

# Comparison of different Lewis acids supported on natural phosphate as new catalysts for chemoselective dithioacetalization of carbonyl compounds under solvent-free conditions

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## Abstract

Various carbonyl compounds can be efficiently converted to their corresponding dithioacetals in the presence of catalytic amounts of ZnCl<sub>2</sub>, NiCl<sub>2</sub> or CuCl<sub>2</sub> supported on natural phosphate. The best catalytic activities were observed with the zinc catalysts. In addition, by employing these catalysts, highly chemoselective dithioacetalization of carbonyl compounds has been achieved.

**Keywords:** Carbonyl compounds, dithioacetals, dithiolanes, dithianes, chemoselective, natural phosphate

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## Introduction

The use of heterogeneous catalysts under solvent-free conditions is becoming very popular as it has many advantages: reduced pollution, reusability, high selectivity, low cost, and simplicity in process and in handling. These factors are especially important in industry.

Recently, an informative review<sup>1</sup> by Toda et al. clearly pointed out the superiority of the solvent-free or the use of dry reaction conditions in chemical synthesis.

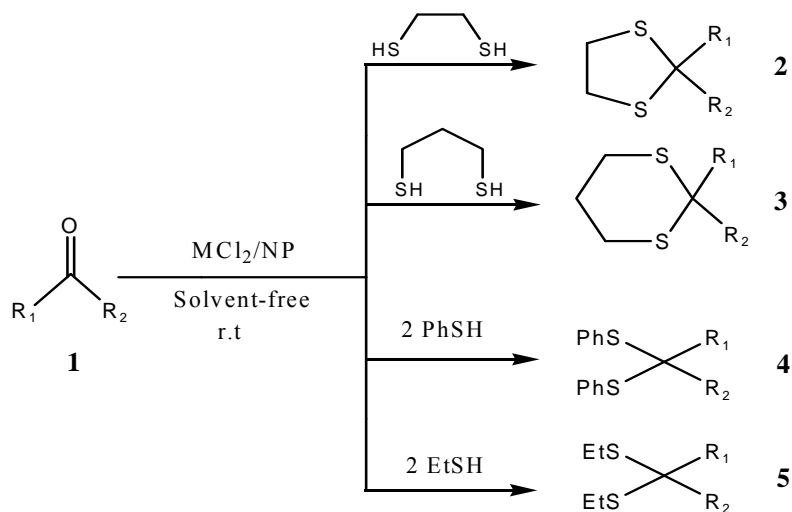
Thioacetalization of carbonyl compounds plays an important role in organic synthesis. Since the introduction of 1,3-dithianes as nucleophilic acylating reagents by Corey and Seebach<sup>2</sup>, dithioacetals have become widely used tools for C-C bond formation. Furthermore, the stability exhibited by 1,3-dithiolanes under acidic and basic conditions has led to their synthetic utility as

carbonyl protecting groups and as intermediates for the conversion of carbonyl compounds to their parent hydrocarbons<sup>3</sup>.

Recently, several acid catalysts have been used in the preparation of thioacetals such as Zn or Mg(OTf)<sub>2</sub><sup>4</sup>, BF<sub>3</sub>.Et<sub>2</sub>O<sup>5</sup>, ZrCl<sub>2</sub>/SiO<sub>2</sub><sup>6</sup>, titanium tetrachloride<sup>7</sup>, SOCl<sub>2</sub>/SiO<sub>2</sub><sup>8</sup>, Zeolite<sup>9</sup>, WCl<sub>2</sub><sup>10</sup>, 5 M LiClO<sub>4</sub>/Et<sub>2</sub>O(LPDE)<sup>11</sup>, TaCl<sub>5</sub>/SiO<sub>2</sub><sup>12</sup>, MoO<sub>2</sub>(acac)<sub>2</sub><sup>13</sup> and Yttrium triflate<sup>14</sup> and other catalysts with more or less success<sup>15</sup>. Many of these methods require long reaction times and reflux temperatures and result in unwanted side reactions, whilst offering poor selectivity when applied to mixtures of aldehydes and ketones. Although some recent methods employing LiBr<sup>16</sup>, InCl<sub>3</sub><sup>17</sup>, and LiBF<sub>4</sub><sup>18</sup> have been reported to show chemoselectivity, these Lewis acids are destroyed in the work-up procedure and cannot be recovered and reused.

On the other hand, we have used natural phosphate (NP)<sup>19</sup> alone and doped as the new heterogeneous catalysts for several reactions such as Knoevenagel condensation<sup>20</sup>, construction of carbon-carbon<sup>21</sup>, carbon-sulfur<sup>22</sup> and carbon-nitrogen<sup>23</sup> bonds, epoxidation of alkenes<sup>24</sup>, Claisen-Schmidt condensation<sup>25</sup> and synthesis of unsaturated arylsulfones<sup>26</sup>. NP has been used also as a Lewis acid catalyst or support in Friedel-Crafts alkylation<sup>27</sup>, 1,3-dipolar cycloaddition<sup>28</sup> and acyclonucleoside synthesis<sup>29</sup>.

In continuation of our interest to develop environmentally safe methods, herein we wish to report an efficient method for the thioacetalization of carbonyl compounds in good to high yields, as well as the chemoselective protection of various carbonyl compounds by employing ZnCl<sub>2</sub> supported on natural phosphate (Scheme 1, Table 1).



**Scheme 1**

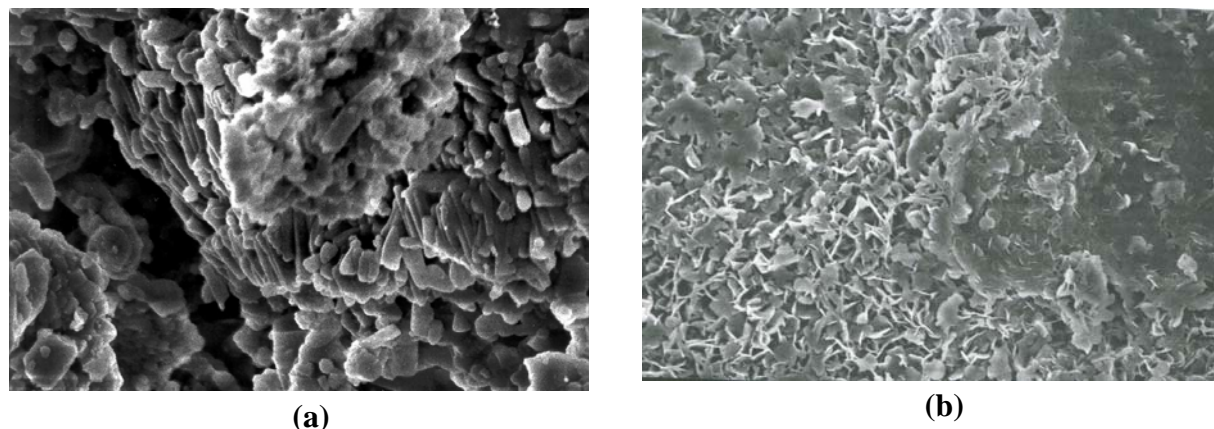
## Experimental Section

### Preparation of the catalyst and structural characteristics

Natural phosphate (NP) used in this work was obtained in the Khouribga region (Morocco)<sup>19</sup>. Prior to use this material requires initial treatments such 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  $\mu\text{m}$  that is rich in phosphate and has the following chemical composition  $\text{P}_2\text{O}_5$  (34.24%),  $\text{CaO}$  (54.12%),  $\text{F}^-$  (3.37%),  $\text{SiO}_2$  (2.42%),  $\text{SO}_3$  (2.21%),  $\text{CO}_2$  (1.13%),  $\text{Na}_2\text{O}$  (0.92%),  $\text{MgO}$  (0.68%),  $\text{Al}_2\text{O}_3$  (0.46%),  $\text{Fe}_2\text{O}_3$  (0.36%),  $\text{K}_2\text{O}$  (0.04%) and several metals (Zn, Cu, Cd, V, U, Cr) in the range of ppm. The structure of the material is similar to that of fluoroapatite ( $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ ). In sedimentary rocks, phosphates are formed from compounds derived from apatite by partial isomorphic substitution:  $\text{Ca}^{2+}$  ions by  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Fe}^{3+}$ , or  $\text{Al}^{3+}$ ,  $\text{PO}_4^{3-}$  ions by  $\text{VO}_4^{3-}$ ,  $\text{SO}_4^{2-}$ ,  $\text{CO}_3^{2-}$  or  $\text{MnO}_4^-$ , and  $\text{F}^-$  by  $\text{HO}^-$  or  $\text{Cl}^-$ . 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 low surface area (BET) at *ca.* 1-1.43  $\text{m}^2 \text{g}^{-1}$ .

The preparation of  $\text{MCl}_2/\text{NP}$  ( $\text{M} = \text{Zn}, \text{Cu}$  or  $\text{Ni}$ ) was as follows: 10 mmol of  $\text{MCl}_2$  and 10g of NP were mixed in 100 ml of water and then evaporated to dryness and dried for 2h at 150°C before use.

The modification of the apatite structure solid by  $\text{MCl}_2$  impregnation does not change the crystalline structure of the solid material [30]. It should be noted that no  $\text{MCl}_2$  phases were detected on the doped materials in all cases, indicating that  $\text{MCl}_2$  were highly dispersed in the solid material. Interestingly, some changes of structure of doped catalysts were observed in scanning electron micrographs (SEM). Thus, the comparison of the images of  $\text{ZnCl}_2/\text{NP}$  with NP (Figure 1) shows some modification in the particle morphology of doped materials. This result suggests that  $\text{ZnCl}_2$  interacted with the surface of NP. So, we can reasonably suspect that the modification of the surface morphology of the apatites was responsible for the enhancement of the catalytic activity observed with the doped materials.



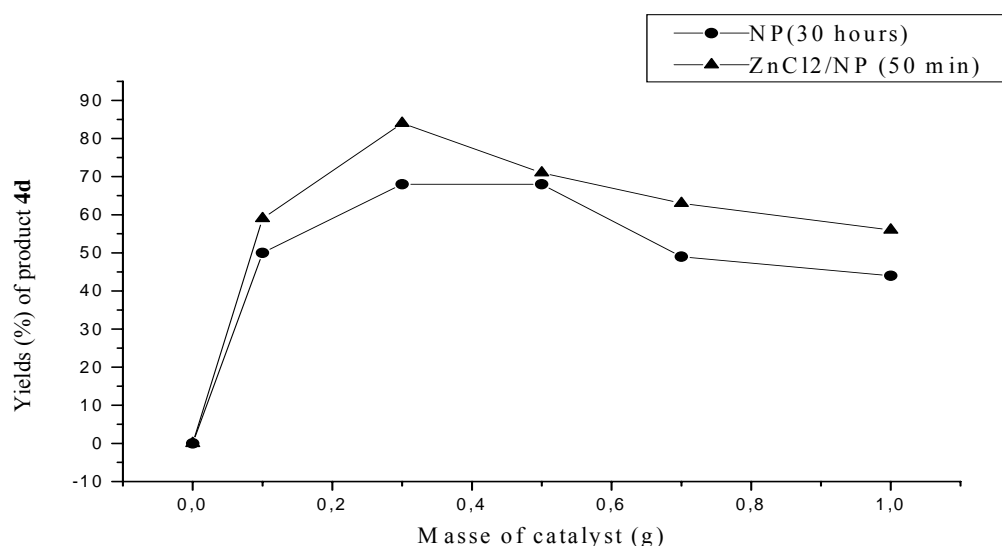
**Figure 1.** Scanning electron micrograph (SEM) images of (a) NP and (b)  $\text{ZnCl}_2/\text{NP}$

### General procedure for the thioacetalization of carbonyl compounds

To a freshly prepared catalyst  $MCl_2/NP$  (0.3 g) under stirring, a mixture of carbonyl compound **1** (2 mmol) and di- or mono-thiol (2.1 or 4.2 mmol, respectively) was added and the mixture was stirred 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 leading to the respective thioacetal (**2** to **5**, Scheme 1, Table 1). The product structure was analysed by  $^1H$ ,  $^{13}C$ -NMR, IR spectrometry and melting points.

### Results and Discussion

First of all, we have tested the natural phosphate alone (0.1, 0.3, 0.5, 0.7, 1g) as the acidic catalyst in the thioacetalization of carbonyl compounds (Figure 2). Thus, various amount of NP alone have been used to catalyse the thioacetalization of *p*-chlorobenzaldehyde by thiophenol. A low yield of **4d** was obtained with NP alone (Figure 2). The yields seem to be limited even if the time of the reaction is prolonged. However, the reaction time is very long (30 hours).

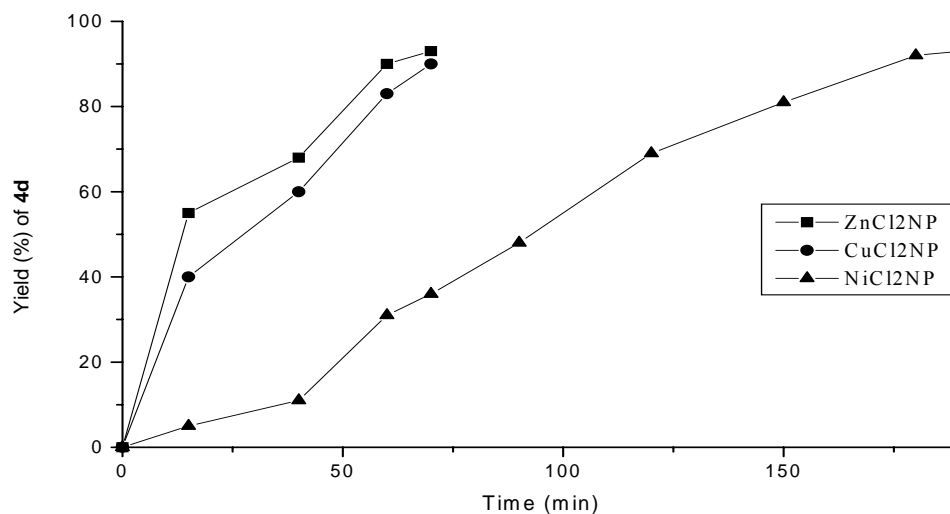


**Figure 2.** Weight effect of the catalyst NP alone and doped with  $ZnCl_2$  in the thioacetalization of *p*-chlorobenzaldehyde by thiophenol.

In view of the established beneficial effects of solid supports, we have investigated the use of the NP impregnated with metal halides for the thioacetalization of carbonyl compounds under mild conditions. These impregnation catalysts have been prepared as indicated before.

Firstly, we have tested the NP impregnated with  $\text{ZnCl}_2$  as the solid catalyst for the thioacetalization of *p*-chlorobenzaldehyde by thiophenol. The best weight of  $\text{ZnCl}_2/\text{NP}$  is 300 mg (Figure 2). In a blank reaction in the presence of 40 mg (quantity present in  $\text{ZnCl}_2/\text{NP}$  catalyst) of  $\text{ZnCl}_2$  alone without NP the thioacetal **4d** was obtained with low yields (25%, 70 min).

Furthermore, the metal halide effect was also examined. Thus, we have tested  $\text{CuCl}_2$  and  $\text{NiCl}_2$  alone and supported on NP. The thioacetalization of *p*-chloro benzaldehyde by thiophenol with  $\text{CuCl}_2$ ,  $\text{CuCl}_2/\text{NP}$ ,  $\text{NiCl}_2$  and  $\text{NiCl}_2/\text{NP}$  are 21, 83, 18, and 40, respectively, after 70 min of reaction time. The results obtained with product **4d** using impregnated catalysts are regrouped in Figure 3. Among these catalysts, satisfactory results have been obtained with  $\text{ZnCl}_2$  supported on the NP. The NP was the preferred choice as support to keep the reaction medium under mild and neutral conditions (Figure 3).



**Figure 3.** Kinetic curves of product **4d** synthesis catalysed by  $\text{ZnCl}_2/\text{NP}$ ,  $\text{CuCl}_2/\text{NP}$  and  $\text{NiCl}_2/\text{NP}$ .

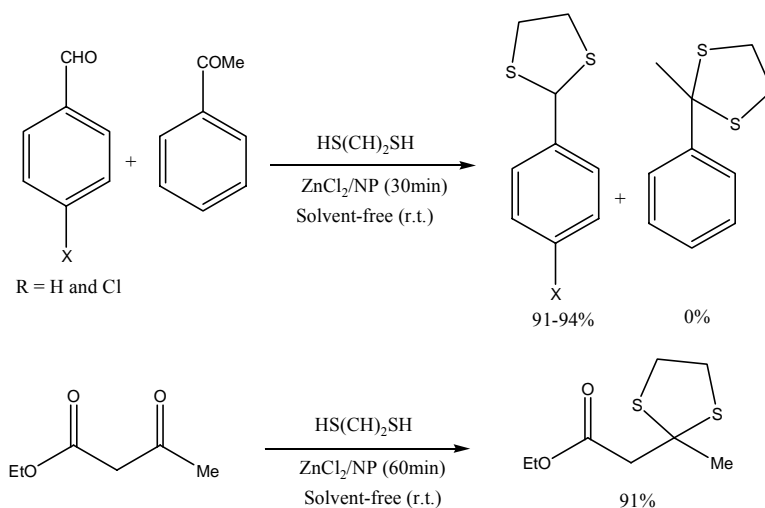
The best conditions for the thioacetalization of *p*-chlorobenzaldehyde by thiophenol are generalized to other carbonyl compounds. Accordingly, dithioacetals and 1,3-dithiolanes have been obtained by the reaction of thiols (ethanethiol and thiophenol) and dithiols (1,2-ethanedithiol, 1,2-propanedithiol), respectively, in the presence of catalytic amounts of  $\text{ZnCl}_2/\text{NP}$  (Scheme 1); the results are illustrated in Table 1.

**Table 1.** ZnCl<sub>2</sub>/NP catalysed protection of carbonyl compounds as dithioacetals, 1,3-dithiolanes and 1,3-dithianes

Entry	Products	Substrate	Reagent	Yield/% (time/min) <sup>a</sup>
1	2a	Benzaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	91(25)
2	2b	<i>p</i> -Methoxybenzaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	94(20)
3	2c	<i>p</i> -Methylbenzaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	93(25)
4	2d	<i>p</i> -Chlorobenzaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	89(25)
5	2e	<i>p</i> -Nitrobenzaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	87(35)
6	2f	Acetophenone	HS(CH <sub>2</sub> ) <sub>2</sub> SH	85(75)
7	2g	Cyclohexanone	HS(CH <sub>2</sub> ) <sub>2</sub> SH	89(60)
8	2h	Cinnamaldehyde	HS(CH <sub>2</sub> ) <sub>2</sub> SH	92(25)
9	3a	Benzaldehyde	HS(CH <sub>2</sub> ) <sub>3</sub> SH	89(25)
10	3b	<i>p</i> -Methoxybenzaldehyde	HS(CH <sub>2</sub> ) <sub>3</sub> SH	96(25)
11	3c	<i>p</i> -Methylbenzaldehyde	HS(CH <sub>2</sub> ) <sub>3</sub> SH	90(25)
12	3d	<i>p</i> -Chlorobenzaldehyde	HS(CH <sub>2</sub> ) <sub>3</sub> SH	92(30)
13	3e	<i>p</i> -Nitrobenzaldehyde	HS(CH <sub>2</sub> ) <sub>3</sub> SH	91(40)
14	3f	Acetophenone	HS(CH <sub>2</sub> ) <sub>3</sub> SH	78(75)
15	3g	Cyclohexanone	HS(CH <sub>2</sub> ) <sub>3</sub> SH	80(60)
16	4a	Benzaldehyde	PhSH	71(20), 90(40)
17	4b	<i>p</i> -Methoxybenzaldehyde	PhSH	80(20), 94(35)
18	4c	<i>p</i> -Methylbenzaldehyde	PhSH	76(20), 90(40)
19	4d	<i>p</i> -Chlorobenzaldehyde	PhSH	55(20), 93(70)
20	4e	<i>p</i> -Nitrobenzaldehyde	PhSH	40(20), 88(55)
21	4f	Acetophenone	PhSH	91(90)
22	4g	Cyclohexanone	PhSH	87 (60)
23	4h	Acetone	PhSH	91 <sup>b</sup> -(60)
24	5a	Benzaldehyde	EtSH	90-(30)
25	5b	<i>p</i> -Methoxybenzaldehyde	EtSH	93-(25)
26	5c	<i>p</i> -Methylbenzaldehyde	EtSH	92-(30)
27	5d	<i>p</i> -Chlorobenzaldehyde	EtSH	88-(40)
28	5e	<i>p</i> -Nitrobenzaldehyde	EtSH	85-(45)
29	5f	Cyclohexanone	EtSH	90-(60)

<sup>a</sup>Yields refer to isolated in pure products.<sup>b</sup>Yields based on thiol as reagent, as the acetone is volatile.

Because the conversion of aldehydes is faster than that of ketones, as shown in Table 1, the present method can be used for the chemoselective protection of aldehydes in the presence of a ketone function [31]. For example, when an equimolar mixture of aldehyde and ketone was allowed to react with 1,2-ethanedithiol in the presence of a catalytic amount of  $\text{ZnCl}_2/\text{NP}$ , only the 1,2-dithiane derivative of the corresponding aldehyde was obtained; ketone was recovered quantitatively (Scheme 2). Furthermore, the thioacetalization of ethyl acetoacetate also exhibited splendid selectivity towards the acetyl group (Scheme 2). In addition, this method is free from the problem of Michael addition encountered in some cases of  $\alpha,\beta$ -unsaturated systems with some reagents [32] (entry 8, Table 1).



## Scheme 2

To evaluate the effect of the presence of an electron acceptor or donor on the aromatic ring of benzaldehyde, the reaction was carried out between thiophenol and substituted benzaldehyde derivatives using  $\text{ZnCl}_2/\text{NP}$  as catalyst (Scheme 1). Results in Table 1 show that the presence of electron-withdrawing groups on the aromatic ring of the aldehydes (entry 19-20, Table 1) decreases the yields proportionally to the value of Hammett constant. Meanwhile, the presence of electron-donating groups (entry 16-18, Table 1) increases the yields, demonstrating the participation of both the aldehydes and the thiol in the rate controlling step of the reaction. The activity of  $\text{ZnCl}_2/\text{NP}$  seems to be higher than other known catalysts (Table 2).

**Table 2** Comparison of ZnCl<sub>2</sub>/NP with several heterogeneous homogeneous catalysts in the synthesis of products **3a** and **3g**

Entry	Solid catalyst	Yields(time) [(%)(time/min)] <sup>a</sup>	
		Product 3a	Product 3g
1	ZnCl <sub>2</sub> /NP	89(25)	78(75)
2	NP	44(1440) <sup>b</sup>	---
3	I <sub>2</sub> /NP[33]	93(4)	87(20)
5	Se(OTf) <sub>3</sub> [15b]	94(30)	---
6	Y(OTf) <sub>3</sub> [14]	89(45)	87(360)
7	CoCl <sub>3</sub> [15c]	91(60)	---
8	Zeolite-HY [11]	96(60)	87(60)
9	Zeolite-CaY [11]	91(60)	89(60)
10	Zeolite-MgY [11]	86(60)	80(60)
11	MoO <sub>2</sub> (acac) <sub>2</sub> [13]	94(180)	85(180)
12	Li(OTf) <sub>3</sub> [15d]	99(5) <sup>c</sup>	96(35) <sup>c</sup>

<sup>a</sup>Yields refer to isolated and chromatographically pure compounds; <sup>b</sup>Reaction carried out solvent-free conditions; <sup>c</sup>Reaction carried at 90-110 °C.

## Conclusions

We have developed a simple and efficient method for the chemoselective protection of carbonyl compounds as dithioacetals, dithiolanes and dithianes using a catalytic amount of a Lewis acid supported on natural phosphate in solvent-free conditions at room temperature. Further, the natural phosphate of non-toxic and inexpensive catalysts can be readily recovered and reused, thus making this procedure more environmentally acceptable.

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