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Approach to green chemistry of DMT-MM: recovery and recycle of coproduct to chloromethane-free DMT-MM

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Abstract—A simple procedure for the isolation of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT), a coproduct arising from dehydrating condensation using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) has been established. HO-DMT can be recycled by treatment with $POCl_3$ to give 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), which is further converted to DMT-MM. Alternatively, reaction with triflic anhydride followed by addition of *N*-methylmorpholine gives DMT-MM triflate. © 2002 Elsevier Science Ltd. All rights reserved.

Although the formation of by-products resulting from undesirable side reactions can be avoided by improving reaction conditions, formation of coproducts, i.e. accompanying reactions leading to a desired product, is inevitable. Unless isolation and conversion of such coproducts into other useful compounds are very easy, they become waste materials. To be useful on an industrial scale, it is particularly important to avoid column chromatography in the isolation procedure. Thus, development of effective and efficient methods for recovery and reuse of coproducts is highly desirable from both an environmental and economic perspective.

Recently, we have introduced 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) as a new dehydrating condensing agent[1] that enables us to carry out amidation of carboxylic acid in protic solvents such as water, MeOH, EtOH, and *i*-PrOH.[2] Condensation using DMT-MM gives 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT) as a coproduct along with the formation of the desired product. For a good example of salvage of HO-DMT, we developed a method for converting it to benzyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Z-DMT), which is a promising new *N*-benzyloxycarbonylating agent.[3] To make this or other salvage pathways useful, it is necessary to establish a convenient procedure for recovery of HO-DMT. However, the high water solubility of HO-DMT, which makes it very easy to separate it from typical organic products by extraction, would seem to make isolation of HO-DMT from a protic as well as aportic reaction mixture difficult. In this communication, we report a simple procedure for isolation of HO-DMT and regeneration of DMT-MM from it.

As shown in Chart 1, HO-DMT can be readily recovered by filtration from the reaction mixture of a dehydrating condensation. A methanolic solution of cinnamic acid and phenylethanamine (0.1 mol/L each) was treated with DMT-MM for 2.5 h. The resulting

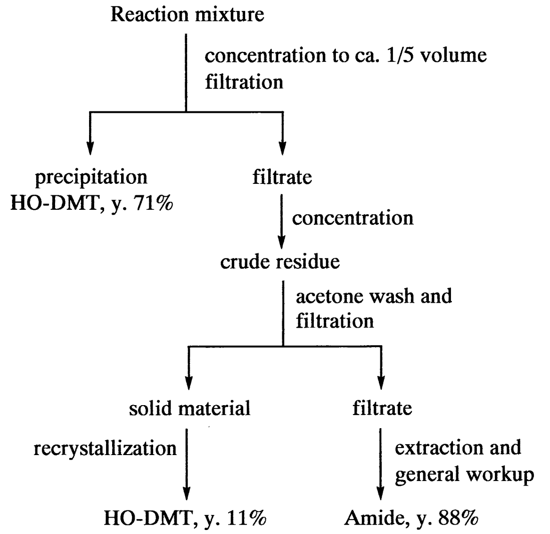

Chart 1. Recovery of HO-DMT from the reaction mixture.

Keywords: triazines; condensations; amides.

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Table 1. Dehydrating condensation of carboxylic acids and amines with DMT-MM

$$RCOOH + R'NH_2 \xrightarrow{\text{DMT-MM or DMT-MM (TfO)}} RCONHR'$$

Run	RCOOH	$R'NH_2$	Condensing agent	Solvent	Conditions	Yield[a] (%)
1	PhCH=CHCOOH	$Ph(CH_2)_2NH_2$	DMT-MM	MeOH	Rt, 2.5 h	88
2	PhCH=CHCOOH	$Ph(CH_2)_2NH_2$	DMT-MM (TfO)	MeOH	Rt, 2.5 h	96[b]
3	$Ph(CH_2)_2COOH$	$Ph(CH_2)_2NH_2$	DMT-MM	CH_2Cl_2	Rt, 1 h	83
4	$Ph(CH_2)_2COOH$	$Ph(CH_2)_2NH_2$	DMT-MM (TfO)	CH_2Cl_2	Rt, 1 h	84
5	PhCOCOOH	$Ph(CH_2)_2NH_2$	DMT-MM	CH_2Cl_2	Rt, 1 h	88
6	PhCOCOOH	$Ph(CH_2)_2NH_2$	DMT-MM (TfO)	CH_2Cl_2	Rt, 1 h	87
7	Boc-Leu-OH	H-Phe-OMe	DMT-MM	CH_3CN	Rt, 1 h	94
8	Boc-Leu-OH	H-Phe-OMe	DMT-MM (TfO)	CH_3CN	Rt, 1 h	98

[a] Isolated yield.

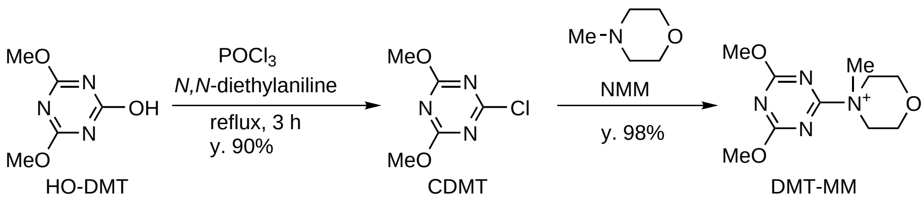
[b] HO-DMT (93% yield) and sodium triflate (88% yield) were recovered.

mixture was concentrated by a rotary evaporator to about one-fifth of its original volume to precipitate a white solid, which was collected by suction to give almost pure HO-DMT in 71% yield. An additional HO-DMT (11%) was recovered from the filtrate by further concentration followed by washing of the resulting residue with acetone. The amide was obtained from the resulting acetone washings by general workup in 88% yield (Table 1, run 1). When condensation is conducted in other low-boiling organic solvents, HO-DMT can be isolated from a concentrated crude residue in a similar manner.

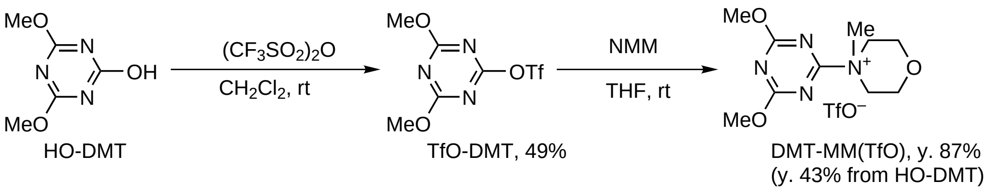
We have developed two procedures for recycling HO-DMT to DMT-MM. Chlorination of the hydroxyl group of HO-DMT with $POCl_3$ and diethylaniline gave 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in 90% yield,[4] which was quantitatively converted to DMT-MM by coupling with *N*-methylmorpholine (NMM) (Eq. (1)).[1a] Alternatively, HO-DMT was treated with triflic anhydride to give 4,6-dimethoxy-2-trifluoromethylsulfonyl-1,3,5-triazine (TfO-DMT) in 49% yield, and then coupled with NMM to give [DMT-MM (TfO)] in 87% yield, with triflate instead of chloride as the counter anion (Eq. (2)).[6] Since TfO-DMT is unstable and decomposes considerably during isolation, we attempted to convert HO-DMT directly to DMT-MM (TfO) without isolation of the intermediate. We found that treatment of HO-DMT with triflic anhydride in CH_2Cl_2 followed by addition of NMM afforded DMT-MM (TfO) in a good yield (Eq. (3)).[7] An equimolar amount of triflate ion arising from triflic anhydride during the reaction could be recovered as sodium triflate,[7] which can be converted into triflic anhydride.[8]

In contrast to the original DMT-MM, DMT-MM (TfO) appears to be soluble in organic solvents to some extent. However, the reactivity of DMT-MM (TfO) as a dehydrating condensing agent is similar to that of the original DMT-MM which has a chloride counter ion. As shown in Table 1, all the reactions took place in good to excellent yields in both polar and nonpolar solvents. Both HO-DMT and a triflate (as its sodium salt) resulting from reactions using DMT-MM (TfO) could be also recovered in 93 and 88% yields, respectively (run 2).

When DMT-MM is suspended at room temperature in organic solvents, especially CH_2Cl_2 or $CHCl_3$, it readily



(1)



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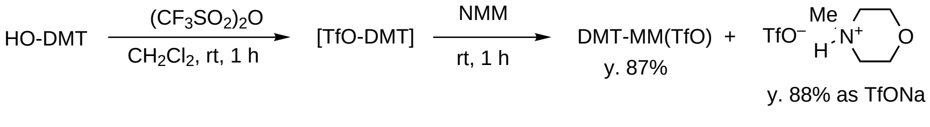

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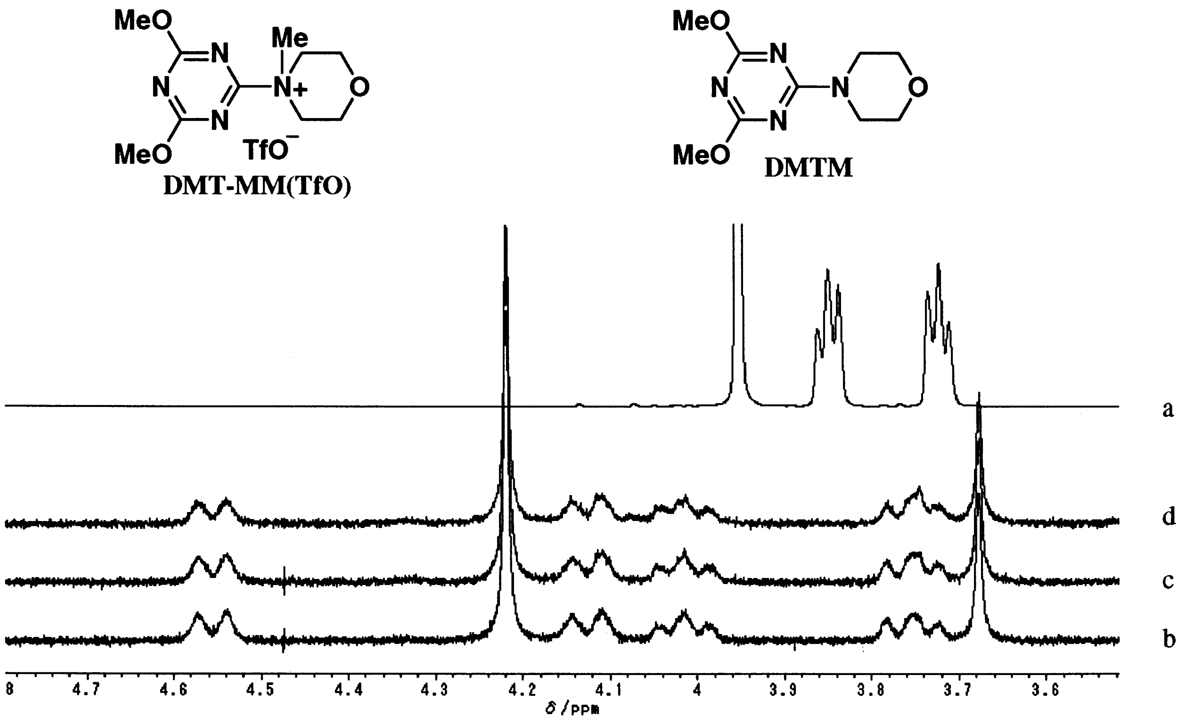

Chart 2. NMR analysis for the stability of DMT-MM (TfO) in $CDCl_3$. (a) DMTM arising from DMT-MM by demethylation. (b–d) DMT-MM (TfO) after 15 min (b), 6 h (c), and 100 h (d) at rt.

undergoes demethylation at the morpholinium nitrogen by attack of chloride anion, and chloromethane, which is an undesirable air pollutant, evolves.[1c] Since the demethylation appears to be slower than the reaction of DMT-MM with carboxylic acids, these organic solvents can be employed for condensation using DMT-MM. A small amount of chloromethane, however, would be formed in most condensation reactions conducted in less-polar organic solvents.[1,2] In contrast with DMT-MM, DMT-MM (TfO) is quite stable in $CHCl_3$, presumably due to the lower nucleophilicity of triflate ion than that of chloride. Thus, when DMT-MM (TfO) was suspended in $CDCl_3$ at room temperature, no decomposition was observed by NMR analysis even after 100 h, as illustrated in Chart 2. Other analogues that circumvent the evolution of chloromethane were prepared by counter ion exchange; DMT-MM nitrate or perchlorate were obtained by treatment with $AgNO_3$ or $LiClO_4$, respectively.

DMT-MM is one of several promising dehydrating condensing candidates that are attractive to industry because of the synthetic advantages that they offer, which are superior to other dehydrating condensing agents such as carbodiimides. HO-DMT is widely formed as a coproduct in reactions using not only DMT-MM but also CDMT,[9] Z-DMT,[3] and a cyclodextrin-based artificial acyltransferase.[10] Thus, the present procedures for isolation and reuse of HO-DMT, which are environmentally friendly and economically favorable, should become very useful in future.

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4. For regeneration of CDMT from HO-DMT: According to the literature describing chlorination of heterocyclic alcohols,[5] a mixture of HO-DMT (5.0 g, 31.8 mmol) and *N*,*N*-diethylaniline (9.5 g, 636 mmol) dissolved in phosphoryl chloride (89 mL) was refluxed for 3 h. After removal of the excess phosphoryl chloride at 35°C/45 mmHg, the residue was poured into ice-water and stirred for 50 min. The resulting mixture was extracted with $CHCl_3$, and the organic layer was washed successively with HCl, $NaHCO_3$, and brine. Purification of the crude material by silica gel column chromatography gave CDMT (5.0 g) in 90% yield.
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6. The abbreviations DMT-MM and DMT-MM (TfO) refer to the chloride and the triflate salts, respectively.
7. For direct formation of DMT-MM (TfO) from HO-DMT: Triflic anhydride (9.90 g, 35.0 mmol) was added dropwise to a solution of HO-DMT (5.0 g, 31.8 mmol) in

CH_2Cl_2 (318 mL) under nitrogen at room temperature. After stirring the mixture for 1 h, NMM (7.10 g, 70.0 mmol) was added dropwise to the solution, and then the mixture was allowed to react for another 1 h. The solvent was evaporated, and the residue was dissolved in MeOH (100 mL), and then Et_2O (400 mL) was added to give 10.8 g (87% yield) of DMT-MM (TfO). The resulting organic layer including 4-methylmorpholinium triflate was concentrated, and treated with 1 M NaOH in MeOH followed by evaporation. The residue was dissolved in acetone followed by filtered, and the filtrate was poured into CH_2Cl_2 to give a precipitate, which was recrystallized from acetone to give sodium triflate (5.32 g, 88% yield). DMT-MM (TfO): colorless needles; mp 156–159°C, IR (KBr) 1634, 1541, 1487, 1391, 1276, 1133, 1031 cm^{-1}; ^1H NMR (CD_3OD) δ 3.52 (s, 3H), 3.79–3.92 (m, 4H), 4.02–4.11 (m, 2H), 4.18 (s, 6H), 4.48–5.58 (m, 2H). Anal. calcd for $C_{11}H_{17}F_3N_4O_6S$: C, 33.85; H, 4.39. Found. C, 33.55; H, 4.16%.

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