

# PEG-dichlorotriazine (PEG-DCT): A New Soluble Polymer-Supported Scavenger for Alcohols, Thiols, Phosphines, and Phosphine Oxides

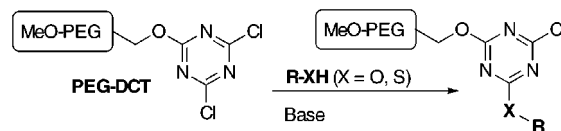
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Received August 7, 2000

## ABSTRACT



Trichlorotriazine was reacted with MeO-PEG-OH ( $M_w$  5000) to give a PEG-dichlorotriazine (PEG-DCT) that was used as a soluble electrophilic scavenger. PEG-DCT was added at the end of reactions to completely remove nucleophilic reactants or byproducts. The soluble polymer sequestered alcohols, thiols, triphenylphosphine, and triphenylphosphine oxide.

A new technique called solid-supported scavenging is emerging as one of the most useful for the parallel purification of collections of compounds prepared by solution phase methodology. The technique involves preparing a product in solution using an excess of one starting material to force the reaction to completion and then sequestering (or scavenging) the excess of the reactant by immobilization onto a solid support. Therefore, purification does not involve complex workup or chromatography.

This process has recently been the subject of several reviews<sup>1</sup> containing lists of reactants and complementary functionalized sequestrants. Surprisingly, very few examples of scavenging of alcohols are reported.<sup>2</sup> Since we recently described the preparation of a dichlorotriazine supported on cross-linked polystyrene,<sup>3</sup> we thought that such a product could be an ideal scavenger for alcohols.<sup>4</sup> Thus, we reacted benzoyl chloride with 2 equiv of cyclohexenol in  $\text{CH}_2\text{Cl}_2$  in

the presence of NMM and we added a dichlorotriazine supported on a Wang type resin at the end of the reaction. The excess of the alcohol was effectively taken away from the solution after 12 h of stirring in the presence of an excess of the solid-supported reagent. We surmised that this sluggish reactivity was due to the low nucleophilic character of the alcohol that must react to completion in heterogeneous phase.

We therefore considered the possibility of loading the dichlorotriazine on poly(ethylene glycol) (PEG), taking advantage of quenching in homogeneous phase, and then

(2) In the reviews cited in ref 1, we found just one reference to alcohol scavenging: Starskey, G. W.; Parlow, J. J.; Flynn, D. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2385. Nevertheless, several companies advertise sulfonyl chloride resins as scavengers for alcohols although this kind of functional group has been mainly used as a linker. See: Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1999**, *39*, 975. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1999**, *39*, 979.

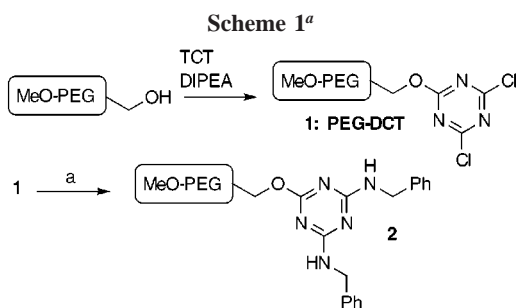
(3) Masala, S.; Taddei, M. *Org. Lett.* **1999**, *1*, 1355.

(4) Alcohols are known to undergo nucleophilic substitution on 2-alkoxy-4,6-dichloro-[1, 3, 5]-triazines easily. Dudley, J. R.; Thurston, J. T.; Schaefer, F. C.; Holm-Hansen, D.; Hull, C. J.; Adams, P. *J. Am. Chem. Soc.* **1951**, *73*, 2986. Menicagli, R.; Malanga, C.; Peluso, P. *Synth. Commun.* **1994**, *24*, 2153. Falorni, M.; Giacomelli, G.; Mameli, L.; Porcheddu, A. *Tetrahedron Lett.* **1998**, *39*, 7607.

(1) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035. Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324. Drery, D. H.; Coe, D. M.; Poon, S. *Med. Chem. Res.* **1999**, *9*, 97. Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18. Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. See also: Warmus, J. S.; da Silva, M. I. *Org. Lett.* **2000**, *2*, 1807 and references therein.

separating the formed alkoxy-triazine-PEG by selective precipitation.<sup>5</sup> To our surprise, we only found one report on the use of a soluble polymer supported borane for “fishing out” a product from a reaction mixture.<sup>6</sup>

PEG-dichlorotriazine<sup>7</sup> (PEG-DCT, **1**) was simply prepared by reaction of MeO-PEG-OH ( $M_w = 5000$ ) with 5 equiv of 2,4,6-trichloro[1,3,5]triazine (TCT) in  $\text{CHCl}_3$  in the presence of *N,N'*-diisopropylethylamine (DIPEA). After 12 h of reaction, the product was separated by selective precipitation with diethyl ether, filtered, and dried. The monosubstitution of a single chlorine atom of TCT was identified through the  $^1\text{H}$  NMR analysis of the product obtained by reaction of **1** with an excess of benzylamine (**2**) (Scheme 1).<sup>8</sup>

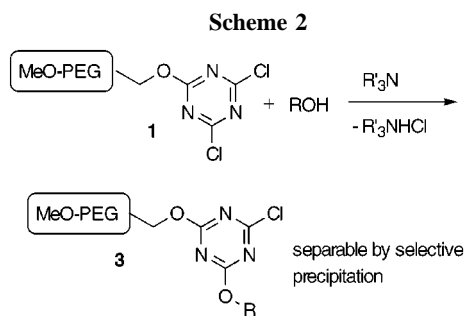


<sup>a</sup> (a) 10 equiv of  $\text{PhCH}_2\text{NH}_2$ ,  $\text{CH}_3\text{CN}$ , reflux 24 h.

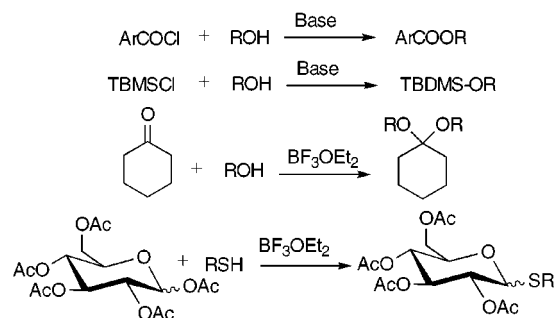
The presence of two chlorine atoms on **1** was confirmed by microanalytical data. Product **1** was stable at room temperature and can be stored for long time in the refrigerator or prepared in the required amount immediately before the use.

We repeated the reaction of benzoyl chloride with 2 equiv of cyclohexenol described above. When the TLC analysis suggested that all the  $\text{PhCOCl}$  was consumed, **1** was added, and after 45 min of stirring the spot of the residual cyclohexenol disappeared. Diethyl ether was added to induce the settlement of the PEG material as a precipitate that was separated by filtration. The ethereal solution was washed with a diluted HCl solution<sup>9</sup> and the solvent evaporated to give pure ester ( $^1\text{H}$  NMR analysis) in 90% yield (Scheme 2).

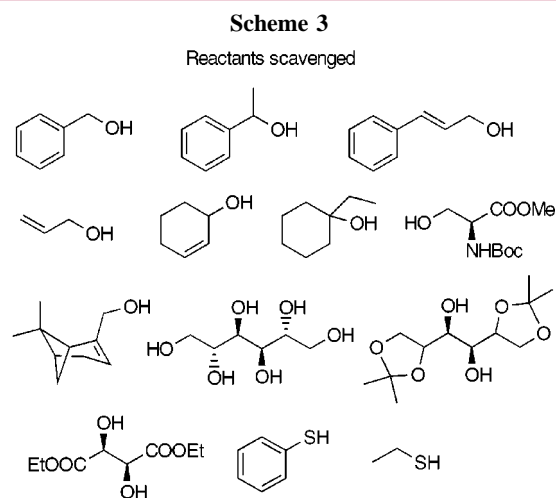
PEG-DCT (**1**) was used as scavenger for primary, secondary, and tertiary alcohols, for diols, for polyalcohols such as D-mannitol, and for thiols in different kinds of reactions such



**Reactions tested**



as the formation of esters, silyl ethers, acetals, thioacetals, and thioglycosides (Scheme 3).



For formation of esters or silyl ethers, the procedure described above can be followed. For the acid-catalyzed preparation of an acetal, PEG-DCT was added at the end of the reaction together with an excess of solid  $\text{Na}_2\text{CO}_3$ . After 1 h, diethyl ether induced the separation of the PEG material and the desired product was isolated after filtration and evaporation. An analogous procedure was followed in the case of the preparation of thioglycosides starting from  $\alpha$ -D-glucose pentaacetate in the presence of  $\text{BF}_3\text{OEt}_2$ . The use of an excess of  $\text{Na}_2\text{CO}_3$  as the base allowed the separation of the excess of the thiols and the acid employed in the reaction.<sup>10</sup>

(5) For the use of soluble polymer supported reagents or catalysts, see: Reed, N. N.; Janda, K. D. *Org. Lett.* **2000**, *2*, 1311. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Org. Lett.* **2000**, *2*, 1737. Sieber, F.; Wentworth, P., Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188. Bonora, G. M.; Rossin, R.; Zaramella, S.; Cole, D. L.; Eleuteri, A.; Ravikumar, V. T. *Org. Process Res. Dev.* **2000**, *4*, 225. For review articles, see: Wentworth, P., Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1971. Grevert, D. J. Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. See also: Bonora, G. M.; Veronese, F. M. *Chim. Ind (Milan)* **1998**, *80*, 887.

(6) Hori, M.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 889

(7) Shafer, S.; Harris, J. M. *J. Polym. Sci.: Polym. Chem.* **1986**, *24*, 375.

(8) The spectrum of **2** showed the presence of 10 aromatic protons in respect to the MeO group of PEG.

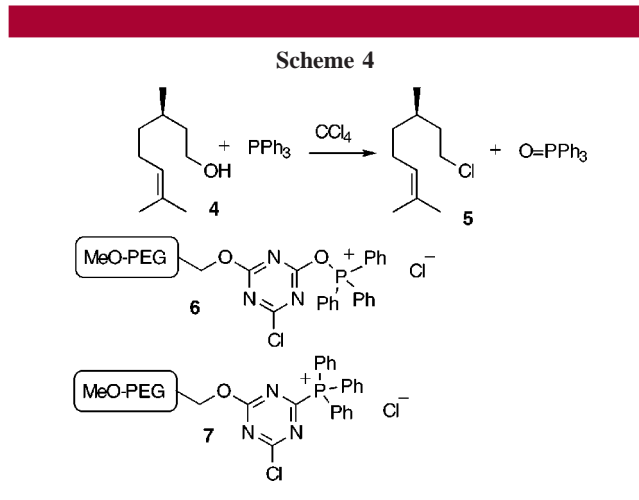
(9) This aqueous workup removes the excess of base and can be substituted by a “dry” treatment of the organic solution with Amberlite IRC-86.

We tried also to use **1** in the transformation of citronellol (**4**) into the corresponding chloride (**5**) using  $\text{CCl}_4$  and  $\text{PPh}_3$ .<sup>11</sup> At the end of the reaction we obtained a mixture of chloride **4** and triphenylphosphine oxide together with unreacted citronellol and triphenylphosphine. After the addition of **1**, we observed that the spots of citronellol, triphenylphosphine, and triphenylphosphine oxide disappeared from the plate. After precipitation with ether and filtration, we isolated chloride **5** in 65% yield.

As additional proof, we mixed together 25 mg of  $\text{Ph}_3\text{PO}$ , 25 mg of  $\text{PPh}_3$ , and 50 mg of cyclohexanone in  $\text{CH}_3\text{CN}$ . PEG-DCT (1.1 g, 1.2 equiv with respect to the phosphorus compounds) was added, and after 2 h of stirring, precipitation of the scavenger with ether (20 mL), and evaporation of the solvent, we recovered 48 mg of cyclohexanone. The  $^1\text{H}$  NMR spectra of the product showed no trace of aromatic signals.<sup>12</sup> The PEG reaction product was submitted to  $^1\text{H}$  NMR spectra, which clearly showed the presence of the aromatic moiety. Although not completely investigated, we propose that sequestered species have structures **6** and **7** as shown in Scheme 4.

PEG-DCT was also used as a scavenger for  $\text{Ph}_3\text{PO}$  in a Mitsunobu reaction giving excellent results.<sup>13</sup>

In principle, PEG-DCT **1** can be considered to be a suitable scavenger for any type of nucleophile as the chlorine on triazine undergoes rapidly nucleophilic substitution. Amines



or carboxylates may be also sequestered by **1** even though the use of acidic or basic ion-exchange resins (Amberlite family) may be preferable.

Finally we want to point out that **1** is a moderately priced reagent: the cost is due mainly to the price of MeO-PEG-OH 5000 as the cost of TCT is very low.<sup>14</sup>

In conclusion, we have described a new scavenger system, supported on a soluble polymer, that removes alcohols, thiols, triphenylphosphine, and phosphine oxide from the reaction medium. This result demonstrates that PEG supports can be successfully used also for the preparation of sequestrants of products, reactants, and byproducts. The main advantage, in the case, is the possibility of working in a homogeneous phase and therefore using the PEG-supported reagent together with the PEG-supported scavenger.

**Acknowledgment.** The authors thank Gian Maria Bonora (University of Trieste, Italy) for introducing them to the “world” of PEG-supported reactions. This work was financially supported by MURST (Rome) as a Progetto di Interesse Nazionale (PRIN).

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(10) If necessary, the PEG-scavenged products can be removed by water extraction from the organic solvent; PEG is extremely soluble in water.

(11) Apple, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *14*, 801.

(12) To verify that the result observed was not simply due to precipitation of the phosphorous compounds with diethyl ether, we repeated the procedure without adding PEG-DCT. More than 60% (w/w) of triphenylphosphine and phosphine oxide was recovered.

(13) For other reports for sequestering or removing phosphines or phosphine oxides, see: Starskey et al. in ref 2 and Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1988**, *41*, 1835. Unfortunately, the hydrazine dicarboxylate, obtained from DEAD in Mitsunobu reaction, was not sequestered by PEG-DCT.

(14) The reagent described here has a low loading (0.2 mmol per gram considering one active chlorine). Nevertheless, the same compound may be prepared with the difunctional PEG or with other types of polyfunctionalized PEG such as those described in Toy, P. H.; Reger, T. S.; Janda K. D. *Org. Lett.* **2000**, *2*, 477 and references therein.