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A Convenient Large Scale Synthesis of N, N'-Disuccinimidyl Carbonate

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A CONVENIENT LARGE SCALE SYNTHESIS OF N, N'-DISUCCINIMIDYL CARBONATE

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Abstract: An improved method for the large scale preparation of N, N'-disuccinimidyl carbonate from triphosgene and N-hydroxysuccinimide has been developed.

Esters of N-hydroxysuccinimide have been used widely for many years for the activation of carboxylic acids. Condensation reactions of esters of N-hydroxysuccinimide with nucleophiles such as amines are known to proceed under mild conditions and can be used to modify proteins under aqueous conditions. A preferred method of preparation of such activated esters (Figure 1, **3**) is by the reaction of a molar equivalent of a carboxylic acid (**1**), N, N'-disuccinimidyl carbonate (**2**, DSC), and a

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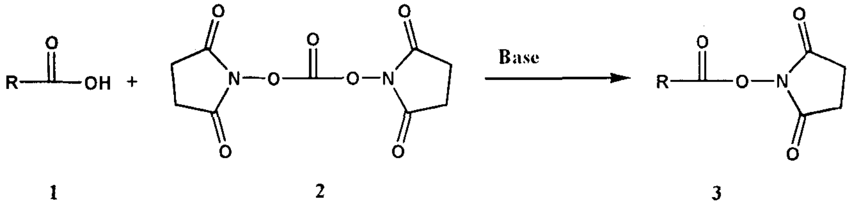
base such as triethylamine or pyridine in acetonitrile at room temperature. Under these conditions yields of activated esters (**3**) ranging from 80% to nearly 100% may be obtained. Such a method of preparation of activated esters is preferred because the reaction is convenient and proceeds at room temperature; the reaction is marked by the evolution of carbon dioxide gas and is complete when gas evolution ceases; and esters sensitive to rearrangement or degradation may be obtained in high yield without detectable degradation.

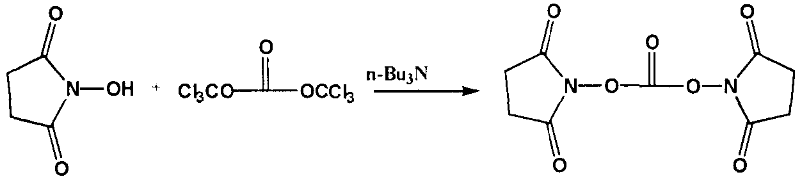
Figure 1.



In the course of our work on the crosslinking and modification of proteins, in particular hemoglobin, with a variety of novel reagents, we needed kilogram quantities of DSC. A search of the literature revealed that DSC could be prepared by any one of five methods[1-6]. These methods have the following features in common. All require the use of phosgene or phosgene-equivalents [e.g., alkyl or aryl chloroformates; bis(trichloromethyl)carbonate]. All are multistep processes requiring purification of DSC by recrystallization. The yields of the above methods range from 50-94 %. Although the yields of DSC by several of the methods are quite good, all of the methods had drawbacks for the preparation of DSC on a large scale.

During our study of the synthesis of DSC from N-hydroxysuccinimide (**4**), bis(trichloromethyl)carbonate (triphosgene) (**5**), and triethylamine in a variety of solvents, we observed that in THF, a precipitate was formed. Analysis of the precipitate by ^{1}H-NMR showed that the precipitate was a mixture primarily of DSC, N-hydroxysuccinimide and triethylamine hydrochloride. We reasoned that if we used a base that had a corresponding hydrochloride salt soluble in THF, a high yield of DSC could be obtained. We found that the substitution of tri-*n*-butylamine for triethylamine provided DSC as a precipitate that was free of tri-*n*-butylamine hydrochloride and contained only a trace of N-hydroxysuccinimide. More importantly, these reaction conditions provided DSC that does not require recrystallization. Using this methodology we have produced almost 800 g of DSC in an 89% yield.

Figure 2.



4 5 2

Experimental:

N, N′-Disuccinimidyl carbonate (**2**). The reaction was carried out in an inert (nitrogen) atmosphere. N-Hydroxysuccinimide (805.0 g, 7 mol) and triphosgene (417.0 g, 1.4 mol) were dissolved in 6 L of THF, and the resulting solution was cooled in an ice bath. A solution of tri-*n*-butylamine (1567.6 g, 8.43 mol) in 2 L of THF was added dropwise at a rate such that the reaction temperature was maintained in the range 0-5 °C. A precipitate formed. After the addition was complete, the solution was allowed to stir at room temperature for 12-16 hours. The resulting slurry was cooled in an ice bath for 30 minutes, and then the solid was collected by filtration. The filter cake was washed with two, 500-mL portions of cold THF. The solid was dried under vacuum. A yield of 796.5 g of DSC (89% of theoretical) was obtained. DSC had a melting point of 218-220°C (uncorrected). The NMR spectrum of the product showed that it had excellent purity with a trace of N-hydrosuccinimide.

^{1}H-NMR (DMSO-d_6): 2.85 (s, 8-H) ppm; trace of N-hydroxy-succinimide at 2.58 ppm.

^{13}C-NMR (DMSO-d_6): 25.5; 149.5; 169.2 ppm; trace of N-hydroxy-succinimide at 25.3, 172.5 ppm.

Anal. Calcd. for $C_9H_8N_2O_7$: C, 42.20%; H, 3.15%; N, 10.94%. Found: C, 41.88%; H, 3.16%; N, 10.81%.

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