

## Strategies for safe evaporation of solutions containing Hydrochloric acid.

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### Introduction

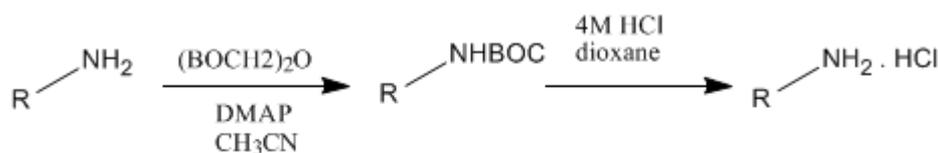
When synthesising and purifying organic molecules, such as those created by medicinal chemists during the drug discovery process, hydrochloric acid (HCl) can be a very useful reagent. Its preferential use over other mineral acids (that can produce undesirable side effects) and trifluoroacetic acid (that may leave unwanted fluoroacetate groups behind) is well established in scientific literature. However the removal of excess acid from samples can be problematic especially when working with samples in parallel as most commercial centrifugal evaporators contain non-glass components that are degraded by concentrated HCl.

This paper reviews a selection of organic synthesis / purification reactions where HCl has to be removed post reaction. The paper further discusses evaporation solutions to the problems which routine use of concentrated HCl can create.

### Deprotection using Hydrochloric Acid

Di-tert-butyl dicarbonate is a widely used reagent in organic synthesis. The carbonate ester group in this reagent reacts with amines to give N-tert-butoxycarbonyl or t-BOC derivatives. The t-BOC group can be removed easily from the amine using strong acids such as trifluoroacetic acid (TFA) neat or in Dichloromethane, or HCl in Dioxane. t-BOC derivatives are one of the most widely used amino protecting groups in organic synthesis. Following on from deprotection the reaction mixture containing the free amine is normally concentrated in a vacuum concentrator and the crude mixture either purified or taken to the next stage of reaction. Where HCl is used for the deprotection, the amine is obtained as a HCl salt. Often these salts are more stable and soluble than the free amine and much easier to handle as they are solids. The reaction scheme is shown in figure 1, below.

**Figure 1** – Reaction Scheme of t-BOC Deprotection



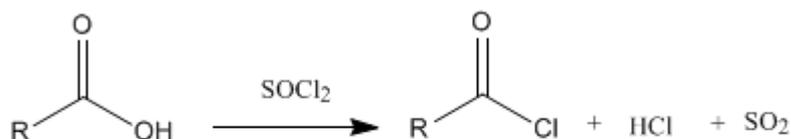
R- alkyl, aryl

### Preparing Acid Chlorides

Acid chlorides are reactive derivatives of carboxylic acids that may be prepared by reacting a carboxylic acid with reagents such as thionyl chloride, phosphorous trichloride, phosphorus pentachloride or oxalyl chloride. The reaction scheme is shown in figure 2, below. In these reactions HCl is generated as a by product. Acyl chlorides are most commonly used as reagents to substitute an acyl group into a

benzene ring (Freidel-Crafts reaction), in reaction with ammonia and primary amines to produce amine salts, and with alcohols to produce carboxylic acids.

**Figure 2** – Reaction Scheme to Prepare Acid Chlorides



R- alkyl, aryl

### Re-salt Formation using Hydrochloric Acid

In the purification of samples by reverse phase high performance liquid chromatography (HPLC) - TFA is commonly used as a modifier because this provides superior peak shapes over other acid modifiers. However, when drying samples TFA can be difficult to remove, and/or the sample elutes as the TFA salt. In such cases a re-salt formation can be achieved by passing the collected sample through a Solid Phase Extraction (SPE) column to bind the sample to the column.

By washing with an excess of base in solution the TFA salt is neutralised and the sample eluted. This can then be converted to a stable, more useful HCl salt using a similar process in a second column by eluting with an HCl solution, commonly methanolic HCl. The solvent is evaporated to leave a dry sample.

### Post Reaction Handling

In the applications described above HCl is either used as a reagent or it is generated in the reaction. When using HCl care must be taken when selecting the equipment to handle this corrosive acid unless the reaction is immediately quenched. Standard laboratoryware is commonly made of glass, and is therefore resistant to HCl. However when concentrating or evaporating samples containing HCl a range of problems exist that can befall the unwary.

Single samples containing HCl are often dried in a rotary evaporator in which the majority of the wetted components are made of glass and are therefore resistant to acid attack. Commonly commercially available rotary evaporators use a dry running PTFE lined vacuum pump to create the vacuum. However, even with a dry ice cooled condenser installed on the rotary evaporator, highly volatile HCl vapour is not efficiently condensed and consequently travels through the pump and into the exhaust. Users of such systems should therefore check that their fume extraction system can safely accommodate HCl vapours or else costly damage may result. Additionally, users should ensure that the vacuum pump outlet pipe is correctly fitted and does lead vapours away safely, otherwise the HCl vapours may be drawn into the vacuum pump motor increasing its likelihood of early failure.

When working with multiple samples in parallel, a centrifugal evaporator is the method of choice for drying samples. In such situations the problems of handling HCl are compounded further as nearly all centrifugal evaporators have tube holders, rotors, condensers and pumps containing steel or aluminium parts which corrode easily and can result in potentially dangerous and costly system failures. For laboratories tasked with regular removal of HCl, from multiple samples in parallel, Genevac has developed a range of HCl resistant centrifugal evaporators (Figure 3). In these specialist systems Genevac has replaced standard metal parts that come into contact with HCl with corrosion resistant alternatives such as Hastelloy® steel or glass. Similarly rubber seals are replaced with Kalrez® or similar resistant elastomeric seals. Where parts in the vapour path cannot be replaced Genevac has elected to coat them with PTFE to considerably enhance their HCl resistance.

**Figure 3** - Genevac EZ-2 HCl resistant system



## Conclusions

HCl is a versatile reagent used by many chemists to synthesise and purify high quality organic molecules. Traditionally there have been problems associated with using evaporators for removal of HCl from multiple samples in parallel where even low concentrations of the acid can cause corrosion leading to system failure. These problems have been resolved by development of a range of optimised HCl resistant centrifugal evaporators containing wetted components made from suitable acid resistant steels, coatings and elastomers enabling the chemist to use HCl in reactions and not compromise on their preferred organic synthetic route pathway.

## Acknowledgements

Kalrez® is a trade mark of DuPont Performance Elastomers LLC.  
Hastelloy® is a trade mark of Haynes International Inc.

## About the Author

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