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## AN IMPROVED PROCEDURE FOR THE LARGE SCALE PREPARATION OF 2-CHLORO-4,6-DIMETHOXY-1,3,5-TRIAZINE

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**Abstract:** A robust process for the preparation of multikilogram quantities of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) is described.

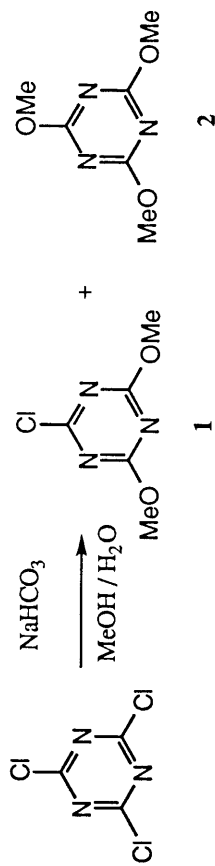
Recent advances in the preparation of esters, amides, anhydrides and peptides have utilized 2-chloro-4,6-dimethoxy-1,3,5-triazine **1** as a carboxylate activating agent<sup>1</sup>. Racemization of the position  $\alpha$  to the carboxylate functionality is minimized with the use of **1**, thereby making it especially useful for peptide synthesis and other chiral syntheses<sup>1</sup>. The preparation of **1** from cyanuric chloride and methanol has been previously described in the literature<sup>2</sup>. The reaction utilizes methanol and water as the solvent system with 2 equivalents of sodium bicarbonate as the hydrogen chloride scavenger (Scheme 1)<sup>3</sup>. The reaction temperature is controlled at 30°C. In our hands, the application of this protocol to the production of kilogram quantities of **1** was not successful.

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Due to the requirement for kilogram quantities of **1**, we required a robust synthesis. In our studies of the reaction, we observed the production of the trimethoxytriazine **2** as the reaction neared completion. Analysis using reaction calorimetry indicated a significant exotherm was associated with the conversion of the **1** to **2**. Additional experimentation demonstrated that the conversion of **1** to **2** was facilitated by higher temperatures. Given the concern of temperature control ability at a larger scale, we investigated alternative reaction conditions which might provide for a more robust process.

We discovered that the addition of 3 equivalents of sodium bicarbonate to the reaction mixture significantly decreased the conversion of **1** to **2** and eliminated the observed exotherm at the end of the reaction in which only 2 equivalents of sodium bicarbonate were used. Table 1 is a comparison of the results obtained from the two reaction procedures<sup>4</sup>. The data in Table 1 suggest

**Table 1. Production of 2,4,6-Trimethoxy-1,3,5-triazine 2 as a Function of Reaction Conditions**

entry	equivalents of base	reaction temperature	% 2 30 minutes after endpoint <sup>5</sup>	time for conversion of <b>1</b> to <b>2</b>
1	2.0	30° C	>10%	100% @ (2 hr)
2	2.0	40° C	>20%	100% @ (1 hr)
3	3.0	30° C	1%	3% @ (12 hr)
4	3.0	40° C	2%	9% @ 12 hr

that the use of an additional equivalent of base provides a good measure of robustness to the synthesis. Only 9% of the trimethoxy derivative **2** was formed at the higher temperature after 12 hours compared to quantitative conversion of **1** to **2** in 1 hour under the same conditions with 2 equivalents of base. Application of the protocol using 3 equivalents of sodium bicarbonate yields **1** in 65% yield. The procedure improves the yields of **1** and results in less conversion of **1** to **2** as the reaction approaches completion. This protocol has been run successfully on a scale of 20 Kg.

### Experimental

A mixture of 12.3 equivalents of methanol, 2.7 equivalents of water and 3 equivalents of sodium bicarbonate is cooled to 10 to 15° C. Cyanuric chloride is added and the resulting mixture is warmed to 35° C<sup>6</sup>. The reaction mixture is stirred until the intermediate 2,4-dichloro-6-methoxy-1,3,5-triazine is no longer present (about 12 hours as demonstrated by gas chromatographic analysis<sup>4</sup>). Water (5 volumes) is added and the resulting mixture stirred for 30 minutes. The product is isolated by filtration and the filter cake is washed with deionized water. The wet cake is dried under vacuum at 30° C to give a 65% yield of **1** as white crystals: mp 72 - 74.6 (lit<sup>2b</sup> 74.2 - 76.2); Anal. Calcd for C<sub>5</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>Cl: C, 34.21; H, 3.45; N, 23.93. Found: C, 34.47; H, 3.72; N, 23.68.

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3. Potassium bicarbonate functioned equally well in the reaction. Other bases such as sodium, potassium, and cesium carbonate gave increased levels of 2 and/or lower yields of 1.
4. The reaction mixture was analysed using a Hewitt Packard 5980 capillary GC with an DB-1 crosslinked methyl-silicon column, 30m x 0.25mm x .25µm, at a column temperature of 250° C and flow rate of 1.7 mL/min. The retention times are as follows: 2,4-dichloro-6-methoxy-1,3,5-triazine: 2.5 min; 2-chloro-4,6-dimethoxy-1,3,5-triazine: 3.0 min; 2,4,6-trimethoxy-1,3,5-triazine: 3.4 min.
5. The endpoint of this reaction is defined as the time at which >97% conversion of the intermediate 2,4-dichloro-6-methoxy-1,3,5-triazine to CDMT has occurred. There is no residual cyanuric chloride.
6. The conversion of cyanuric chloride to 2,4-dichloro-6-methoxy-1,3,5-triazine is accompanied by an exotherm. This appears to start at around 20° C and facilitates the warm-up to 35° C.

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## NITRONIUM ION MEDIATED FUNCTIONALIZATION OF ADAMANTANE AND ITS DERIVATIVES

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Abstract : Functionalization of adamantane and its derivatives using claycop and nitronium trifluoromethanesulfonate is described.

Functionalization of saturated hydrocarbons<sup>1,a,b</sup> using a variety of reagents such as GoAgg,<sup>1,c</sup> nitronium salts<sup>1,d-f</sup> etc., is of current interest to organic chemists. Although clay supported reagents<sup>2</sup> have assumed a significant role in introducing various functional groups into the organic molecules, lately "claycop", (copper (II) nitrate impregnated on montmorillonite K-10), under Minke's conditions,<sup>3</sup> has extensively been used in functionalizing aromatic compounds.<sup>4</sup> However a study of the corresponding reaction with saturated hydrocarbons is yet to be explored. As a part of our continuing program on the synthesis and chemistry of polycyclic carbocycles,<sup>5</sup> we have undertaken a study of nitronium ion mediated reactions with adamantane<sup>6</sup> and its derivatives. In this report, we describe our results on functionalization of adamantane and diamantane with claycop and nitronium trifluoromethanesulfonate.<sup>7</sup>

**Results and Discussion:** The reaction of adamantane (1) and N-(1-acetamido) adamantane (2) with claycop in the presence of trifluoroacetic anhydride in carbon tetrachloride (or dichloromethane or nitromethane<sup>8</sup>) at room temperature

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