SYNLETT Spotlight 407

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

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) is a highly effective coupling reagent used for both amide synthesis and for the preparation of esters.^{1,2} The advantages of using DMTMM as a coupling reagent include excellent product yields and the possibility that reactions can be performed in one step at room temperature and under atmospheric conditions.¹ Readily removed and solubilising solvents (e.g. MeOH, EtOH, *i*-PrOH) including water, can be used in reactions with DMTMM and no drying requirements are needed for the reaction solvents.³ Furthermore, no additives are required and acids can be activated *in situ*.²

The by-product of the reaction with DMTMM (2-hydroxy-4,6-dimethoxy-1,3,5-triazine, HO-MDT) is highly water soluble and can be easily removed from the main re-

action product.^{2,4} The recovered by-product can also be converted back into the starting material via 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT).

DMTMM is commercially available, but can also be prepared in a straightforward manner by reaction between CDMT and *n*-methylmorpholine (NMM) or from cyanuric chloride.^{3,5} The reagents for the preparation of DMTMM are inexpensive, providing an economical benefit when using this reagent.

Scheme 1 Preparation of DMTMM from CDMT

Abstracts

(A) Hojo and colleagues developed a method for the effective, environmentally friendly and organic solvent-free, solid-phase peptide synthesis in aqueous 50% ethanol with DMTMM in the presence of NMM.⁶ In this manner, the authors synthesised Leu-enkephalin on solid phase using water-dispersible nanoparticles in good yield and purity.

(B) A series of novel naphthoquinone aromatic amides was prepared by Pradiphol and co-workers as anticancer agents, following a new route. DMTMM proved to be a better reagent than DCC for coupling the amine to benzoic acid.⁷ All compounds were prepared in high yields (>68%).

(C) Hyun and colleagues have reported the synthesis of mono-, di-, and triazidated polyrotaxanes from polyethylene glycol (PEG) and the azidated α -cyclodextrins using DMTMM as coupling reagent.⁸ The reaction was performed overnight at room temperature. The functionalized polyrotaxanes can be utilized for a variety of biological applications.

(D) Tanaka et al. prepared novel glycosidic compounds, 4,6-dialkoxy-1,3,5-triazin-2-yl β -lactosides (DAT- β -Lac) for cellulose-catalysed lactosylation, from lactose in water using 4,6-dialkoxy-1,3,5-triazine-type agents in aqueous media with DMTMM.⁹ Authors found that the yield of DAT- β -Lac was dependant on the anomeric ratio (β/α) of the starting material.

(E) Pudlo and colleagues used DMTMM as coupling reagent for the acylation of a series of *o*-iodoanilines to prepare a range carboxylic acid intermediates in good yields (62–87%).¹⁰

(F) After successful preparation of secondary and tertiary amides using DMTMM, Mizuhara et al. reported a method for the synthesis of primary amides from carboxylic acids and ammonia using DMTMM in good yield (63%).¹¹

(G) Shieh and co-workers reported the synthesis of sterically-hindered peptidomimetics using DMTMM and demonstrated its efficiency compared to HBTU/HOBt and CDMT in controlling racemization and N-arylation.¹² The desired diastereomer was prepared in high yield (98%).

(H) Wu and colleagues synthesised fidarestat, an aldose reductase inhibitor, via a novel method using DMTMM for the amidation in the final step of the procedure.¹³

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