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An improved process for the synthesis of DMTMM-based coupling reagents

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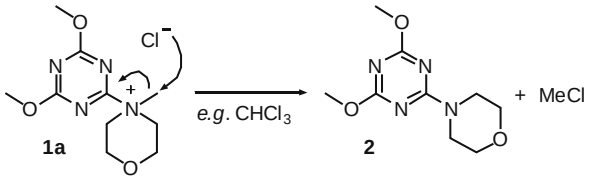
ABSTRACT

A simple, robust and high-yielding process for the preparation of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate (DMTMM BF_4) and hexafluorophosphate (DMTMM PF_6) has been developed, which avoids the use of expensive or unusual reagents.

In recent years, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride **1a** (DMTMM Cl)[1] has come to prominence as an effective coupling agent, finding applications in amidation,[2] esterification,[2b,3] glycosidation[4] and phosphonylation[5] methodology. However, the utility of DMTMM Cl **1a** as a coupling agent is compromised, especially at large scale, by its instability in organic solution as it undergoes self-immolative degradation, yielding 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-morpholine **2** and chloromethane (Scheme 1). In chloroform at ambient temperature, this results in complete degradation in just 3 h[1a] (97% degradation is observed in 2 h[6]).



Scheme 1. Self-immolative degradation of DMTMM Cl.

The second order rate constants for this degradation in DMF and DMSO at ambient temperature have been determined as $1.06 \pm 0.48 \times 10^{-2}$ and $1.42 \pm 0.12 \times 10^{-3}$ $dm^3\ mol^{-1}\ s^{-1}$, respectively.[6] So, for example, at a typical process concentration of 0.1 M, DMTMM Cl **1a** would degrade by 50% in approximately 15 min in DMF and approximately 120 min in DMSO (assuming **1a** is completely dissolved). For further qualitative stability studies on DMTMM, see Kunishima et al.[2b] This degradation will of course have an impact on the stoichiometry of the reaction. The production of chloromethane will also have ramifications for the yield and purity of the final products as it could methylate carboxylate substrates (giving the corresponding esters) or alkylate elsewhere in the substrate or product.[2d]

To avoid this degradation, Kamiński et al. have developed DMTMM BF_4 **1b** as an alternative to **1a**.[7] The non-nucleophilic BF_4^- counterion does not take part in the degradation process and organic solutions of **1b** are stable for several days at least.[6] DMTMM BF_4 **1b** has been shown to be equally effective in peptide couplings as **1a**[7a] and can be considered as a direct replacement.

As part of a recent multi-kilogram scale development programme, the use of a DMTMM-based amidation was investigated. In early development, some of the main issues encountered when using DMTMM Cl **1a** were, as mentioned above, the distortion of stoichiometry and esterification of our carboxylate coupling partner by methyl transfer. Consequently, the use of DMTMM BF_4 **1b** was considered. In order to complete the development studies, a practical, robust, high-yielding process for the generation of **1b** was required.

The two published methods[7] for the preparation of DMTMM BF_4 **1b** have significant drawbacks, especially if one intends to operate on large scale, and these impact upon its utility in process research and development. One method[7a] employs initial formation of DMTMM Cl **1a** in dichloromethane followed by precipitation of DMTMM BF_4 **1b** by addition of silver tetrafluoroborate suspended in acetonitrile. This is followed by isolation by filtration and a subsequent recrystallisation. The yield reported is 73%. The issues here are: (1) Given its sensitivity in chloroform, one may expect significant degradation of the DMTMM Cl **1a** to occur in dichloromethane, even at the suggested temperature of 5 °C, distorting stoichiometry and eroding yield. (2) Slurry transfers can be problematic in a pilot plant, and any disruptions in transfer will have significant impact on such a sensitive first stage. (3) Use of $AgBF_4$ may be prohibitively expensive on multi-kilo scale. The second method[7b] involves long reaction times (normally 20 h) and requires *N*-methylmorpholinium tetrafluoroborate, which is not commercially available (presumably this is synthesised from *N*-methylmorpholine and tetrafluoroboric acid). The yield reported is 75%.

Unlike in most organic solvents, DMTMM Cl **1a** is stable as an aqueous solution for significant time periods, i.e., over 24 h at ambient temperature.[2b,6] It was postulated that DMTMM BF_4 **1b**

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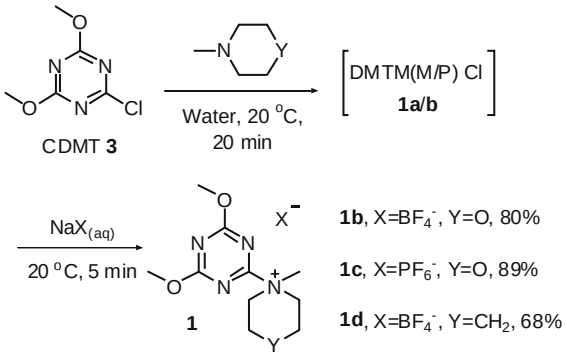
could be precipitated from an aqueous solution of **1a** by addition of sodium tetrafluoroborate.[8] Initial small-scale trials (approximately 250 mg) showed immediate success: when aqueous $NaBF_4$ was added dropwise to an aqueous solution of **1a** at ambient temperature, DMTMM BF_4 **1b** precipitated immediately, and was easily recovered in a good yield (approximately 75%).

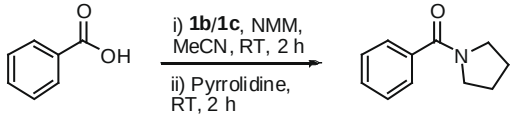
Though DMTMM Cl **1a** is commercially available, even in the solid state it can degrade via the mechanism discussed above,[7a] and so we were keen to develop a synthesis of **1b** from the cheaper and more stable precursor, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) **3**. Furthermore, the ideal was a one-stage, two-step process, avoiding any isolation of **1a**. Given the initial success of the precipitation of DMTMM BF_4 **1b** from aqueous solution and the proven stability of aqueous solutions of **1a** to degradation, the formation of **1a** from **3** in aqueous media was investigated. To this end, CDMT **3** was suspended in water and *N*-methylmorpholine (NMM) added. Analysis by HPLC showed complete consumption of the CDMT **3** in just 20 min. Dropwise addition of an aqueous solution of $NaBF_4$ to this mixture over 5 min caused precipitation of DMTMM BF_4 **1b**. The product was isolated by filtration in an overall yield of 80% from CDMT **3** (Scheme 2).



Scheme 2. Synthesis of DMTMM BF_4, DMTMM PF_6 and DMTMP BF_4.

With a viable process for the synthesis of DMTMM BF_4 **1b** in hand, we were keen to investigate its application to other related salts. Accordingly, synthesis of DMTMM PF_6 **1c** was attempted by an analogous procedure (Scheme 2). Gratifyingly, the desired product **1c** was isolated in 89% yield. Furthermore, the protocol is applicable to other amines, such as *N*-methylpiperidine, delivering DMTMP BF_4 **1d**[7a] in an *unoptimised* yield of 68%, using a slightly modified procedure.[9]

To prove that the novel DMTMM PF_6 **1c** is as active as DMTMM BF_4 **1b** in coupling reactions, both salts were employed in the amidation of benzoic acid with pyrrolidine (Scheme 3), following a protocol developed by Kamiński et al.[7a] In directly comparable reactions, the yields obtained were essentially identical, being 78% with **1b** and 79% with **1c**.



Scheme 3. Amidations with DMTMM BF_4 and PF_6.

In conclusion, a new practical, robust and high-yielding process for the production of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate (DMTMM BF_4) **1b**,[10] its hexafluorophosphate (DMTMM PF_6) **1c**[12] and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylpiperidinium tetrafluoroborate (DMTMP BF_4) **1d**[13] has been developed, which provides material of high quality. The process avoids all the drawbacks associated with previous syntheses,[7] as it does not involve the use of expensive $AgBF_4$, unstable solutions of DMTMM Cl **1a** and non-commercially available reagents. It also delivers the products **1b** and **1d** in higher yields than previously reported syntheses.[7] An added benefit from a process perspective is that the only effluent stream is aqueous, and the main by-product of the process is NaCl (alongside small excesses of *N*-methylmorpholine and $NaBF_4$ or $NaPF_6$).

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The author would like to thank Ian W. Ashworth and Brian R. Meyrick for their contributions to the investigations concerning the degradation of DMTMM salts in various solvents[6] and for the useful discussions with respect to the work reported herein. The author also thanks Anthony W.T. Bristow for HRMS analysis.

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5. For a recent example see: Wozniak, L. A.; Góra, M.; Stec, W. J. *J. Org. Chem.* **2007**, *72*, 8584–8587.
6. Ashworth, I. W.; Meyrick, B.; Raw, S. A., Unpublished results. Our investigations into the degradation kinetics of DMTMM Cl **1a** and related salts in a variety of solvents will be fully disclosed in due course.
7. (a) Kamiński, Z. J.; Kolesińska, B.; Kolesińska, J.; Sabatino, G.; Chelli, M.; Rovero, P.; Błaszczyk, M.; Głowka, M. L.; Papini, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 16912–16920; (b) Kamiński, Z. J.; Papini, A. M.; Jastrabek, K.; Kolesińska, B.; Kolesińska, J.; Sabatino, G.; Bianchini, R. Int. Pat. Appl., 2007, WO2007/051496; *Chem. Abstr.* **2007**, *146*, 482097.
8. $NaBF_4$ is a very economic commercial source of BF_4^- (being marginally cheaper than HBF_4 and less than 1% of the cost of $AgBF_4$). Furthermore, it is far easier to handle than HBF_4.
9. Preliminary small-scale studies indicate that DMTMP BF_4 **1d** is more soluble than the analogous DMTMM BF_4 **1b** in both acetonitrile and water. When the unmodified process is used, the isolated yield of **1d** is 47%, product loss to the mother liquors accounting for this significantly lower yield. Conducting the reaction at higher concentration significantly improves recovery.
10. *4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate* (**1b**): 2-Chloro-4,6-dimethoxy-1,3,5-triazine **3** (7.39 g, 41.4 mmol) was suspended in water (110 mL). To this was added *N*-methylmorpholine (5.0 mL, 45.6 mmol) in one portion. After 20 min, the solid had dissolved to give a colourless solution (analysis by HPLC showed complete consumption of **3**). Sodium tetrafluoroborate (5.57 g, 49.7 mmol) was dissolved in water (37 mL), and the resulting solution charged to the reactor dropwise over 5 min. Crystallisation began immediately and continued throughout the addition. The mixture was stirred for a further 45 min before the solid was collected by vacuum filtration. The cake was washed sequentially with water (2 × 22 mL) and methanol (37 mL). The material was dried to a constant weight in vacuo to give the title compound **1b** (11.12 g, 97.4% (w/w) strength,[11] 33.0 mmol, 80% yield) as a colourless crystalline solid: ^{1}H NMR (400 MHz, MeCN-d_3): $\delta_{(ppm)}$ 3.39 (3H, s), 3.68–3.79 (4H, m), 3.95–4.04 (2H, m), 4.12 (6H, s), 4.40–4.49 (2H, m); ^{13}C NMR (100 MHz, MeCN-d_3): $\delta_{(ppm)}$ 56.9, 57.8, 61.1, 62.8, 171.2, 175.0. The data are in good agreement with those published in the literature.[7a]
11. Material strength was determined by ^{1}H NMR spectroscopic assay in DMSO-d_6, using 1,2,4,5-tetrachloro-3-nitrobenzene as an internal standard.
12. *4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium hexafluorophosphate* (**1c**): This was synthesised in a manner analogous to that described above for **1b**, using 2-chloro-4,6-dimethoxy-1,3,5-triazine **3** (7.50 g, 42.0 mmol) and sodium hexafluorophosphate (8.56 g, 50.4 mmol) with the other reagents scaled accordingly. This gave the *title compound* **1c** (14.85 g,

96.9% (w/w) strength,[11] 37.3 mmol, 89% yield) as a colourless crystalline solid: ^{1}H NMR (400 MHz, DMSO-d_6): $\delta_{(ppm)}$ 3.47 (3H, s), 3.78 (2H, ddd, *J* 13.3 Hz, *J* 10.2 Hz, *J* 1.6 Hz), 3.88 (2H, ddd, *J* 12.7 Hz, *J* 10.2 Hz, *J* 2.8 Hz), 4.01 (2H, ddd, *J* 13.3 Hz, *J* 2.8 Hz, *J* 2.8 Hz), 4.10 (6H, s), 4.36 (2H, br d, *J* 12.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta_{(ppm)}$ 55.2, 56.6, 59.5, 61.3, 170.2, 173.4; ^{19}F NMR (470 MHz, DMSO-d_6): $\delta_{(ppm)}$ −70.6 (6F, d, *J* 710 Hz); ^{31}P NMR (200 MHz, DMSO-d_6): $\delta_{(ppm)}$ −143.0 (1P, septet, *J* 710 Hz); ^{1}H NMR (400 MHz, MeCN-d_3): $\delta_{(ppm)}$ 3.38 (3H, s), 3.66–3.79 (4H, m), 3.93–4.05 (2H, m), 4.11 (6H, s), 4.44 (2H, br d, *J* 10.6 Hz); ^{13}C NMR (100 MHz, MeCN-d_3): $\delta_{(ppm)}$ 56.9, 57.8, 61.1, 62.8, 171.2, 175.0; *m*/*z* (Positive ion ESI) 241 (DMTMM^{+}) [HRMS (Positive ion ESI) calcd for $C_{10}H_{17}N_4O_3$ 241.1295. Found 241.1297 (0.6 ppm error)].

13. *4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylpiperidinium tetrafluoroborate* (**1d**): 2-Chloro-4,6-dimethoxy-1,3,5-triazine **3** (7.55 g, 42.3 mmol) was suspended in water (60 mL). To this was added *N*-methylpiperidine (5.7 mL, 46.6 mmol) in one portion. After 20 min, the solid had dissolved to give a colourless solution (analysis by HPLC showed complete consumption of **3**). Sodium tetrafluoroborate (5.69 g, 50.8 mmol) was dissolved in water (15 mL), and the resulting solution charged to the reactor dropwise over 5 min. Crystallisation began after approximately 40% of the solution had been charged and continued throughout the remainder of the addition. The mixture was stirred for a further 75 min at ambient temperature. It was then cooled to 0 °C (ice/acetone bath) and stirred for a further 30 min before the solid was collected by vacuum filtration. The cake was washed twice with chilled water (15 mL and 8 mL). The material was dried to a constant weight in vacuo at 40 °C to give the title compound **1d** (9.75 g, 99.2% (w/w) strength,[11] 28.6 mmol, 68% yield) as a colourless crystalline solid: ^{1}H NMR (500 MHz, MeCN-d_3): $\delta_{(ppm)}$ 1.50–1.81 (4H, m), 1.85–1.96 (2H, m), 3.29 (3H, s), 3.52 (2H, ddd, *J* 12.5 Hz, *J* 12.5 Hz, *J* 2.7 Hz), 4.11 (6H, s), 4.41 (2H, br d, *J* 12.5 Hz); ^{13}C NMR (125 MHz, MeCN-d_3): $\delta_{(ppm)}$ 21.3, 21.9, 55.5, 57.7, 62.6, 171.8, 175.0. The data are in good agreement with those published in the literature.[7a]