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Fluorous 2,4-Dichloro-1,3,5-triazine (F-DCT) as Amide Coupling Agent

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Keywords

Fluorous; 2,4-Dichloro-1,3,5-triazine; Amide coupling; Solid-phase extraction

Introduction

Substituted 1,3,5-triazines, such as 2-chloro-4,6-dimethoxy-1,3,5-triazine **1** (CDMT) [1], 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) **2** [2], polymer-supported 2,4-dichloro-1,3,5-triazine (PS-DCT) **3** [3], and fluorous CDMT **4** [4], represent an important class of coupling reagents for synthesis of amide bonds [5]. These reagents are derivatives of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) [6]. Three chlorines of cyanuric chloride have different reactivity. Selective displacement of chlorines with MeOH for example, is performed at 0 °C for the first chlorine, at room temperature for the second one, and at 100 °C for the third one [5]. Commercially available 1,3,5-triazine-based reagents usually employ only one reactive site for coupling reactions. The other two active sites are blocked by alkoxy groups or a fluorous tag. PS-DCT **3** has two chlorines, but only one is reported to be involved in the coupling reaction [3a]. We describe here a new fluorous 2,4-dichloro-1,3,5-triazine (F-DCT) **5** which has one fluorous chain and two active sites for amide coupling reactions.

A decade ago, fluorous technology was first introduced as a new phase-tagging strategy for biphasic catalysis [7]. The scope of fluorous chemistry has been well advanced since then and now it covers many aspects of organic synthesis [8]. A series of fluorous catalysts, reagents, scavengers, and protecting groups have been developed for solution-phase parallel and combinatorial synthesis of small molecules, peptides, and oligosaccharides [8b-d]. Recent development of “light fluorous” synthesis employs low fluorine content-tags such as single C₈F₁₇ chain. No fluorous solvents are used in reaction or separation processes [8d,9]. In addition to unique fluorous solid-phase extraction (F-SPE) [10], other conventional separation techniques such as precipitation and chromatography are still useable in fluorous synthesis. Separation of F-CDMT derivatives, for example, was accomplished by simple filtration of

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fluorous precipitates from amide coupling reaction mixtures with an appropriate organic solvent [4]. Based on the success of two fluorous-tagged CDMT **4** reported by Dembinski, we decided to develop F-DCT **5** as a new reagent which reduces the number of fluorous tag and increases active sites for amide coupling reactions.

Results

The preparation of **5** was accomplished by modifying literature procedures [11] using one equiv of 3-(perfluorooctyl)propanol, 1.05 equiv of cyanuric chloride, and 2,4,6-collidine as a base. The reaction was conducted in benzotrifluoride (BTF) at 25 °C for 10 h. After filtration to remove the salt, the concentrated crude product was crystallized from hexanes to give **5** in 60% as a white solid. Crude product can also be purified by flash column chromatography with normal silica gel. Compound **5** is slowly decomposed if it is not stored under nitrogen in a sealed bottle. Its purity can be easily determined by GC analysis.

Taking advantage of the fact that fluorous compounds can be easily analyzed by conventional analytical methods [12], we first conducted a model reaction using F-CDT **5** in deuteriated THF and monitored each reaction step by ¹H NMR analysis. It is noteworthy that THF is a good solvent for coupling reactions with chlorinated triazines. Other solvents such as CH₂Cl₂ may cause demethylation of *N*-methylmorpholine (NMM)-triazine complex [13]. At the first step, one equiv of **5** and two equiv of *p*-bromobenzoic acid was mixed in THF-*d*. Analysis of the mixture showed no reaction occurred at room temperature (Figure 1a). At the second step, 2.1 equiv of NMM was added and a small amount of white precipitate (presumably NMM-HCl salt) was generated immediately at room temperature. Chemical shift changes of aromatic protons indicated the formation of activated acid **6** (Figure 1b). The displacement of the first chlorine with acid increases the electrophilicity of the triazine and facilitates the displacement of the second chlorine [14]. At the third step, two equiv of *p*-methylbenzylamine was added, more white precipitate was formed. ¹H NMR analysis of the reaction mixture indicated the formation of targeted amide coupling product **7** (Figure 1c). The reaction mixture was then concentrated and subjected to F-SPE [15]. The product was collected in 80:20 MeOH-H₂O fraction, while F-DCT derivative was retained on the cartridge until wash with MeOH. Concentration of the MeOH-H₂O fraction gave amide product in 93% yield with good purity (Figure 1d).

To evaluate the scope of F-DCT **5** for amide coupling, we conducted 20 parallel reactions with an array of four amines and five carboxylic acids (Table 1). In addition to primary and secondary amines, an aniline was also included. The selection of carboxylic acids covers aromatic and aliphatic acids, sterically hindered acids and acids with additional functional groups. The plate of twenty reaction vials each containing 0.12 mmol of acids, 0.13 mmol of NMM, and 0.06 mmol of F-DCT were shaken at room temperature for 20 min, then 0.1 mmol of amines were added to each vial and vials were shaken at room temperature for 2 h. After the reactions were over, 0.6 mmole of macroporous polystyrene anion-exchange resin MP-CO₃ was added to each vial to free the basic product from the salt. The resin beads were then filtered off and washed with MeOH. The filtrates were collected in a 4x6 well plate and concentrated in Speedvac. The residues were dissolved in 0.5 mL of DMF and loaded onto a 4x6 SPE plate equipped with 3 g-FluoroFlash cartridges for plate-to-plate SPE [16]. Each cartridge on the plate was eluted with 6 mL of 80:20 MeOH/H₂O and the products were collected in a 4x6 receiving plate. The plate containing the products was concentrated in Speedvac to afford twenty amide coupling products. Results in Table 1 show nineteen reactions had yields between 45-89%. The product generated from *N*-methylcyclohexylamine and hindered amino acid Cbz-Aib only gave 6% yield. However, the purity of this product was still good (93%). Seventeen out of twenty products had greater than 90% purities after the plate-to-plate SPE.

In summary, F-DCT has been developed as a coupling reagent for formation of two equiv of amides. The reaction mixtures generated from parallel synthesis are purified by plate-to-plate F-SPE. The application of F-DCT as a nucleophile scavenger to remove amines or thiols is reported in another paper in this issue [17].

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(a) mixture of 1.0 equiv of 5 and 2.0 equiv of *p*-bromobenzoic acid in THF-*d*₆; (b) added NMM, form activated acid 6; (c) added amine, form amide 7; (d) F-SPE purified product 7.

Figure 1.
Monitoring the coupling reaction progress by ¹H NMR analysis

Scheme 1.
Synthesis of F-DCT **5**

Table 1

Amide coupling with F-DCT 5

58% (98%)*	48% (95%)	45% (83%)	50% (95%)	56% (96%)	74% (76%)	62% (99%)	79% (91%)	79% (94%)	89% (91%)	75% (98%)

* yield% (purity%), purities were determined by LCMS with UV210 detection