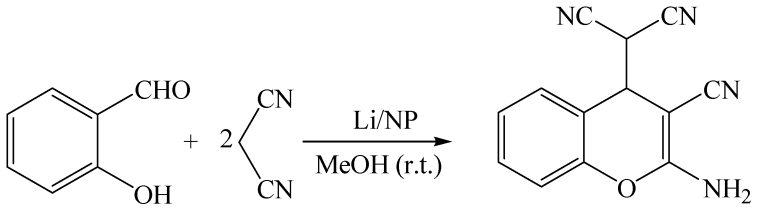
[a] Yields in pure products isolated by recrystallization with AcOEt/CH_2Cl_2 or distillation under vacuum and identified by ^1H, ^{13}C-NMR, and IR spectroscopies.

[b] Reference 10a.

[c] Reaction found 85% of 1,4-addition product and 15% of 1,3-addition product.

nitromethane with various α,β-unsaturated carbonyl compounds **1** at 65°C gives traces of polymerization products (not isolated).

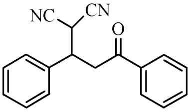
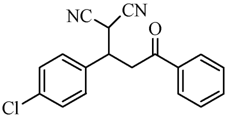
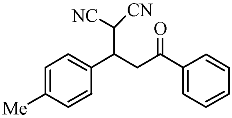
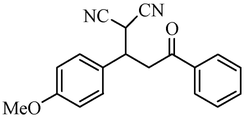
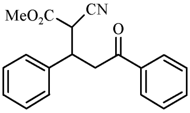
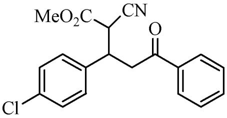
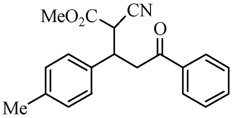
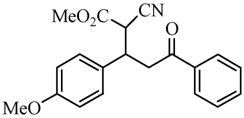
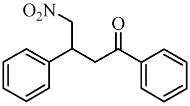
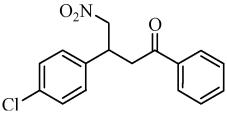
The reaction of salicylaldehyde **16** with an excess of malononitrile gave 4*H*-chromene **17** in an excellent yield (Scheme 6).



16 **17** **90% (6 min)**

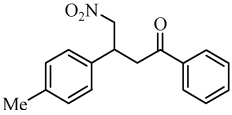
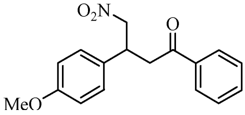
SCHEME 6

TABLE III Construction of a Carbon–Carbon Bond by Michael Addition Using NP and Li/NP

				Yield (%) (Time [min])[a]	
R	X	Y	Products	NP[b]	NP/Li
H	CN	CN **15a**		95 (30)	94 (15)
Cl	CN	CN **15b**		56 (40)[c]	92 (25)[c]
Me	CN	CN **15c**		94 (150)	95 (35)
OMe	CN	CN **15d**		79 (120)	90 (45)
H	CN	CO_2Me **15e**		95 (60)	94 (20)
Cl	CN	CO_2Me **15f**		46 (60)	90 (55)
Me	CN	CO_2Me **15g**		75 (240)	93 (65)
OMe	CN	CO_2Me **15h**		83 (240)	91 (98)
H	NO_2	H **15i**		90 (180)[b]	90 (40)[b]
Cl	NO_2	H **15j**		50 (180)[b]	91 (50)[b]

(Continued on next page)

TABLE III Construction of a Carbon–Carbon Bond by Michael Addition Using NP and Li/NP *(Continued)*

				Yield (%) (Time [min])[a]	
R	X	Y	Products	NP[b]	NP/Li
Me	NO_2	H **15k**		90 (180)[b]	92 (55)[b]
OMe	NO_2	H **15l**		60 (180)[b]	88 (65)[b]

[a] Yields of pure products isolated by recrystallization with AcOEt/CH_2Cl_2 or distillation under vacuum and identified by ^1H, ^{13}C-NMR, and IR spectroscopies.

[b] The reaction mixture was stirred at 65°C; traces of polymerization products were observed.

[c] Reference 15a.

In all cases, the use of NP doped by lithium nitrate (Li/NP) remarkably increases the catalytic activity and decreases the reaction time in the construction of carbon–nitrogen, carbon–sulfur, and carbon–carbon bonds (Tables I–III). For the catalytic activity of Li/NP in this Michael addition, we speculate that the reaction occurs at the surface rather than inside tunnels of the catalyst. The acidic character of the NP surface[25] probably induces the polarization of the C=O bond and the basic sites enhance the thiol nucleophilicity. Consequently, the S—C or C—C bond formation is accelerated, and the final product is obtained after protonation of the resulting enolate. In the case of the construction of a carbon–nitrogen bond, the basic sites depronate RH_2N^+-C after addition to the C=C electron-poor bond.

TABLE IV Comparison of the Activity of Li/NP With Other Phosphate Catalysts

	Yield/% (Time)	
Catalysts	**13a**	**3a**
Li/NP	90 (3 min)	93 (3 h)
NP	95 (15 min)[10a]	25 (2 h); 9 (8 h)[10a]
KF/NP	96 (5 min)[10b]	95 (1 h)[10b]
$Na_2CaP_2O_7$[7]	94 (20 min)	—
FAP[8]	93 (20 min)	—
HAP[9]	93 (5 min)	—

The results obtained in this reaction with Li/NP as a catalyst were compared to those of other phosphates. Thus the activity of Li/NP was higher than NP,[10] synthetic phosphate $Na_2CaP_2O_7$,[6] fluoroapatite (FAP),[7] and hydroxyapatite (HAP),[8] and slightly lower than potassium fluoride–doped natural phosphate (KF/NP; Table IV).[10]

CONCLUSION

NP doped with lithium nitrate calcined at 900°C is an efficient basic catalyst for the construction of carbon–nitrogen, carbon–sulfur, and carbon–carbon bonds. The results depend on several factors, with the nature and amount of solvent a playing decisive role. NP doped with lithium nitrate is used as a catalyst for the facile synthesis of β-amino acids, β-sulfur acids, and 4*H*-chromenes under heterogeneous conditions. These results open the possibility for the use of this inexpensive solid as a basic catalyst for other applications.

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