4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride (DMT-MM)

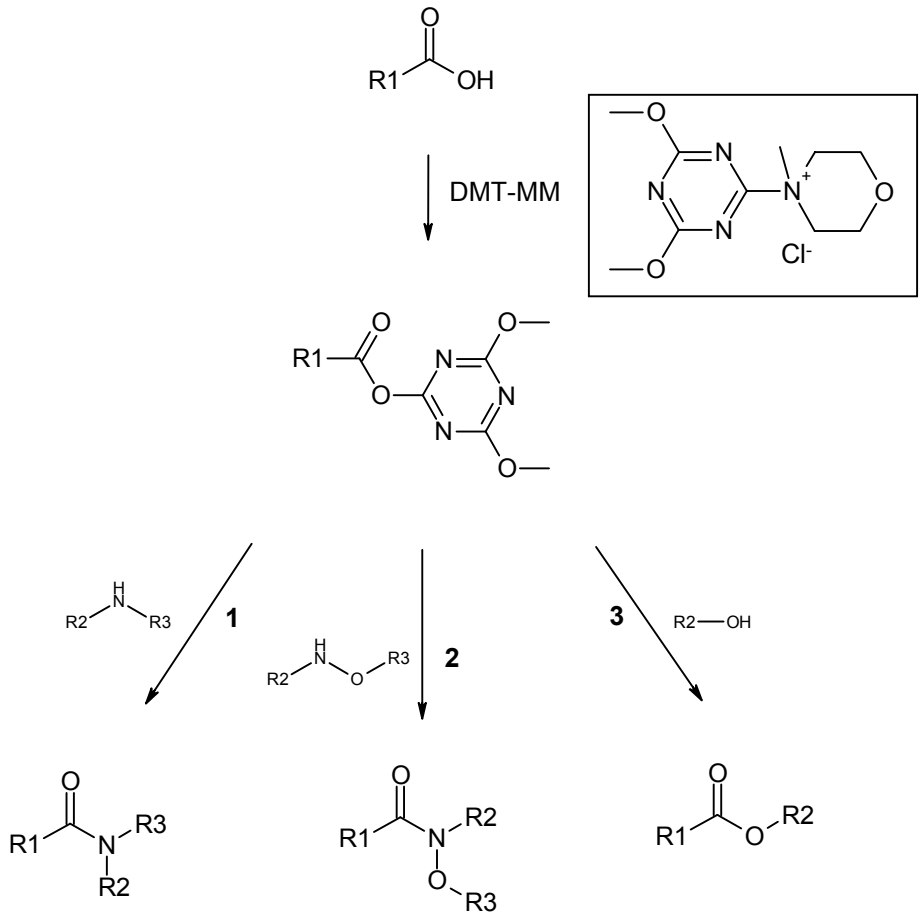
It is preferable to avoid the isolation of an activated acid derivative if possible: in some methods, however, where activation of the acid needs to be completed prior to the addition of amine or alcohol, completion of the first step must be confirmed if the reaction is to proceed successfully. By contrast, carbodiimides and many kinds of phosphorous agents such as phosphonium salts, phosphonates or phosphoramides, enable the activation of acids in the presence of amines, and therefore, serve as useful and convenient coupling agents. Reactions using these reagents are generally conducted in less polar solvents such as CH_2Cl_2, Et_2O, THF and MeCN, but when substrates are insoluble in these solvents, a more polar solvent like DMF and DMSO must be used. The removal of high-boiling polar solvents is particularly troublesome. In the case of carbodiimides, a side reaction forming an *N*-acylurea by-product becomes serious in THF, DMF and acetone.

Recently, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) has been described as a versatile reagent for the selective formation of amides[1]. Although CDMT has been shown to be a useful non-carbodiimide reagent, in terms of stability, mild reaction conditions and cost, it has the disadvantage to be irritating to the eye and nose. In addition, reactions are generally conducted under dry conditions by a two-step procedure: the carboxylic acid is first treated with CDMT in the presence of *N*-methylmorpholine to activate the acid, then an amine or an alcohol is added to obtain the product. This requires confirmation of the completion of the first step for successful results. To resolve these issues, a more convenient one-step approach is desired.

In 1999 Kunishima et. al. reported the synthesis[2] and use of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in amide and ester forming reactions. This coupling agent is a crystalline, air-stable, non-hygroscopic, easy-to-handle compound. In comparison with a carbodiimide reaction, the co-products formed may be easily removed from the reaction mixture (by washing with water), offering a convenient preparation of the acid derivative. Though comprehensive toxicological data is not yet available, this material is expected to be a less toxic agent than the many alternatives mentioned already.

Preparation of amides (path 1)[3-6]:

DMT-MM is a very powerful reagent for condensing a variety of carboxylic acids and amines to yield the corresponding carboxamides in a one-step procedure. In most cases, the transformation is completed by stirring the carboxylic acid and amine at room temperature for 3-4 hours. All reactions may be conducted in a flask open to the atmosphere, using commercial solvents (eg. THF, CH_2Cl_2) without purification and drying. The method is applicable to aliphatic, aromatic, sterically hindered and □,□-unsaturated acids. Both primary and secondary amines can be condensed to give the corresponing amides. N-Acetylation of amino acids proceeds readily on simply mixing the amino acid ester hydrochloride with sodium acetate and DMT-MM[4]. The coupling has also been applied very effectively for the acylation of rather complicated compounds such as cephalosporin derivatives[3].



Condensation reactions using DMT-MM

The rate of aminolysis of the active ester intermediate formed by the reaction of DMT-MM and carboxylic acid can be estimated to be about $2x10^4$ times greater than that of the alcoholysis. The amide/ester selectivity observed using DMT-MM is much larger than that obtained with DCC or EDC. Condensation of polar substrates such as amino acid esters and their hydrochlorides, carbohydrates, sodium carboxylates, dicarboxylic acids proceeds successfully in MeOH, water or aqueous MeOH in good yields[5].

DMT-MM is also found to be an effective coupling agent for solid phase peptide synthesis – an economic alternative to other condensing agents such as DCC and PyBOP. Several oligopeptides have been prepared on Wang-resin using this reagent, and the yield and purity of the product were always comparable with those obtained with the PyBOP agent[5].

Preparation of hydroxamic acids (path 2)[7]:
Similarly to the above mentioned amide synthesis, *O,N*-alkylsubstituted hydroxamic acids (Weinreb amides) can be prepared from carboxylic acid and amino acids with the corresponding substituted hydroxylamine with DMT-MM.

Preparation of esters (path 3)[3,8]:
Reaction of carboxylic acids with DMT-MM in alcohol in the presence of *N*-methylmorpholine (as base to form the ammonium carboxylate active species) affords the corresponding ester. The esterification can take place in 1.5-5 hrs with excellent yield in the alcohol as solvent or with an equimolar alcohol in THF. This procedure is suitable for preparation of both aliphatic (methyl, ethyl, isopropyl and *tert*-butyl) and benzylic esters.

Reduction of Carbocylic acid to Aldehyde[9]:

Though DMT-MM is found to be a versatile condensing agent in the preparation of acid derivatives, the easy formation of active esters permits its use in other field of synthetic organic chemistry. An example is the reduction of carboxylic acids to aldehydes. The active ester formed in the reaction of DMT-MM and a carboxylic acid can be hydrogenated over palladium on charcoal catalyst to the corresponding carbonyl compound in 30-84% yield. This transformation works well, especially in case of aliphatic carboxylic acids, and allows the preparation of N-protected aminoaldehydes starting from □-amino acids[9].

DMT-MM is available in commercial quantities from Ubichem

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