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Acetyl Chloride-Methanol as a Convenient Reagent for: A) Quantitative Formation of Amine Hydrochlorides B) Carboxylate Ester Formation C) Mild Removal of N-t-Boc-Protective Group.

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**ACETYL CHLORIDE-METHANOL AS A CONVENIENT
REAGENT FOR:
A) QUANTITATIVE FORMATION OF AMINE
HYDROCHLORIDES
B) CARBOXYLATE ESTER FORMATION
C) MILD REMOVAL OF N-t-BOC-PROTECTIVE GROUP.**

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Abstract. Hydrogen chloride quantitatively generated *in situ* by the addition of acetyl chloride to alcoholic solutions is a useful reagent for carboxylic acid esterification, N-t-Boc deprotection and phosphoramidate solvolysis reactions.

Hydrogen chloride in organic solvents is a useful reagent for many reactions, primarily ones involving formation of amine salts, esterification of carboxylic acids and the removal of protective groups. A major drawback of the reported procedures stems from the large excess of the acid present in solution, the organic solvent commonly being saturated with gaseous HCl; preparation of organic solutions containing stoichiometric amounts of the acid are difficult. Moreover,

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the use of gaseous HCl is accompanied by corrosion of the gas valves and unpleasant side effects upon escape of the gas following saturation of the solvent. Esterification catalyzed by HCl generated *in situ* via the addition of TMSCl to methanol has been described.¹ Selective removal of N-t-Boc by HCl generated from TBDMSCl was reported to take place only at reflux temperature.²




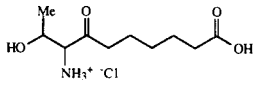
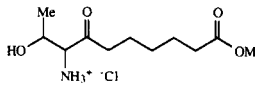
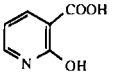
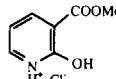
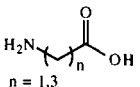
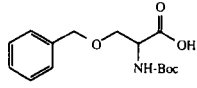
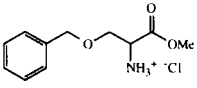
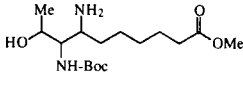
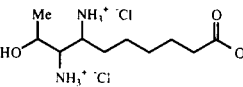
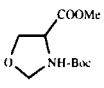
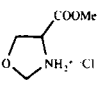
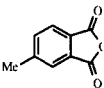
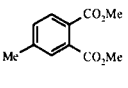
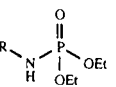
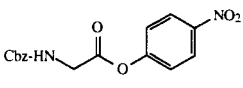
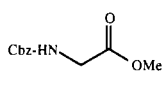
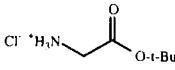
In this communication, we report a simple and highly convenient method for the preparation and use of solutions of HCl of known concentration in organic solvents. The solutions may be prepared by the addition of either a stoichiometric amount of acetyl chloride to an inert organic solvent containing an equivalent amount of methanol (or ethanol), or by addition of a known amount of acetyl chloride to an organic solvent containing a molar excess of the alcohol.

Among the uses described below, the present procedure provides a convenient method for the removal of N-t-Boc protective groups, having the advantage that it proceeds smoothly at room temperature and does not require expensive trifluoroacetic acid.³

The following representative reactions (Table I) were carried out:

- a) Mono and poly-amines were reacted with the AcCl/MeOH/solvent mixture to give quantitative yields of the corresponding amine or polyamine hydrochloride salts, which frequently crystallized from the reaction mixture (Entry 1).
- b) Acids were converted into esters (Entry 2).
- c) In the presence of an excess alcohol, amino acids and N-t-Boc-amino acids were readily converted in high yield to the corresponding amino acid ester hydrochlorides (Entries 3-6).
- d) N-t-Boc-amino acid esters were converted into the corresponding ester hydrochlorides (Entries 7, 8).

Table 1.

Entry	Compound	Product	Solvent media	Yield %
1		$\text{Cl}^- \text{H}_3\text{N}^+ \text{---} \text{NH}_3^+ \text{Cl}^-$	AcCl/EtOH EtOAc	100
2			AcCl/EtOH	57
3			AcCl/MeOH	93
4			AcCl/MeOH	100
5	 $n = 1,3$	$\text{Cl}^- \text{H}_3\text{N}^+ \text{---} \text{NH}_3^+ \text{OMe}$	AcCl/MeOH	95-100
6			AcCl/MeOH	100
7			AcCl/EtOH EtOAc	95
8			AcCl/MeOH EtOAc	96
9			AcCl/MeOH	96
10	 $\text{R} = p\text{-MeO-C}_6\text{H}_4\text{-}; n\text{-C}_6\text{H}_{13}\text{-}$	$\text{R-NH}_3^+ \text{Cl}^-$	AcCl/MeOH	100
11			AcCl/MeOH	product detected by NMR
12		no reaction	AcCl/MeOH	

- h) Diesters were obtained from the corresponding cyclic anhydrides (Entry 9).
- f) Phosphoramides were converted to amine hydrochlorides (Entry 10)
- e) When the reaction was carried out in MeOH, p-NO₂-phenyl esters underwent transesterification to the corresponding methyl esters (Entry 11).
- g) t-Butyl esters as well as N-CBZ protective groups were found to be stable under the reaction conditions (Entries 11, 12).

A typical experimental procedure involves dropwise addition of a known amount of acetyl chloride, usually via a weighed syringe, to an ice cold solution of an equivalent or excess amount of methanol (or ethanol) in an inert organic solvent, such as ethyl acetate, containing an equivalent amount of the compound to be reacted. The acidic solution may also be prepared in the pure alcohol. Ice cold solutions are used in order to increase the solubility of the HCl and prevent its escape, the initial generation of the HCl being exothermic. In cases where simple esterifications are carried out, excess acetyl chloride may be used without detrimental effects, since the workup involves simple evaporation of the solvent(s) and excess HCl. The solutions were allowed to warm to room temperature and the reactions were completed within 0.5-24 h.

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