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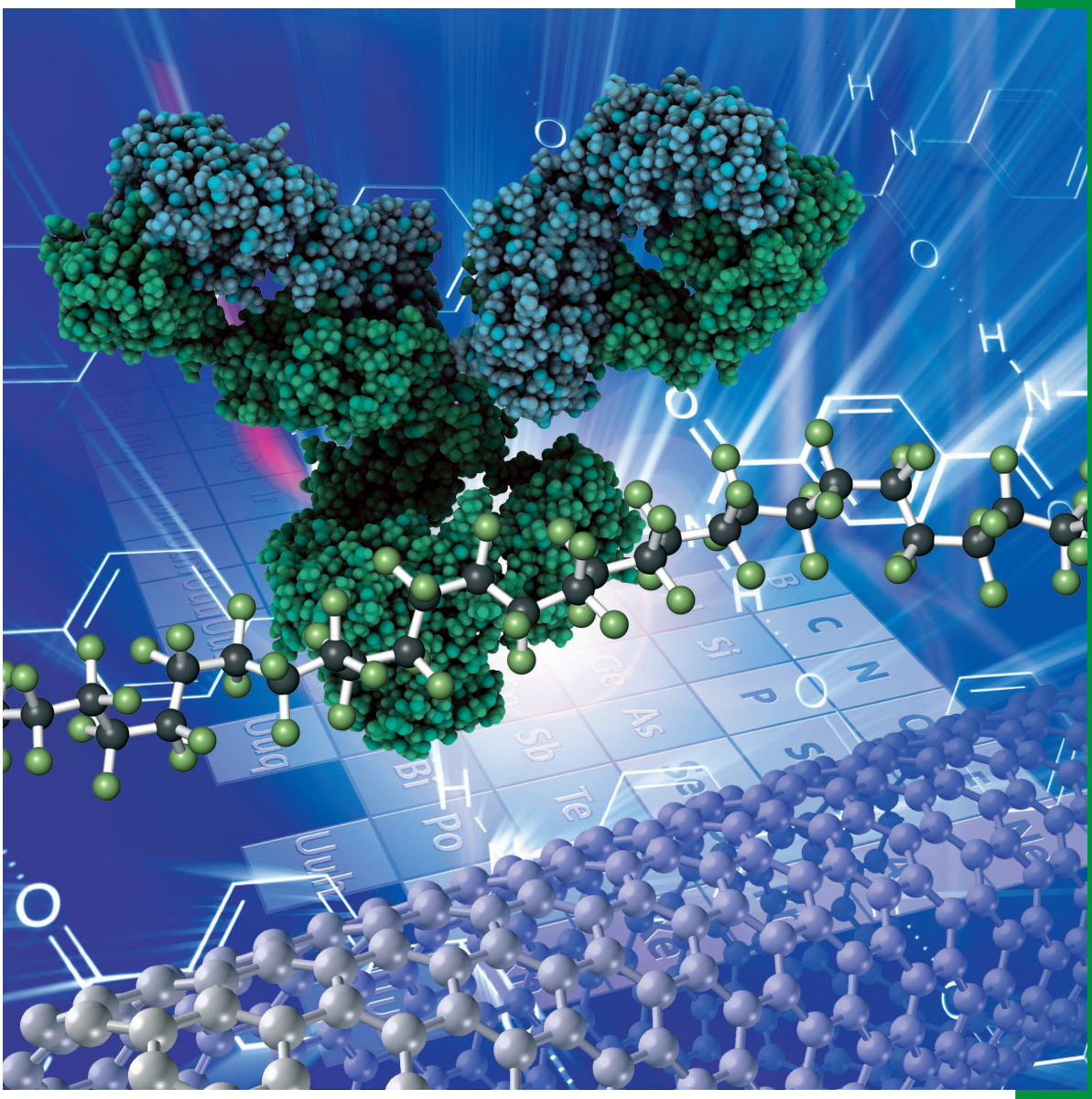

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Reduction of Trichloromethyl to *gem*-Dichloromethyl Group with Triphenylphosphine and Water in Ethyl Acetate

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A novel and efficient way of reducing trichloromethyl to *gem*-dichloromethyl compounds using environmentally friendly conditions has been developed. This reduction process consists of the treatment of a trichloromethyl compound with water and triphenylphosphine using ethyl acetate as solvent. This reaction proceeds in good yield when a strong electron-withdrawing group is attached to the trichloromethyl derivative.

Introduction

It is known that the *gem*-dichloromethyl group is an important backbone present in a number of biologically active compounds; they can act as inhibitors of cytochrome P-450's,[1] antibiotics,[2] diuretics,[3] and even some possess anti-cancer properties,[4] see Figure 1. Furthermore, *gem*-dichloromethyl compounds are versatile intermediates for the synthesis of heterocycles,[5] α,β-unsaturated ketones,[6] α-chloroacrylates[7] and cyclopropanes.[8] Additionally, they are used as synthetic precursors to afford the corresponding aldehydes under basic conditions,[9] as well as to generate free radicals that can add onto alkenes[10] and alkynes.[11]

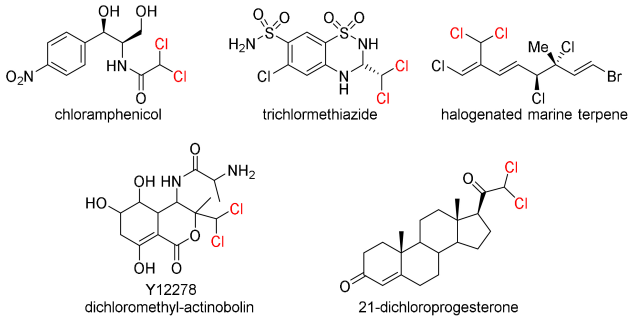

Figure 1. Biologically active *gem*-dichloromethyl compounds.

Traditional methods to prepare *gem*-dichloromethyl compounds involve chlorination of methyl ketones, which implicates using different types of chlorine sources, such as sulfuryl chloride,[12] thionyl chloride,[13] copper chloride,[14] *N*-chlorosuccinimide,[15] *N*-chloro-*N*-methoxybenzenesulfonamide,[16] trichloroisocyanuric acid,[17] benzyltrimethylammonium tetrachloroiodate,[18] and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).[19] Although the transformation of the trichloromethyl group to the *gem*-dichloromethyl group by the mono-dechlorination (partial hydrogenation) is regarded as a direct and efficient method due to the easy preparation and the commercial availability of various trichloromethyl substrates, few methods have been described to allow the formation of *gem*-dichloromethyl compounds. Some of them require the use hydrogen-donors, induced by transition metals, their complexes or salts at temperatures above 100 °C,[20] a catalytic hydrogenation with Pt/C,[21] *n*-tributyltin hydride,[22] sodium hydride,[23] or Grignard reagents as electron donors to synthesize substituted α,α-dichloroketones.[24] However, these methods display limitations and disadvantages such as poor yields, use of high temperatures, side-products formation, low chemoselectivity, and a limitation to tolerate different functional groups under reactions conditions. Therefore, the preparation of these compounds with a more efficient, simple and general route is highly desirable.

In 2011 Gilheany's group reported the use of 2-naphthol in toluene solution to the synthesis of pentachloroacetone[25] in moderate yield from hexachloroacetone under the conditions of Appel reaction,[26] however no systematic work was done using different substrates containing another functional group reactive. Recently, we reported a method to reduce trichloromethyl compounds to *gem*-dichloromethyl groups according to Appel's reaction protocol using methanol.[27] Although this methodology affords excellent yields of *gem*-dichloromethyl derivatives with high chemoselectivity, the use of methanol produces as a by-product toxic residue (methyl chloride); this could be regarded as a disadvantage when large scale of the dichloromethyl compound is required. In this perspective, based in our previous experience, we decided to investigate a friendly protocol for the reduction of trichloromethyl com-

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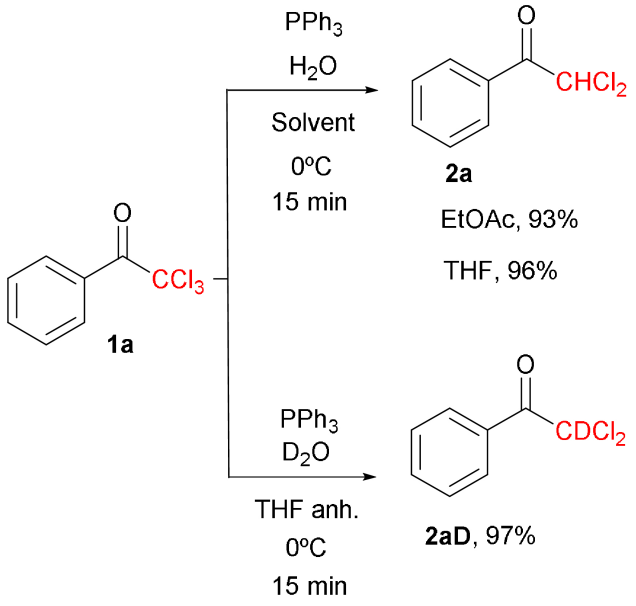
pounds to *gem*-dichloromethyl using a green solvent and water as a source of protons.

Results and Discussion

We considered evaluating the reduction process of trichloromethyl compounds **1** in the presence of triphenylphosphine and water, employing tetrahydrofuran or ethyl acetate as a solvent, Scheme 1. Using trichloroacetophenone (**1 a**) as a



Scheme 1. Reduction of Trichroloacetophenone **1 a.** Reaction conditions: **1 a** (1.0 equiv), PPh_3 (1.05 equiv), H_2O or D_2O (3.0 equiv), EtOAc or THF (5.0 ml) at 0 °C.

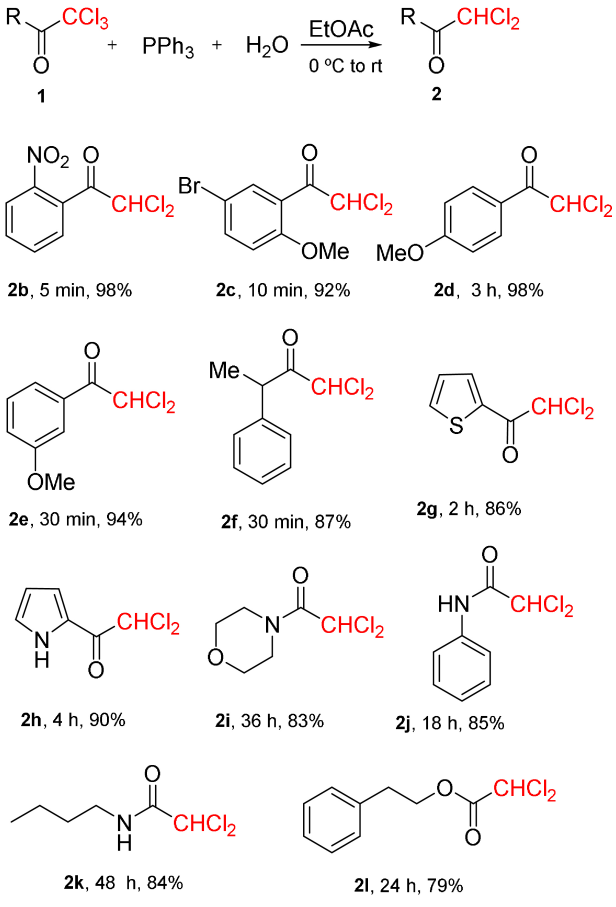
model, when it was reacted with 1.05 equiv. of triphenylphosphine and 2 equiv. of water in THF at room temperature, a mixture of **2 a** along with monochloroacetophenone (85% and 7% yield respectively) were obtained after 10 min. When the reaction temperature was lowered to 0 °C, dichloroacetophenone **2 a** was obtained in 96% yield and the over-reduction product was not detected after 10 min. We also investigated the influence of the amount of water in the reaction. Using three different amounts of water (1.0, 3.0 or 10.0 equiv) we observed no significant changes in the yield of the reduction reaction.

In order to verify that the water did in fact function as a source of protons, **1 a** was reacted with 1.05 equiv. of triphenylphosphine, 3.0 equiv. of D_2O in anhydrous THF, after 15 min **2aD** was obtained in 97% yield. The presence of deuterium in **2aD** was confirmed by ^1H NMR analysis, as we observed that the signal corresponding to the hydrogen of the dichloromethyl group (6.70 ppm) showed a considerable decrease of intensity due to the presence of deuterium. Unfortunately, we only observe 55% of deuterium incorporation due possibly to the low quality of D_2O used in this experiment (see the supporting information) verifying the source of protons (Scheme 1).

To make the reaction more attractive, 3.0 equiv. of water were reacted using ethyl acetate as the solvent, under these conditions **2 a** was obtained after 15 min in 93%. The experimental process is very simple to carry out and consist in the AcOEt elimination under reduced pressure (the AcOEt can be *re*-used) and obtain the respective product easily by flash chromatography. According to this result and given the high availability and the green solvent criteria of ethyl acetate,[28] we decided to use these general conditions for the following experiments.

With this well-established protocol, we proceeded to extrapolate the methodology to different derivatives with similar reactivity to trichloroacetophenone (**1 a**). The reductions of **1 b-h** were carried out successfully obtaining the desired product in good yields (Table 1). Interestingly, when 4-methoxytrichloroacetophenone (**1 d**), was treated under the same conditions, the reduction reaction time was 3 h, a lot more time compared to the other trichloroacetyl derivatives (**1 b**, **1 c** and **1 e**). A reason for this could be due to the electronic

Table 1. Synthesis of Dichloroacetyl Compounds 2.[a]



[a] Reaction conditions: 1a (1.0 equiv), PPh_3 (1.05 equiv), H_2O (3.0 equiv), EtOAc (5.0 ml) at 0 °C.

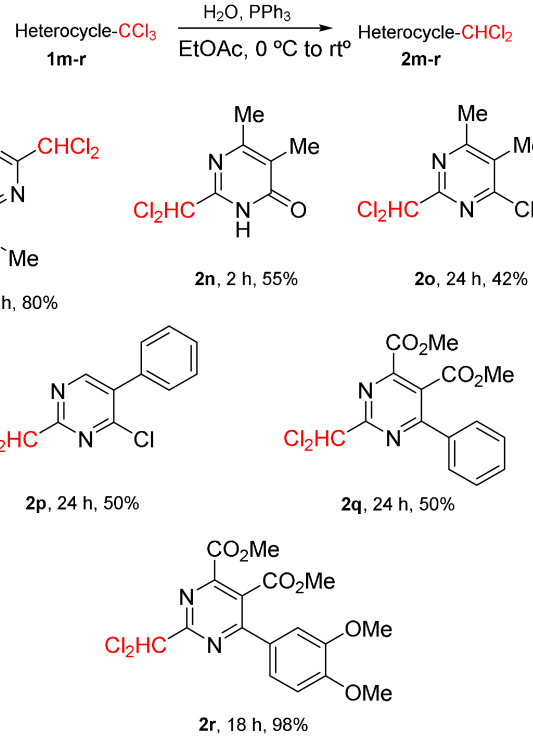
properties of the *p*-methoxy group which acts as an electron-donating group making the trichloroacetyl group less susceptible to reduction under these reaction conditions.

Additionally, the reductions of trichloroacetamides **1 i-k** were carried out successfully to the desired dichloroacetyl compound **2 i-k**. The reaction times were longer as expected. This type of compounds are electron-rich in comparison with **1 b-e**. Because of the presence of the unshared electron pair of nitrogen, this gives the trichloroacetyl group a richer electron density and in consequence longer reaction time. It is interesting to note that when the reaction was carried out in boiling ethyl acetate the reduction of **1 j** decreased (from 18 to 8 h) and **2 j** was obtained in 87% yield. This clearly establishes that the time of reduction of the trichloroacetyl group could be assumed to be generally shorter for others trichloromethyl compounds **2** and is not restricted merely to **2 j**. Furthermore, the compounds **1 k-l**, were converted to the corresponding dichlorocompound **2 k-l** without any problem. A library of compounds was created showing the compatibility of the reaction with different functional groups.

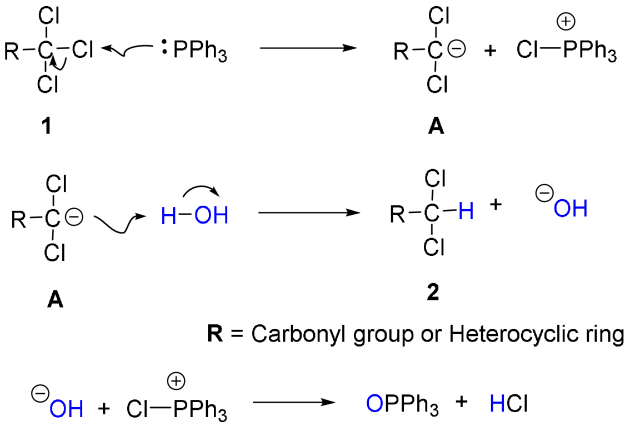
Finally, this reduction process was extrapolated to other trichoromethyl compounds possessing different scaffolds such as pyrimidines and some derivatives. As shown in Table 2, *gem*-dichloromethyl **2 m** and **2 r** compounds were obtained in high yields under moderate periods of time (4 and 18 hrs respectively). The reduction process was then tested to **1 n-q**, although thin layer chromatography analysis showed that the respective starting material was completely consumed and transformed to the dichloromethyl compound **2**, low yields were obtained after column chromatography purification. We consider that this is probably due, in part, to the formation of a persistent insoluble white solid, which may arise from strong complexation of this kind of products with the triphenylphosphine oxide formed as by-product in this reduction reaction. For the cases of **1 o** and **1 p** we obtained exclusively the corresponding *gem*-dichloromethyl compound **2**, without any dechlorination of the aromatic chloride. Notably, when the procedure was extended to the trichloromethyl derivatives **1 b-1 p**, the over-reduced products were not obverved. In fact, 1.0 equiv. of triphenyl phosphine is essential for the reaction to proceed even in excess of water.

We believe that this reduction process involves the formation of a key intermediate dichloromethyl carbanion **A** (Scheme 2). The nucleophilic phosphorus atom attacks the trichloromethyl compound, forming the stabilized carbanion **A** and chlorotriphenylphosphonium ion. Then, the high-energy intermediate **A**, in the presence of water is protonated to give the respective *gem*-dichloromethyl compound **2** and one equivalent of hydroxyl ion, which reacts with chlorotriphenylphosphonium ion to give finally, triphenylphosphine oxide and hydrogen chloride. This mechanistic sequence is supported by the deuterium capture of the stabilized carbanion intermediate when the reduction process was carried out in D_2O, providing direct evidence on reaction mechanism. Additionally, we found a strong acidic media generated in the reaction media measured directly in the flask (pH ≈ 1) when a large scale (3.0 g) reduction process of **1 a** was carried out in the presence of 1.0 mL of H_2O in AcOEt solution, and **2 a** was still isolated in high yield (93%) after column chromatography.

Table 2. Synthesis of Dichloromethyl Heterocyclic Compounds **2**.[a]



[a] Reaction conditions: **1 m-r** (1.0 equiv), PPh_3 (1.05 equiv), H_2O (3.0 equiv), EtOAc (5.0 ml) at 0 °C.



Scheme 2. Mechanism for the reduction of the trichloromethyl group to *gem*-dichloromethyl compound **2**.

Conclusions

In summary, we have reported an efficient and simple process to prepare *gem*-dichloromethyl compounds from trichloromethyl derivatives using friendly environmental conditions. Under the optimal conditions only the *gem*-dichloromethyl compounds were obtained, and the monochloromethyl derivatives (over-reduction products) were not observed. Although, the efficiency of this method of reduction has been demonstrated by synthesizing a gram-scale the dichloromethyl derivative **2 a**, this reaction may be applied to other trichloromethyl derivatives and is not restricted merely to trichloroacetophenone. This dechlorination reaction was highly chemoselective and is expected to be particularly useful in those instances where the trichloromethyl compounds are the usual precursors of *gem*-dichloromethyl derivatives, which are not affordable in good yields by other routes.

Supporting Information Summary

The supporting information provides complete experimental procedures and spectral data (^{1}H, ^{13}C and HRMS) of new synthesized compounds **2 j-l**, **2 n**, **2 o**, **2 q-r** and **2 aD**.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chemoselectivity · Dechlorination reaction · *gem*-Dichloromethyl compounds · Reduction process · Trichloromethyl compounds

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