

A mild and efficient method for the protection of carbonyl compounds as dithioacetals, dithiolanes and dithianes catalysed by iodine supported on natural phosphate

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Abstract

Carbonyl compounds have been successfully converted into their corresponding dithioacetals, dithiolanes and dithianes derivatives in excellent yields with thiol (ethanethiol and thiophenol), 1,2-ethanedithiol and 1,3-propanedithiol using a catalytic amount of iodine supported on natural phosphate. In addition, by employing this catalyst, high chemoselective thioacetalization of carbonyl compounds have been achieved. © 2005 Elsevier B.V. All rights reserved.

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1. Introduction

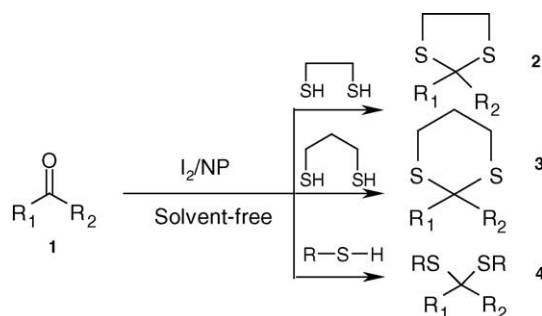
The protection of carbonyl groups as acetals or thioacetals is an integral part of organic manipulations such as the preparation of monomer building blocks, fine chemicals, precursors for pharmaceuticals, and natural products and these reactions often involve the use of acidic, basic or hazardous and corrosive reagents and toxic metal salts.

Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in industry. These reactions are effected by the reagents immobilized on the porous solid supports [1] and have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, enhanced reaction rates, cleaner product, and easier work-up.

In the literature there are numerous methods reported for the preparation of thioacetals from carbonyl compounds

employing acid catalysts such as $ZnCl_2$ [2], $BF_3 \cdot Et_2O$ [3], $ZrCl_2/SiO_2$ [4], titanium tetrachloride [5], magnesium or zinc triflate [6], $SOCl_2/SiO_2$ [7], Zeolite [8], WCl_2 [9], 5 M $LiClO_4/Et_2O(LPDE)$ [10], $TaCl_5/SiO_2$ [11], $MoO_2(acac)_2$ [12] and Yttrium triflate [13]. Most 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 $LiBr$ [14], $InCl_3$ [15], and $LiBF_4$ [16] have been reported to show chemoselectivity, these Lewis acids are destroyed in the work-up procedure and cannot be recovered and reused. However, the developments in this area demand further searches for better catalysts [16] that could be superior to the existing ones with regard to toxicity, handling, selectivity and recyclability. During the past seven years we have studied the use of natural phosphate (NP) [17] to promote organic transformation [18] and have shown that its mild basic and acidic properties can be exploited in many synthetic applications [19]. Among the different inorganic solids, NP has advantages because

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Scheme 1.

it is cheap, readily available, stable in water, non-toxic, and not a pollutant. Recycling of the NP renders the relatively environmental procedure by utilizing these properties.

In this paper we 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 iodine supported on natural phosphate (Scheme 1).

2. Experimental

2.1. Preparation of the catalyst and structural characteristics

Natural phosphate (NP) used in this work was obtained in the Khouribga region (Morocco) [17]. 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 μm that is rich in phosphate and has following chemical composition: P₂O₅ (34.24%), CaO (54.12%), F⁻ (3.37%), SiO₂ (2.42%), SO₃ (2.21%), CO₂ (1.13%), Na₂O (0.92%), MgO (0.68%), Al₂O₃ (0.46%), Fe₂O₃ (0.36%), K₂O (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 (Ca₁₀(PO₄)₆F₂). In sedimentary rocks, phosphates are formed from compounds derived from apatite by partial isomorphic substitution: of: Na⁺, Mg²⁺, Co²⁺, Fe³⁺, or Al³⁺ for Ca²⁺ ions, VO₄³⁻, SO₄²⁻, CO₃²⁻ or MnO₄²⁻ for PO₄³⁻ ions, and OH⁻ or Cl⁻ for F⁻. 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 m² g⁻¹.

The catalyst was prepared by treating natural phosphate (300 mg) with a solution of 51 mg (0.20 mmol) of iodine in 2 mL of dichloromethane. The slurry was stirred magnetically at room temperature for 15 min and the excess solvent was removed by evaporation under reduced pressure and low temperature.

2.2. General procedure for the thioacetalization of carbonyl compounds

To a freshly prepared catalyst (0.3 g, 0.2 mmol of iodine) under stirring, a mixture of carbonyl compound 1 (2 mmol) and monothiol or dithiol (4.2 or 2.1 mmol, respectively) 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 leading to the respective thioacetal (2, 3 or 4, Scheme 1). The product structure was analysed by ¹H, ¹³C NMR, IR spectrometry and melting points. When NP and I₂ are mixed one pot in the reaction mixture without previous absorption the thioacetal (2, 3 or 4) was obtained in slightly lower yields.

3. Results and discussion

p-chlorobenzaldehyde, thiophenol and iodine (Scheme 1) were chosen as model substrates to determine suitable conditions. The optimum weight of NP is 300 mg (Fig. 1). In a blank reaction (4 min), NP alone without iodine was found to give no product. However, in the presence of 0.2 mmol of iodine alone without NP the thioacetal 4d was obtained with low yields (37%, 20 min). The NP was the preferred choice as a support to keep the reaction medium under mild and neutral conditions.

Interestingly, the experimental procedure for thioacetalization is remarkably simple and does not require the use of solvents or inert atmospheres. A catalytic quantity of I₂ supported on natural phosphate was added to the carbonyl compound, to this was added the required monothiol or dithiol (2.1 or 1.1 equiv., respectively) and the mixture was stirred at room temperature. The generality of this process has been proved in a wide range of aromatic, aliphatic and α, β-unsaturated carbonyl compounds. Accordingly, dithioacetals, 1,3-dithiolanes and 1,3-dithianes have been obtained by the reaction of thiol (ethanethiol and thiophenol), 1,2-ethanedithiol and 1,3-propanedithiol, respectively, in the

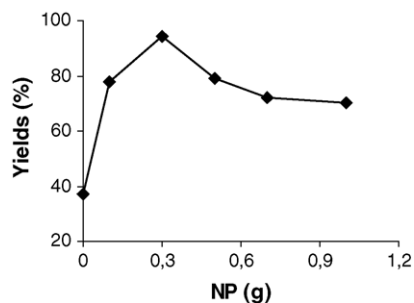


Fig. 1. Influence of NP weight in the protection of *p*-chloro benzaldehyde by thiophenol.

Table 1
I₂/NP catalysed protection of carbonyl compounds as dithioacetals, 1,3-dithiolanes and 1,3-dithianes

Entry	Products	Substrate	Reagent	Yield ^a (%) (time/min)
1	2a	Benzaldehyde	HS(CH ₂) ₂ SH	90 (3)
2	2b	<i>p</i> -Methoxybenzaldehyde	HS(CH ₂) ₂ SH	96 (2)
3	2c	<i>p</i> -Methylbenzaldehyde	HS(CH ₂) ₂ SH	94 (3)
4	2d	<i>p</i> -Chlorobenzaldehyde	HS(CH ₂) ₂ SH	91 (3)
5	2e	<i>p</i> -Nitrobenzaldehyde	HS(CH ₂) ₂ SH	93 (4)
6	2f	Acetophenone	HS(CH ₂) ₂ SH	91 (25)
7	2g	Cyclohexanone	HS(CH ₂) ₂ SH	93 (15)
8	2h	Cinnamaldehyde	HS(CH ₂) ₂ SH	95 (3)
9	3a	Benzaldehyde	HS(CH ₂) ₃ SH	93 (4)
10	3b	<i>p</i> -Methoxybenzaldehyde	HS(CH ₂) ₃ SH	94 (3)
11	3c	<i>p</i> -Methylbenzaldehyde	HS(CH ₂) ₃ SH	91 (4)
12	3d	<i>p</i> -Chlorobenzaldehyde	HS(CH ₂) ₃ SH	92 (4)
13	3e	<i>p</i> -Nitrobenzaldehyde	HS(CH ₂) ₃ SH	92 (5)
14	3f	Acetophenone	HS(CH ₂) ₃ SH	92 (35)
15	3g	Cyclohexanone	HS(CH ₂) ₃ SH	87 (20)
16	4a	Benzaldehyde	PhSH	93 (20)
17	4b	<i>p</i> -Methoxybenzaldehyde	PhSH	91 (15)
18	4c	<i>p</i> -Methylbenzaldehyde	PhSH	90 (15)
19	4d	<i>p</i> -Chlorobenzaldehyde	PhSH	94 (20)
20	4e	<i>p</i> -Nitrobenzaldehyde	PhSH	95 (25)
21	4f	Acetophenone	PhSH	87 (70)
22	4g	Cyclohexanone	PhSH	90 (50)
23	4h	Benzaldehyde	EtSH	91 (4)
24	4i	<i>p</i> -Methoxybenzaldehyde	EtSH	93 (3)
25	4j	<i>p</i> -Methylbenzaldehyde	EtSH	90 (4)
26	4k	<i>p</i> -Chlorobenzaldehyde	EtSH	90 (4)
27	4m	<i>p</i> -Nitrobenzaldehyde	EtSH	92 (6)
28	4n	Cyclohexanone	EtSH	90 (30)

^a Yields refer to isolated in pure products.

presence of catalytic amounts of I₂/NP (Scheme 1); the results are illustrated in Table 1.

We observed that the reaction of aldehydes takes place rapidly in the presence of I₂/NP when compared to that of ketones (see Table 1). This method is suitable for aldehydes and ketones both aromatic and aliphatic (cyclohexanone) as well as α , β -unsaturated carbonyl compounds. It is free from the problem of Michael addition encountered in some case of α , β -unsaturated carbonyl systems (Table 1, entry 8) with some reagents [20].

The difference in reactivity of the I₂/NP catalyst towards aldehydes and ketones gave us impetus to study chemoselective reactions. With this objective, as a representative example we carried out some experiments with equimolar mixtures of an aldehyde and a ketone (Scheme 2). It was observed that



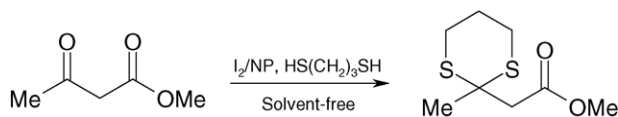
Scheme 2.

in this mixture, the corresponding aldehyde formed the 1,3-dithiolane whilst the ketone was almost completely recovered.

This method has also been extended to the intramolecular chemoselectivity between keto and ester functionalities (Scheme 3). Only keto functionality was thioacetalized by this method in a short period (30 min) with a high yield (92%). When compared with the existing method, the present method was found to be superior in many respects.

The activity of I₂/NP seems to be higher than other known catalysts (Table 2).

We next investigated the stability of the catalyst in order to recycle it. The used and recovered NP has been shown to be reusable after drying at 150 °C in vacuum, and more efficiently after washing with acetone followed by calcinations at 900 °C (Fig. 2). In the last case, the catalyst can be recovered and reused at least five times without appreciable loss of activity.



Scheme 3.

Table 2

Comparison of I₂/NP with several heterogeneous catalysts in the synthesis of products **3a**, **3g** and **2b**

Entry	Solid catalyst	Yields ^a (time) [(%) (time/min)]		
		Product 3a	Product 3g	Product 2b
1	I ₂ /NP	93 (4)	87 (20)	96 (2)
2	I ₂ /Al ₂ O ₃ [21]	–	–	94 (10)
3	I ₂	37 (20) ^b , 99 (30) [22]	97 (240) [22]	–
4	NP	44 (1440) ^b	–	–
5	Y(OTf) ₃ [13]	89 (45)	87 (360)	93 (45)
6	Zeolite-HY [8]	96 (60)	87 (60)	–
7	Zeolite-CaY [8]	91 (60)	89 (60)	–
8	Zeolite-MgY [8]	86 (60)	80 (60)	–
9	Li(OTf) [23]	99 (5) ^c	96 (35) ^c	–
10	InCl ₃ [15]	–	–	92 (15)
11	In(OTf) ₃ [24]	–	–	95 (6)
12	ZrCl ₂ /Si ₂ O [4]	–	–	96 (5)

^a Yields refer to isolated and chromatographically pure compounds.

^b Reaction carried out solvent-free conditions.

^c Reaction carried at 90–110 °C.

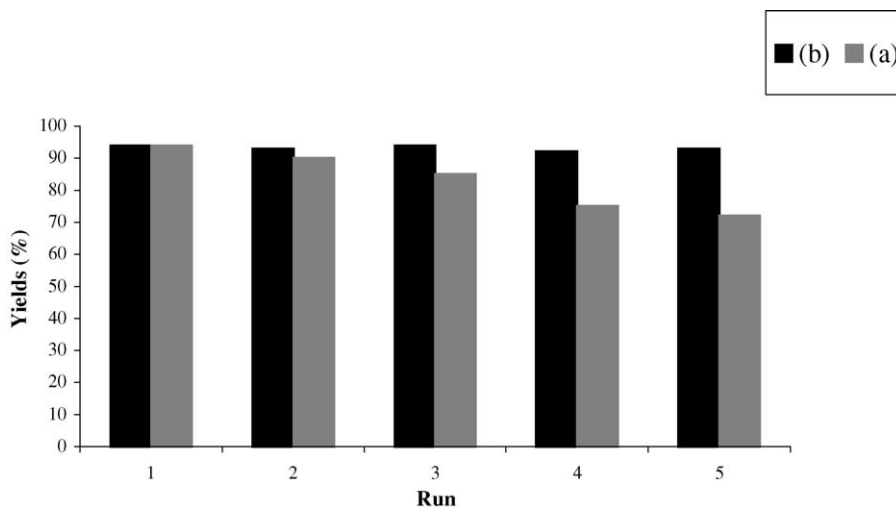


Fig. 2. Recycling of the NP catalyst in the synthesis 3d: (a) catalyst recoverable dried at 150 °C for 1 h; (b) catalyst recoverable, washed with acetone, dried and calcined at 900 °C for 15–30 min.

4. Conclusion

We have shown that iodine supported on natural phosphate can be effectively employed for protection of carbonyl compounds as their thioacetals in good yield at ambient temperature in mild conditions. Furthermore, the relatively slow reaction rate of ketones allows chemoselective protection of aldehydes in the presence of ketones, making this an important tool in the synthetic organic chemistry. The notable advantages of this method are its chemoselectivity, the requirement for minimum amounts of catalyst, the remarkably simple experimental procedure, and no necessity for solvents or inert atmospheres, and use of non-toxic and inexpensive natural phosphate as a catalyst.

References

- [1] (a) H. Hattori, *Stud. Surf. Sci. Catal.* 78 (1993) 35; (b) H. Hattori, *Chem. Rev.* 95 (1995) 537; (c) Y. Ono, T. Baba, *Catal. Today* 38 (1997) 321; (d) J. Bennazha, M. Zahouily, S. Sebti, A. Boukhari, E.M. Holt, *Catal. Commun.* 2 (2001) 101; (e) M. Zahouily, Y. Abrouki, A. Rayadh, *Tetrahedron Lett.* 43 (2002) 7729; (f) M. Zahouily, Y. Abrouki, A. Rayadh, S. Sebti, H. Dhimane, M. David, *Tetrahedron Lett.* 44 (2003) 2463; (g) J. Bennazha, M. Zahouily, A. Boukhari, E.M. Holt, *J. Mol. Catal. A: Chem.* 202 (2003) 247; (h) G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi, P. Righi, *Chem. Rev.* 104 (2004) 199.
- [2] D.A. Evans, L.K. Truesdale, K.G. Grimm, S.L. Nesbitt, *J. Am. Chem. Soc.* 99 (1977) 5009.

- [3] (a) L.F. Fieser, J. Am. Chem. Soc. 76 (1954) 1945;
(b) T. Nakata, S. Nagao, N. Mori, T. Oishi, Tetrahedron Lett. 26 (1985) 6461.
- [4] H.K. Pantey, S. Margan, Tetrahedron Lett. 37 (1996) 4621.
- [5] V. Kumar, S. Dev, Tetrahedron Lett. 24 (1983) 1289.
- [6] V.K. Yadav, A.G. Fallis, Tetrahedron Lett. 29 (1988) 897.
- [7] Y. Kamitori, M. Hojo, R. Masuda, T. Kimura, T. Yoshida, J. Org. Chem. 51 (1986) 1427.
- [8] A. Latitha, K. Pitchumani, C. Srinivasan, Green Chem. (1999) 175.
- [9] H. Firouzabadi, N. Iranpoor, B. Karimi, Synletter (1998) 739.
- [10] V. Geetha Saraswathy, S. Sankararaman, J. Org. Chem. 59 (1994) 4665.
- [11] S. Chandrasekhar, M. Takhi, Y.R. Reddy, S. Mohapatra, C.R. Rao, K.V. Reddy, Tetrahedron 53 (1997) 14997.
- [12] K.K. Rana, C. Guin, S. Jana, S.C. Roy, Tetrahedron Lett. 44 (2003) 8597.
- [13] S. Kanta De, Tetrahedron Lett. 45 (2004) 2339.
- [14] H. Firouzabadi, N. Iranpoor, B. Karimi, Synthesis (1999) 58.
- [15] S. Muthusamy, S. Arulananda Babu, C. Gunanathan, Tetrahedron Lett. 42 (2001) 359.
- [16] J.S. Yadav, B.V.S. Reddy, S.K. Pandey, Synletter (2001) 238.
- [17] Natural phosphate (NP) comes Khouribga region (Morocco). It is readily available (raw or treated) from CERPHOS 37, Bd My Ismail, Casablanca, Morocco.
- [18] (a) S. Sebti, A. Saber, A. Rhihil, Tetrahedron Lett. 35 (1994) 9399;
(b) M. Zahouily, B. Bahlaouan, A. Solhy, S. Sebti, React. Kinet. Catal. Lett. 78 (2003) 129;
(c) M. Zahouily, M. Salah, B. Bahlaouan, A. Rayadh, A. Houmam, E.A. Hamed, S. Sebti, Tetrahedron 60 (2004) 1631.
- [19] (a) H.B. Lazrek, A. Rochdi, Y. Kabbaj, M. Taourirte, S. Sebti, Synth. Commun. 29 (1999) 1057;
(b) Y. Abrouki, M. Zahouily, A. Rayadh, B. Bahlaouan, S. Sebti, Tetrahedron Lett. 43 (2002) 8951;
(c) M. Zahouily, B. Bahlaouan, M. Aadil, A. Rayadh, S. Sebti, Org. Process Res. Dev. 8 (2004) 275;
(d) M. Zahouily, B. Bahlaouan, A. Rayadh, S. Sebti, Tetrahedron Lett. 45 (2004) 4135.
- [20] E.J. Corey, K. Shimoji, Tetrahedron Lett. 24 (1983) 169.
- [21] N. Deka, J.C. Sarma, Chem. Lett. (2001) 794.
- [22] S. Samajdar, M.K. Basu, F.F. Becker, B.K. Banik, Tetrahedron Lett. 42 (2001) 4425.
- [23] H. Firouzabadi, B. Karimi, S. Eslami, Tetrahedron Lett. 40 (1999) 4055.
- [24] S. Muthusamy, S. Arulananda Babu, C. Gunanathan, Tetrahedron 58 (2002) 7897.