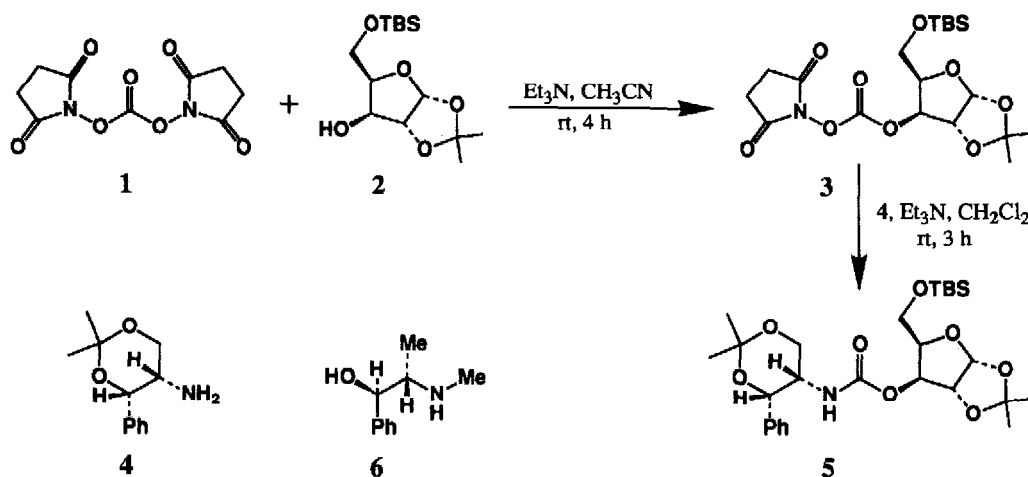


N,N'-Disuccinimidyl Carbonate: A Useful Reagent for Alkoxy-carbonylation of Amines

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Summary: An efficient and mild method for alkoxy-carbonylation of amines is described, utilizing commercially available N,N'-disuccinimidyl carbonate.

The development of mild and efficient methods for alkoxy-carbonylation of amines is of considerable interest in Medicinal Chemistry.¹ Consequently, a number of reagents and synthetic procedures were introduced in the literature² over the past several years. Recently, we have described di(2-pyridyl) carbonate promoted synthesis of variously protected carbamates.³ Continuing our interest in search of other convenient reagents and in view of the synthesis of biologically active polyfunctional molecules for probing enzyme active-sites, we have investigated the scope of N,N'-disuccinimidyl carbonate promoted alkoxy-carbonylation of amines with a host of alcohols. N,N'-Disuccinimidyl carbonate has been recognized as a versatile reagent for active ester synthesis.⁴ However, the reaction of N,N'-disuccinimidyl carbonate and alcohols to form mixed active carbonates and their subsequent utility in the synthesis of functionalized carbamates, is hitherto unknown. In this letter, we report an efficient and more convenient procedure for the synthesis of various carbamate derivatives using commercially available N,N'-disuccinimidyl carbonate (DSC).⁵



Scheme 1

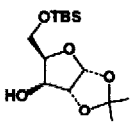
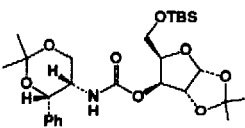
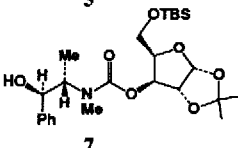
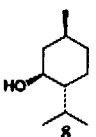
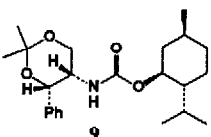
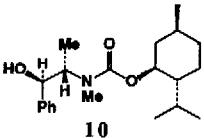
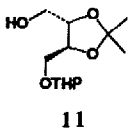
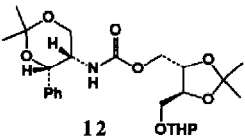
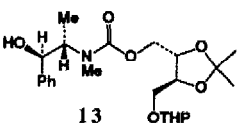
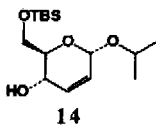
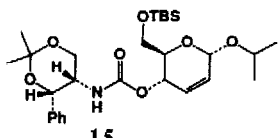
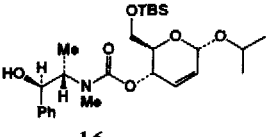
The readily available 1,2-O-isopropylidene-D-xylofuranose was selectively protected⁶ as the t-butyldimethylsilyl ether **2** by treatment with t-butyldimethylsilyl chloride (1.1 equiv) in pyridine at 23°C for 10 h (90% yield). Reaction of protected xylofuranose **2** with DSC (1.5 equiv) in the presence of triethylamine (3 equiv) in dry acetonitrile at 23°C for 4 h furnished the mixed succinimide carbonate **3** after standard workup with aqueous sodium bicarbonate solution. The structure of **3** was typically identified by ¹H-NMR spectrum and mass spectral analysis. Among various solvents examined, the formation of mixed carbonate was found to be rapid and proceeded smoothly in acetonitrile. For example, the above reaction at room temperature in acetonitrile was complete within 4 h, whereas in methylene chloride it took about 12 h for completion. Of particular note, the carbonate **3** is quite stable and can be chromatographed⁷ and stored in the refrigerator for several months. As expected, reaction of mixed carbonate **3** with a slight excess of amine **4** (1.2 equiv) in the presence of triethylamine (2 equiv) in methylene chloride provided the carbamate derivative **5** in very good yield (86%) after flash chromatography over silica gel. Similarly, exposure of mixed carbonate **3** to L-ephedrine **6** in methylene chloride resulted in carbamate **7** in 83% isolated yield. Interestingly, the ¹H-NMR spectrum of carbamate **5** (CDCl₃ or DMSO-d₆) revealed the presence of a 4:1 mixture of rotational isomers at 23°C. When the temperature was raised, the rotation about the N-C bond became appreciable and at coalescence temperature (T_c, ca. 70°C in DMSO-d₆), the mixture of peaks merged into one sharp spectrum.

This alkoxyacylation procedure was employed to a series of four different types of alcohols⁸ and the results are summarized in Table I. As is evident, this procedure allows convenient access to the synthesis of a variety of structurally diverse carbamates derived from primary and hindered secondary alcohols (yield 65-89%). In the case of hindered tertiary alcohols, such as 2-methyl-2-adamantanol, the formation of mixed carbonate with DSC under a variety of reaction conditions was unsuccessful. Further studies are currently in progress to extend the application for tertiary alcohols.

In summary, commercially available N,N'-disuccinimidyl carbonate has been found to be a highly effective alkoxyacylating reagent for a variety of primary and sterically hindered secondary alcohols. The present methodology is advantageous because of the ready availability of DSC, stability of the mixed carbonates, and the mildness of the reaction procedure. The following example is representative of this procedure.⁹

Preparation of Carbamate 5 : To a stirred solution of alcohol **2** (1.0 mmol, 0.31 g) in dry CH₃CN (5 ml) at 23°C were added DSC (1.5 mmol, 0.38 g) and Et₃N (3 mmol, 0.42 ml). The resulting mixture was stirred at 23°C until no starting alcohol remained by TLC (4 h). The mixture was concentrated under reduced pressure and the residue was diluted with aqueous NaHCO₃ solution (10 ml) and extracted thoroughly with EtOAc (2 x 25 ml). The combined extracts were washed with brine (10 ml) and dried over Na₂SO₄. Evaporation of the solvent provided the mixed carbonate **3** which was used directly for the next reaction. IR (neat); 1810, 1750 cm⁻¹; ¹H NMR (CDCl₃) δ 5.9 (d, 1H, J=3.5 Hz), 5.12 (d, 1H, J=2.5 Hz), 4.6 (d, 1H, J=3.5 Hz), 4.4 (m, 1H), 3.8 (m, 2H), 2.8 (s, 4H), 1.5 (s, 3H), 1.3 (s, 3H), 0.9 (s, 9H), 0.05 (s, 6H); MS; 446 (m⁺+H).

Table I : Synthesis of carbamates with DSC^a

Entry	Alcohols	Amines	Carbamates	Yields(%) ^b
1.	 2	4	 5	86
2.	2	6	 7	83
3.	 8	4	 9	77
4.	8	6	 10	65
5.	 11	4	 12	89
6.	11	6	 13	78
7.	 14	4	 15	72
8.	14	6	 16	75

a All reactions were carried out under N₂

b Yield of pure products after silica gel chromatography (0.5-2 mmol scale)

Above mixed carbonate was dissolved in CH_2Cl_2 (2 ml) and added to a stirred solution of amine **4** (1.2 mmol, 0.25 g) containing triethylamine (1.5 mmol, 0.2 ml) in CH_2Cl_2 (5 ml). The resulting mixture was stirred at 23°C until no mixed carbonate remained by TLC (3 h). The mixture was then diluted with CH_2Cl_2 (20 ml) and washed successively with aqueous NaHCO_3 solution (10 ml), brine (10 ml) and dried over Na_2SO_4 . Removal of the solvent, followed by chromatography over silica gel (25% EtOAc-hexanes) afforded the carbamate **5** (462 mg, 86% yield) as a yellow oil. IR (neat); 1740 cm^{-1} ; ^1H NMR (DMSO-d_6 , 70°C) δ 7.2 (m, 5H), 5.8 (br s, 1H), 5.2 (s, 1H), 4.6 (s, 1H), 4.5 (br s, 1H), 4.3 (d, 1H, $J=12$ Hz), 4.1 (m, 2H), 3.5-3.8 (m, 4H), 1.5 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.23 (s, 3H), 0.9 (s, 9H), 0.1 (s, 3H), 0.05 (s, 3H); MS; 538 ($m^+ + \text{H}$).

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- N,N'-Disuccinimidyl carbonate was obtained from Aldrich Chemical Company, Inc., Milwaukee. DSC was also prepared conveniently from N-hydroxysuccinimide (6 equiv) and triphosgene (1 equiv) in CH_3CN in the presence of triethylamine (71%, m.p 178°C); for isolation and recrystallization, see ref 3 (DPC procedure).
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- Crude mixed carbonates obtained after standard workup were used for the reaction with amines.
- Alcohol **11** was obtained by reaction of (-)-2,3-O-isopropylidene-D-threitol (1 equiv) and dihydropyran (1 equiv) in dry methylene chloride in the presence of pyridinium p-toluenesulfonate (65%); for preparation of alcohol **14**, see ref 3.
- All new compounds gave satisfactory spectroscopic and analytical results.