

SYNLETT Spotlight 407

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

Compiled by Ana Zivanovic



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

Ana Zivanovic was born in Nis, Serbia. She graduated in chemistry from the University of Nis in 2007. Currently, she is working towards her PhD degree at the University of Wollongong in Australia under the supervision of Dr. Danielle Skropeta in organic and medicinal chemistry. Her PhD project involves the investigation of protein kinase inhibitors from marine natural products and the synthesis of novel potent isatin-based anticancer agents.

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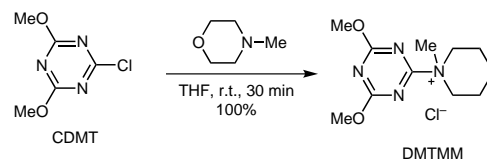
Introduction

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).

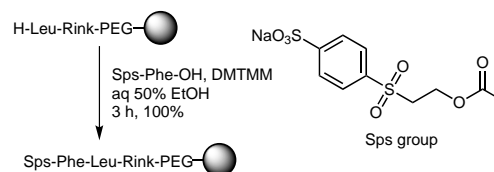
DMTMM is commercially available, but can also be prepared in a straightforward manner by reaction between CDMT and *n*-methylmorpholine (NMM) or from cyanuric chloride.^{3,5} The reagents for the preparation of DMTMM are inexpensive, providing an economical benefit when using this reagent.



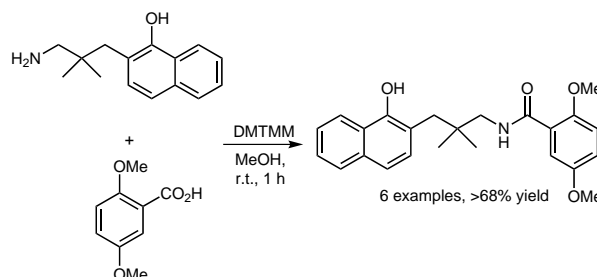
Scheme 1 Preparation of DMTMM from CDMT

Abstracts

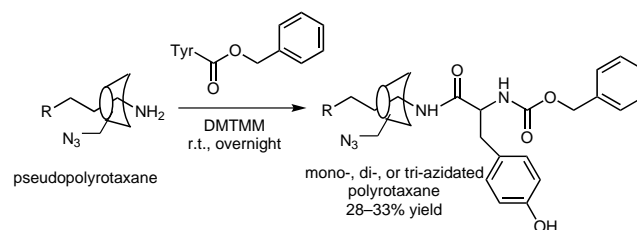
(A) Hojo and colleagues developed a method for the effective, environmentally friendly and organic solvent-free, solid-phase peptide synthesis in aqueous 50% ethanol with DMTMM in the presence of NMM.⁶ In this manner, the authors synthesised Leu-enkephalin on solid phase using water-dispersible nanoparticles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



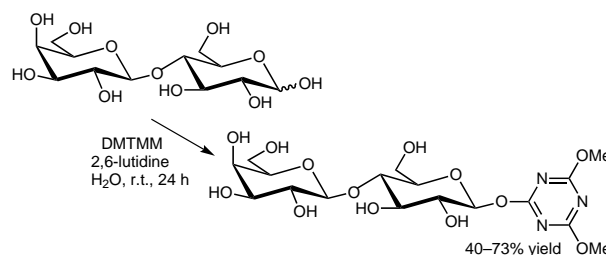
(B) A series of novel naphthoquinone aromatic amides was prepared by Pradidphol and co-workers as anticancer agents, following a new route. DMTMM proved to be a better reagent than DCC for coupling the amine to benzoic acid.⁷ All compounds were prepared in high yields (>68%).



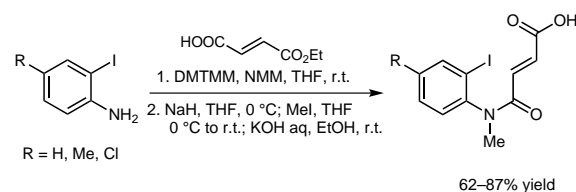
(C) Hyun and colleagues have reported the synthesis of mono-, di-, and triazidated polyrotaxanes from polyethylene glycol (PEG) and the azidated α -cyclodextrins using DMTMM as coupling reagent.⁸ The reaction was performed overnight at room temperature. The functionalized polyrotaxanes can be utilized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



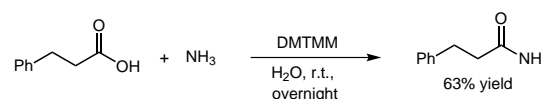
(D) Tanaka et al. prepared novel glycosidic compounds, 4,6-dialkoxo-1,3,5-triazin-2-yl β -lactosides (DAT- β -Lac) for cellulose-catalysed lactosylation, from lactose in water using 4,6-dialkoxy-1,3,5-triazine-type agents in aqueous media with DMTMM.⁹ Authors found that the yield of DAT- β -Lac was dependant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



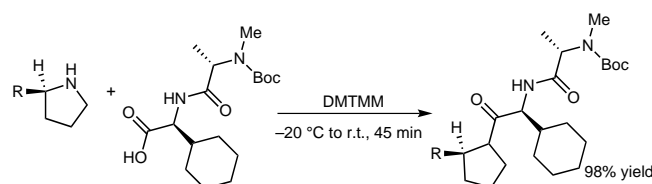
(E) Pudlo and colleagues used DMTMM as coupling reagent for the acylation of a series of *o*-iodoanilines to prepare a range carboxylic acid intermediates in good yields (62–87%).¹⁰



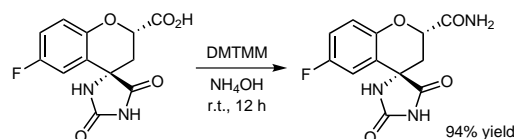
(F) After successful preparation of secondary and tertiary amides using DMTMM, Mizuhara et al. reported a method for the synthesis of primary amides from carboxylic acids and ammonia using DMTMM in good yield (63%).¹¹



(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



References

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