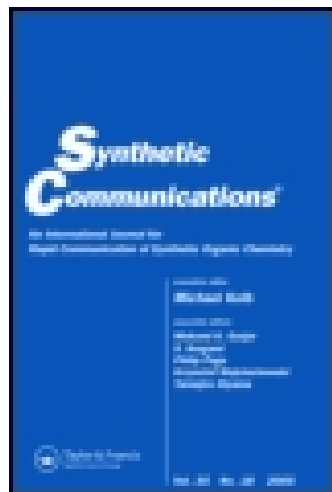


This article was downloaded by: [University of Connecticut]

On: 06 October 2014, At: 16:37

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

Chemoselective and Chemospecific Protection and Deprotection of a Carbonyl Group Using Polystyrene Divinylbenzene Sulfonic Acid

Sanjeev K. Verma^a, Manisha Sathe^a & M. P. Kaushik^a

^a Discovery Centre, Process Technology Development Division, Defence Research and Development Establishment, Gwalior, India
Published online: 06 May 2010.

To cite this article: Sanjeev K. Verma, Manisha Sathe & M. P. Kaushik (2010) Chemoselective and Chemospecific Protection and Deprotection of a Carbonyl Group Using Polystyrene Divinylbenzene Sulfonic Acid, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 40:11, 1701-1707, DOI: [10.1080/00397910903161702](https://doi.org/10.1080/00397910903161702)

To link to this article: <http://dx.doi.org/10.1080/00397910903161702>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms &

Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

CHEMOSELECTIVE AND CHEMOSPECIFIC PROTECTION AND DEPROTECTION OF A CARBONYL GROUP USING POLYSTYRENE DIVINYLBENZENE SULFONIC ACID

Sanjeev K. Verma, Manisha Sathe, and M. P. Kaushik

Discovery Centre, Process Technology Development Division, Defence Research and Development Establishment, Gwalior, India

Chemospecific protection of one carbonyl group of two identical carbonyls of 2,2-dialkyl-1,3-cyclohexanedione and chemoselective protection of aliphatic or aromatic carbonyls in the presence of conjugated carbonyl compounds using cross-linked polystyrene divinyl benzene sulfonic acid (SPS) as a heterogeneous catalyst has been demonstrated.

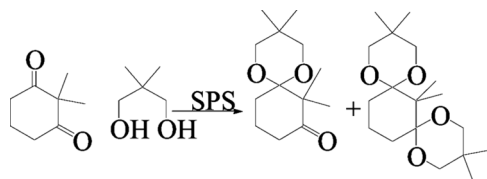
Keywords: 2,2-Dialkyl-1,3-cyclohexanedione; chemoselectivity; chemospecificity; polystyrene divinyl benzene sulfonic acid

INTRODUCTION

Chemoselective and chemospecific protection of carbonyl group is one of the most intriguing tasks in organic synthesis, essentially because of its application in various multistep syntheses.^[1] In various ketones, the chemospecific protection of one carbonyl in 1,3-diones has great importance because of its involvement in various natural product syntheses.^[1] Protection of carbonyl groups mainly involves the formation of acetals or ketals in the presence of an acid.^[1,2] A myriad of catalysts/reagents including ionic liquids,^[3] organometallic^[4] and silyl reagents,^[5] and inorganic compounds [FeCl₃, TiCl₄, Bi(NO₃)₃]^[6] have been employed for the protection of carbonyl groups; however, these reagents show a number of disadvantages. One among them is nonchemoselectivity. Therefore, efforts were made to develop new reagents/catalysts with high activity, selectivity, and generality, which can lead to practical and efficient protection and deprotection of various carbonyl groups. Recently, we have initiated work in the field of solid-supported reagents for various chemical transformations in organic synthesis.^[7] Polymeric catalysts have received much attention because of their stability and reusability.^[8,9] Such catalysts not only simplify purification processes but also are ecofriendly. Considering the significance of protection of carbonyl groups, and in continuation of our work on

Received April 1, 2009.

Address correspondence to M. P. Kaushik, Discovery Centre, Process Technology Development Division, Defence Research and Development Establishment, Jhansi Road, Gwalior 474 002, M.P., India. E-mail: mpkaushik@rediffmail.com



Scheme 1. Protection of carbonyl with SPS.

solid-supported reagents, we report herein an efficient method for the chemospecific and chemoselective protection and deprotection of carbonyl groups using cross-linked polystyrene divinyl benzene sulfonic acid (SPS) as a heterogeneous catalyst (Scheme 1).

RESULTS AND DISCUSSION

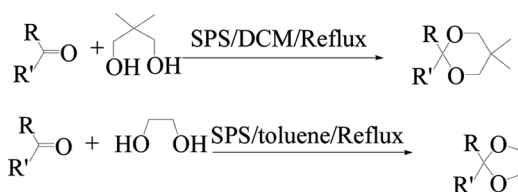
Cross-linked SPS was synthesized by refluxing polystyrene beads with chlorosulfonic acid in dichloromethane (DCM)^[10] and used as a reagent for chemoselective and chemospecific protection of a carbonyl group. 2,2-Methyl-1,3-cyclohexanone was used as reactant to standardize all other parameters (diol, solvent, acid source).

Effect of the diol on chemoselective protection of 2,2-dimethyl-1,3-cyclohexanedione was studied using ethanediol and 2,2-dimethyl-1,3-propanediol. The more hindered 2,2-dimethyl-1,3-propanediol give the best result with SPS, where only a monoprotected product was observed (entry 1, Table 1), whereas with 1,2-ethanediol, the ratio of monoprotected to diprotected product was 9:1 with a lesser conversion rate (entry 16, Table 1).

The effect of acid source on the chemoselective protection of 2,2-dimethyl-1,3-cyclohexanedione with 2,2-dimethyl-1,3-propanediol was studied using different acid sources (Table 2) such as *p*-toluene sulfonic acid (*p*TsOH), camphor sulfonic acid (CSA), and SPS. It was found that with a more hindered acid source (CSA), the percentage of monoprotected product increased. With SPS, only monoprotected product was observed. When compared with traditional reagents such as *p*-TsOH and CSA, the reagent showed shorter reaction time and no azo-tropical removal of water was required.

The effect of solvent on reaction rate was observed with different solvents (Table 3). It was found that SPS gave a better result with only solvent that result in swelling in the beads. The yield in toluene, benzene, or hexane was very poor. DCM gave the best swelling and was the best solvent for protection with 2,2-dimethyl-1,3-propanediol. DCM does not give the desired yield with ethanediol because of its very poor reactivity under the reflux temperature of DCM. Ethanediol show reactivity with toluene, which has a higher boiling point but also less reactivity. The reaction in the given case may be only outside the beads. That is clear from the lesser reactivity.

Chemoselectivity was studied with different cyclohexanediones (Table 1, entries 1–7). Chemospecificity was observed with 2,2 alkyl-1,3-diones only. In various 2,2-dialkyl-1,3-diones, reaction yield or overall conversion decreased with

Table 1. Protection of carbonyl using SPS as catalyst

No.	Aldehyde/ketone	Diol	Time (h)	Yield (%) ^a
1	2,2-Dimethyl Cyclohexan-1,3-dione	2,2-Dimethyl-1,3-propanediol	2	85
2	2-Ethyl-2-methyl cyclohexane-1,3-dione	2,2-Dimethyl-1,3-propanediol	2	75
3	2-Methyl-2-propenyl 1,3-cyclohexanedione	2,2-Dimethyl-1,3-propanediol	7	65
4	2-Benzyl-2-methyl- 1,3-cyclohexanedione	2,2-Dimethyl-1,3-propanediol	7	0
5	2-Methyl cyclohexane-1,3-dione	2,2-Dimethyl-1,3-propanediol	7	0
6	1,3-Cyclohexanedione	2,2-Dimethyl-1,3-propanediol	7	0
7	1,4-Cyclohexanedione	2,2-Dimethyl-1,3-propanediol	2	50
8	Cyclohexanone	2,2-Dimethyl-1,3-propanediol	2	95
9	2-Methyl-cyclohexanone	2,2-Dimethyl-1,3-propanediol	2	90
10	Cyclohex-2-en-1-one	2,2-Dimethyl-1,3-propanediol	2	0
11	Ethyl vinyl ketone	2,2-Dimethyl-1,3-propanediol	2	0
12	Benzaldehyde	2,2-Dimethyl-1,3-propanediol	8	85
13	p-Nitrobenzaldehyde	2,2-Dimethyl-1,3-propanediol	7	92
14	p-Methylbenzaldehyde	2,2-Dimethyl-1,3-propanediol	7	80
15	Cyclohexanone	1,2-Ethanediol	6	40
16	2,2-Dimethyl-cyclohexane-1,3-dione	1,2-Ethanediol	6	36
17	Cyclohex-2-en-1-one	1,2-Ethanediol	6	0
18	Carvone	1,2-Ethanediol	6	0
19	Benzaldehyde	1,2-Ethanediol	6	0
20	p-Methylbenzaldehyde	1,2-Ethanediol	6	0
21	p-Nitrobenzaldehyde	1,2-Ethanediol	6	0

Note. All the products were compared with authentic sample and gave satisfactory IR, NMR, and MS data.

^aIsolated yields. In the case of dione, yield is only of monoprotected carbonyls.

chain length of alkyl groups (Table 1, entries 1–4). This may be the result of a decrease in diffusion rate in the beads with an increase in chain length. In the case of 1,3-cyclohexanedione and 2-methyl-1,3-cyclohexanedione, the reaction was not observed (Table 1, entries 5 and 6). It may be because of their enolic form, which decreases the reactivity of the carbonyl group toward the nucleophilic addition reaction and poor diffusibility of the enolic form in polymer beads. 1,4-Cyclohexanedione shows

Table 2. Comparison of chemoselective protection of 2,2-dimethylcyclohexane-1,3-dione between SPS and other acid sources

No.	Protective reagent	Time (h)	Yield (%) ^{a,b}	Azeotropic removal of water
1	CSA	4	70	Not required
2	SPS	2	85	Not required

^aYield is only of monoprotected product.

^bGC yield.

Table 3. Comparison of protection of 2,2-dimethylcyclohexane-1,3-dione with SPS in different solvents

No.	Solvent	Time (h)	Yield (%)
1	DCM	2	92
2	CHCl ₃	2	78
3	Toluene	6	35
4	Hexane	6	20

the formation of both monoprotected and diprotected products without any chemoselectivity (Table 1, entry 7), which decreases its overall yield.

Protection using a wide range of reactant was also studied with SPS (Table 1, entries 8–21). SPS was able to protect only aliphatic and aromatic carbonyl compounds with 2,2-dimethyl-1,3-propanediol and only the aliphatic carbonyl compound with 1,2-ethanediol. Protection of the conjugated carbonyl group was not observed with any diol even after a long time of refluxing.

To examine the chemoselectivity using SPS with other carbonyl compounds, equimolar mixtures of different aldehydes and ketones were allowed to react with diol (1:3). As shown in Scheme 2, very high chemoselectivity was observed in each case. More active 2,2-dimethyl-1,3-propanediol selectively protected aliphatic or aromatic carbonyl compounds in the presence of conjugated ketones, whereas less active ethanediol was able to protect only aliphatic ketones in a mixture of aromatic and conjugated ketones.

Whenever the chemoselectivity is compared with other solid supports (e.g., mesoporous aluminosilicate,^[11] siliceous mesoporous material,^[12] zeolite,^[13] silica gel-supported AlCl₃,^[14] and SO₃H-functionalized silica,^[15] only SPS was found to differentiate between two identical carbonyls, the aliphatic and aromatic carbonyl compounds, and between conjugated and nonconjugated carbonyl compounds.

The chemoselectivity observed in the SPS may be explained on the basis of a microenvironmental effect that is observed inside the polymer beads. The polymer bead only showed the desirable result with greater yield in DCM solvent, which results

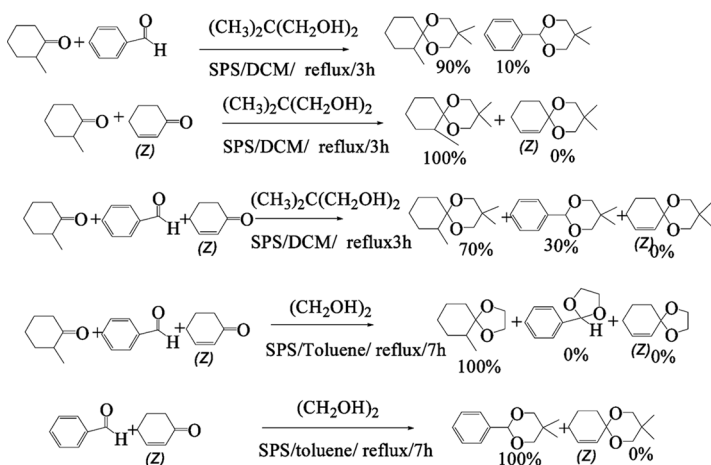
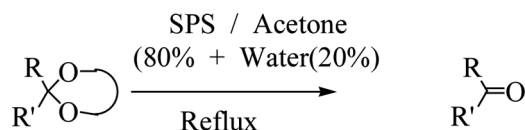
**Scheme 2.** Chemoselective protection of the aliphatic carbonyl groups.

Table 4. Hydrolysis of acetals to respective carbonyl compounds

No.	Acetal	Time (h)	Yield ^a (%)
1	3,3-Dimethyl-1,5-dioxo-spiro(5,5)undecane	2	90
2	3,3,7-Trimethyl-1,5-dioxo-spiro(5,5)undecane	2	88
3	5,5-Dimethyl-2-(4-nitor-phenyl)-(1,3)dioxane	2	88
4	1,4-Dioxo-spiro(4,5)decane	2	80
5	6-Methyl-1,4-dioxo-spiro(4,5)decane	2	75

Note. All the products were compared with authentic samples and gave satisfactory IR, NMR, and MS data.
^aIsolated yield.

in the swelling of SPS to a greater extent, and the reaction is slow in other solvents (Table 3). Probably most of the reaction occurs inside the polymer beads, and the polymer beads not only act as a source of acid but also give some secondary interaction sites inside the polymer beads, where polarity is greater than bulk of the medium. The monoprotected carbonyl compound shows poor diffusion inside the beads as compared to 1,3-diones, so it does not compete for the formation of diprotected product. This can further be supported by the fact that rate of protection decreases with the increase in chain length of alkyl groups in 2,2-dialkyl-1,3-diones, and no protection of carbonyl was observed with conjugated carbonyl compounds and 2-alkyl-1,3-dione. It is well known that diffusion in SPS beads decreases with increase in chain length and with conjugation.^[16] This is also responsible for lack of protection of aromatic and conjugated ketones, which show poor or no diffusion in polymer beads.

The corresponding deprotection of acetals was also achieved using SPS (Table 4), which is superior to conventional methods in terms of reaction conditions, reaction times, and workup procedures.^[17]

CONCLUSION

In conclusion, an efficient and simple method for chemospecific and chemo-selective protection has been described using SPS as a heterogeneous catalyst. The main advantage of this method is that it is only method that gives chemospecific protection of carbonyl compounds. Further reaction required short reaction time, takes place at reflux temperature, has operational simplicity and no azeotropic removal of water, and gives excellent yields.

EXPERIMENTAL

Typical Experimental Procedure for the Synthesis of Acetals with 2,2-Dimethyl-1,3-propanediol

2,2-Dimethyl-1,3-cyclohexandione (1.00 mmol) and 2,2-dimethylpropane-1,3-diol (6.00 mmol) were dissolved in dichloromethane (DCM, 10 mL) at room tem-

perature (ratio of monocarbonyl to diol taken is 1:3). The catalyst (10% w/w) was added, and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature, and the catalyst was removed by filtration through a celite plug, which was washed with DCM (5 × 2.5 mL). Solvent was removed under reduced pressure. Purification by column chromatography gave the desired product.

Typical Experimental Procedure for the Synthesis of Acetals with Ethane 1,2-Diol

2,2-Dimethyl-1,3-cyclohexandione (1.00 mmol) and ethane 1,2-diol (6.00 mmol) were dissolved in toluene (5 mL) (mono carbonyl/diol 1:3). The catalyst (10% w/w) was added, and the reaction mixture was stirred at 65 °C for 8 h. The reaction mixture was cooled to room temperature. The catalyst was removed by filtration through a celite plug and washed with hexane (5 × 2.5 mL). Solvent was removed under reduced pressure to give the product.

Typical Procedure for the Hydrolysis of Acetals

Acetal (1 mmol) was dissolved in acetone and water (5 mL) at room temperature. The catalyst (5% w/w) was added, and the reaction mixture was stirred at 55 °C for 2 h. The reaction mixture was cooled to room temperature. The catalyst was removed by filtration through a celite plug, which was washed with DCM (5 × 2.5 mL). The solvent was removed under reduced pressure to get the desired product.

ACKNOWLEDGMENT

We thank Dr. Vijayaraghavan, director of the Defence Research and Development Establishment, Gwalior, for his keen interest and encouragement.

REFERENCES

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1991; p. 188; (b) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: Stuttgart, 1994; p. 156; (c) Tormokangas, O. P.; Toivola, R. J.; Kaninen, E. K.; Koskinen, A. M. P. A short and convenient way to produce the taxol A ring utilizing the Shapiro reaction. *Tetrahedron* **2002**, *58*, 2175; (d) Raju, N.; Rajagopalan, K.; Swaminathan, S. A transannular reaction in an anionic oxo-cope system. *Tetrahedron Lett.* **1980**, *21*, 1577.
2. (a) Lee, S. H.; Lee, J. H.; Yoon, C. M. An efficient protection of carbonyls and deprotection of acetals using decaborane. *Tetrahedron Lett.* **2002**, *43*, 2699, and references cited therein; (b) Byrne, B.; Wengenroth, K. J. A convenient preparation of ethyl vinyl ketone. *Synthesis* **1986**, *10*, 870; (c) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. A useful and convenient synthetic protocol for interconversion of carbonyl compounds to the corresponding 1,3-oxathiolanes and vice versa employing organic ammonium tribromide (OATB). *Tetrahedron Lett.* **2002**, *43*, 2843.
3. Hai Hong, W.; Fan, Y.; Peng, C.; Jie, T.; Ming-Yuan, H. An efficient procedure for protection of carbonyls in Brønsted acidic ionic liquid [Hmim] BF₄. *Tetrahedron Lett.* **2004**, *45*, 4963.

4. Ott, J.; Ramos Tombo, G. M.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. A versatile rhodium catalyst for acetalization reactions under mild conditions. *Tetrahedron Lett.* **1989**, *30*, 6151.
5. Lillie, B. M.; Avery, M. A. The protection of ketones and aldehydes as 4-trimethylsilylmethyl-1,3-dioxalanes. *Tetrahedron Lett.* **1994**, *35*, 969.
6. (a) Lu, T.; Yang, J.; Sheu, L. An efficient method for the acetalization of α,β -unsaturated aldehydes. *J. Org. Chem.* **1995**, *60*, 2931; (b) Srivastava, N.; Dasgupta, S. K.; Banik, B. K. A remarkable bismuth nitrate-catalyzed protection of carbonyl compounds. *Tetrahedron Lett.* **2003**, *44*, 1191, and references cited therein.
7. (a) Sathe, M.; Gupta, A. K.; Kaushik, M. P. An efficient method for the esterification of phosphonic and phosphoric acids using silica chloride. *Tetrahedron Lett.* **2006**, *47*, 3107; (b) Karade, H.; Sathe, M.; Kaushik, M. P. An efficient method for the synthesis of 2-aminothiazoles using silica chloride as a heterogeneous catalyst. *Catal. Commun.* **2007**, *8*, 741.
8. Akelah, A.; Sherrington, D. C. Application of functionalized polymers in organic synthesis. *Chem. Rev.* **1981**, *81*, 557.
9. Harmer, M. A.; Qun, S. Solid acid catalysis using ion-exchange resins. *Appl. Catal. A: Gen.* **2001**, *221*, 45.
10. Shin, J.-P.; Chang, B.-J.; Kim, J.-H. Sulfonated polystyrene/PTFE composite membranes. *J. Membr. Sci.* **2005**, *251*, 247.
11. Robinson, M. W. C.; Graham, A. E. Mesoporous aluminosilicate-promoted alcoholysis of epoxides. *Tetrahedron Lett.* **2007**, *48*, 4727-4731.
12. Tanaka, Y.; Sawamura, N.; Iwamoto, M. Highly effective acetalization of aldehydes and ketones with methanol on siliceous mesoporous material. *Tetrahedron Lett.* **1998**, *39*, 9457.
13. Lalitha, A.; Pitchumani, K.; Srinivasan, C. Zeolite mediated protection of carbonyl groups. *Green Chemistry* **1999**, *1*, 173.
14. Tamami, B.; Borujeny, K. P. Chemoselective protection of carbonyl compounds as dithioacetals using silica gel-supported aluminum chloride. *Synth. Commun.* **2003**, *33*, 4253.
15. Shimizu, K.-I.; Hayashi, E.; Hatamachi, T.; Kodama, T.; Kitayama, Y. SO_3H -functionalized silica for acetalization of carbonyl compounds with methanol and tetrahydropyranylation of alcohols. *Tetrahedron Lett.* **2004**, *45*, 5135.
16. Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. Preparation of alkyl chlorides, acid chlorides, and amides using polymer-supported phosphines and carbon tetrachloride: Mechanism of these reactions. *J. Org. Chem.* **1983**, *48*, 3721.
17. (a) Deslonchamps, P.; Dory, Y. L.; Li, S. The relative rate of hydrolysis of a series of acyclic and six-membered cyclic acetals, ketals, orthoesters, and orthocarbonates. *Tetrahedron* **2000**, *56*, 3533; (b) Gautier, E. C. L.; Graham, A. E.; Mckillop, A.; Standen, S. P.; Taylor, R. J. Acetal and ketal deprotection using montmorillonite K10: The first synthesis of *syn*-4,8-dioxatricyclo[5.1.0.0]-2,6-octanedione. *Tetrahedron Lett.* **1997**, *38*, 1881.