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Use of copper (ii) salts in solid phase as deprotection method of thioacetals and thiocetals

G. Oksdath Mansilla and A. B. Peñéñory

Instituto de Investigaciones en Físico Química de Córdoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina.
E-mail: penenory@fcq.unc.edu.ar

Introduction

The protection of the carbonyl functional group is often a necessary step for the preparation of an organic compound, and particularly in the total synthesis of natural products as well as multifunctional organic molecules (Komatsu *et al.*, 1995; Greene and Wuts, 1999; Firouzabadi *et al.*, 2001). Among different protective groups, cyclic thioacetals and thiocetals (1,3-dithiolanes or 1,3-dithianes) are currently used because of their easy formation and stability in a variety of reagents and reaction conditions (Grobel and Seebach, 1977).

For the preparation of thioacetals several approaches have been developed (Seebach and Corey, 1975; Firouzabadi *et al.*, 1999), however, deprotection to obtain the target carbonyl compound is not usually an easy process. In recent years, many methods have been reported for thioacetal deprotection. Traditionally, the deprotection of thioacetals requires drastic conditions either toxic reagents, such as Hg (II) salts, or salts of heavy metals. Also several methods have been used on the basis of Fe (III) and Cu (II) salts, as Claycop (Balogh *et al.*, 1984) ($Cu(NO_3)_2$ supported on K-10 clay in a bilayer system) and $CuO/CuCl_2$, and more recently non-metallic reagents. In general these methods have one or more than one of the following disadvantages: prolonged reaction times, high temperatures, toxic expensive or unavailable reagents, and unwanted side reactions.

Recently, the interest in reactions that occur in the absence of solvents has increased due to low pollution, low cost, and simplicity of the process (Hajipour *et al.*, 2002). Montmorillonite K10 is an efficient and versatile catalyst in many organic reactions; it is composed of an octahedral aluminate layer, between two octahedral silicate layers, is non-toxic, non-corrosive, stable and insoluble in polar and non-polar solvents like carbon tetrachloride, *n*-hexane and diethylether (Nasreen Aayesha, 2001).

In this paper we describe a simple method of carrying out the solvent-free dethioacetalization using $Cu(NO_3)_2$ **.** $2.5H_2O$ in the presence of Montmorillonite K10 at room temperature.

Methodology

1,3-Dithiolanes were synthesized under different reaction conditions depending on whether the carbonyl to protect came from an aldehyde or a ketone. In the case of dithiolanes derived from aldehydes, the synthesis was performed in CH_3Cl at 25 °C using I_2 as catalyst in good yields (Firouzabadi *et al.*, 2001). Dithiolanes derived from ketones were synthesized using $FeCl_3$-SiO_2 as a reagent in CH_2Cl_2 at room temperature (Patney, 1991).

Reactions of solid-phase deprotection: representative procedure

Montmorillonite K10 (1.2970 g) was weighed, a portion of which was added to (1 mmol) dithiolane. To the remaining fraction $Cu(NO_3)_2$**.**2.5 H_2O (0.2325g, 1 mmol) was added. Both factions were combined in a 125 ml-flask (erlenmeyer) and the mixture was sonicated for 2 hours. After the disappearance of the starting material monitored by GLC, the mixture was washed with *n*-hexane, filtered and the reaction was analysed by GLC and GC-MS. Products were isolated by radial chromatography and the identity was determined by ^{1}H-and ^{13}C-NMR and mass spectrometry. Reaction yields accounted for isolated product.

Discussion

A simple dethioacetalization method was studied using $Cu(NO_3)_2$ **.**2.5 H_2O as agent under mild reaction conditions. 2-Phenyl-1,3-dithiolane (**1**) was chosen as model substrate, and the reaction was studied by changing conditions, such as solvent and atmosphere. Thus, the treatment of 1,3-dithiolane **1** with $Cu(NO_3)_2$ **.**2.5 H_2O (3 equiv.) in MeCN at room temperature and air-open container resulted in the quantitative cleavage to regenerate benzaldehyde, after 15 minutes stirring (eq. 1).

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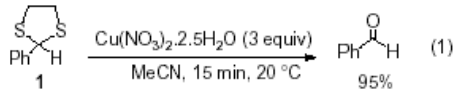
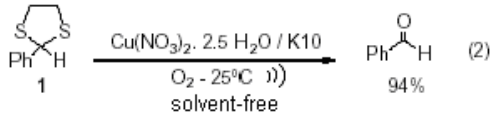
In CH_2Cl_2 the reaction was slower and was completed after 135 minutes. Comparatively, the reaction with claycop (Balogh *et al.*, 1984) in CH_2Cl_2 required 5 hours for complete conversion.



The deprotection of the thioacetal was developed with copper nitrate and Montmorillonite K10 reagent under solvent-free conditions (eq. 2). The reaction was performed using a sonicator. The deprotection to the corresponding benzaldehyde was complete using a 1:1 ratio of **1** with $Cu(NO_3)_2$ **.** 2.5 H_2O and 1.2969g of K10, in a reaction time of 120 minutes.



Moreover, deprotection with K10 in the absence of the nitrate salt was tested, conditions under which dithiolane deprotection was not observed, and a 93.4% of the substrate without reacting was recovered . Finally, the solid-phase deprotection was carried out using $Cu(NO_3)_2$ **.** 2.5 H_2O in a 1:1 ratio with dithiolane **1**, in the absence of K10. After 3 hours reaction 92% of product was obtained, 7% of substrate remaining without reacting. The disadvantage of this reaction is that a good stirring is not achieved to allow a good mixing of reactants due to the small amount of salt used. This is not observed with the use of the K10 reagent, since besides accelerating reaction times, it is added in a 6 times higher ratio than $Cu(NO_3)_2$ **.** 2.5 H_2O, thereby achieving a major uniformity in the reaction system.

The reaction of deprotection in solid phase using the conditions indicated in eq. 2 was spread to other dithiolanes and dithianes. In this instance not only aldehyde derivatives, but also ketone derivatives were used, thus testing the behaviour of $Cu(NO_3)_2$ .2.5 H_2O reagent against several functional groups. All used dithiolanes and dithianes are shown in Fig. 1. In all cases deprotection reactions occurred in very good to excellent yields of isolated products (93-99%).

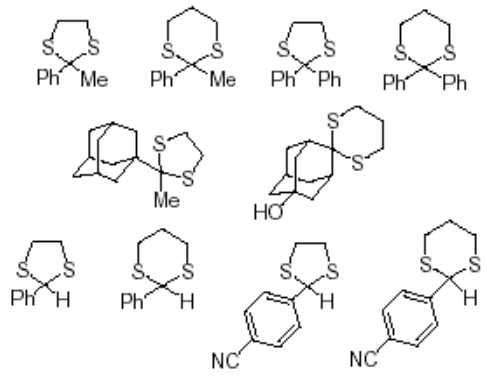


Figure 1

Conclusions

The use of Montmorillonite K10 together with the $Cu(NO_3)_2$ **.** 2.5 H_2O salt allowed to carry out dethioacetalization under solvent-free conditions, at room temperature, in an efficient way and in good yields. This methodology proposed mild reaction conditions, the use of economic, easy to handle and non-toxic reagents, such as $Cu(NO_3)_2$ **.** 2.5 H_2O, thus being a very convenient alternative to conventional methods for deprotection of thioacetals and thiocetals.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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