



Published in final edited form as:

Tetrahedron Lett. 1991 ; 32(34): 4251–4254. doi:10.1016/S0040-4039(00)92141-5.

Di(2-Pyridyl) Carbonate Promoted Alkoxy carbonylation of Amines: A Convenient Synthesis of Functionalized Carbamates

Arun K. Ghosh, Tien T. Duong, and Sean P. McKee

Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Summary:

The reaction of di(2-pyridyl) carbonate with a variety of alcohols including hindered secondary, tertiary and protected glycols afforded the corresponding mixed carbonate which was efficiently transformed into various carbamates in high yield under mild conditions.

The alkoxy carbonylation of amines is an important reaction which is used frequently in the synthesis of pharmacologically important organic molecules. In recent years, several alkoxy carbonylation methods have appeared in the literature. However, the scope of existing methodologies are limited by the need for specialized reagents, poor reactivity towards sterically hindered alcohols and operational complexity due to use of highly toxic phosgene. In connection with work aimed at synthesizing biologically active compounds for probing enzyme active-sites, we required a general and synthetically reliable method for the synthesis of various carbamate derivatives. In this letter, we describe the utility of di(2-pyridyl) carbonate as an efficient, high-yielding and convenient alkoxy carbonylation reagent for amines that overcomes many of the limitations of existing methodologies.

Di(2-pyridyl) carbonate (DPC) **1** was readily prepared from commercially available 2-hydroxypyridine and triphosgene in methylene chloride in the presence of triethylamine. The product was isolated by extractive workup with aqueous sodium bicarbonate followed by the crystallization of the crude residue from ether and petroleum ether (mp=78°C, 81%). DPC is quite stable and can be stored at room temperature for several months without any noticeable decomposition.

(+)-Menthol **2** was reacted with 1.5 equiv. of DPC and 1.5 equiv. of triethylamine in methylene chloride at 23°C for 12 h to provide the mixed carbonate **3** after work-up with aqueous sodium bicarbonate solution. The carbonate **3** was fairly stable and was purified by silica gel chromatography to obtain analytically pure **3**. The identity of structure **3** was confirmed by ¹H-NMR spectrum and mass spectral analysis. Reaction of mixed carbonate **3** with 1.2 equiv. of protected riboseamine **4** in methylene chloride afforded the corresponding pure carbamate **6** after silica gel chromatography (81%). Furthermore, reaction of carbonate **3** with 1.2 equiv. of amine **5** under the same reaction conditions resulted in carbamate **7** (70%).

As evidenced in table I, these reaction conditions were shown to be suitable for functionally diverse primary and secondary alcohols (entry 1-8). In the case of entry 9 and 10, the

reaction of tertiary alcohol **17** with DPC in the presence of various amine bases afforded only a low yield (<10%) of the desired mixed carbonate. However, treatment of **17** with potassium hydride (1.5 equivalents at 0°C to 23°C for 1 h) and DPC (1.5 equivalents at 23°C for 4 h) in dry tetrahydrofuran, followed by workup with saturated ammonium chloride furnished the corresponding mixed carbonate. Reaction of the amines **4** and **5** (1.2 equivalents) with the mixed carbonate of **17** in methylene chloride provided the corresponding carbamates **18** and **19** in good yield.

In conclusion, the results presented in this paper considerably extend the scope and utility of di(2-pyridyl) carbonate in the synthesis of a variety of functionalized carbamates. Application of this methodology in the synthesis of various biologically active carbamates is currently under investigation. The following procedures are illustrative.

Preparation of Di(2-pyridyl) carbonate 1:

To a stirred solution of triphosgene (10 mmol, 3 g) and 2-hydroxypyridine (60 mmol, 5.7 g) in CH₂Cl₂ (500 ml) at 0°C was added Et₃N (75 mmol, 10.5 ml) dropwise over 15 min. The mixture was stirred at 23°C for 5 h and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (500 ml), washed with sat'd NaHCO₃ (300 ml), brine (200 ml) and dried over Na₂SO₄. Removal of the solvent and subsequent recrystallization of the residue from ether and petroleum ether afforded di(2-pyridyl) carbonate (5.2 g, 81% yield) as a white solid: mp 76–78°C.

Preparation of Carbamate 6 (method A):

To a stirred solution of (+)-menthol **2** (1.0 mmol, 0.16 g) in CH₂Cl₂ (5 ml) at 23°C were added DPC (1.5 mmol, 0.32 g) and Et₃N (1.5 mmol, 0.2 ml). The contents were stirred for 12 h and then diluted with CH₂Cl₂ (25 ml). The mixture was washed with sat'd NaHCO₃ (10 ml), brine (10 ml) and dried over Na₂SO₄. The solvent was evaporated and the residue was used directly for the next reaction.

The residue was dissolved in CH₂Cl₂ (2 ml) and added to a stirred solution of amine **4** (1.2 mmol, 0.24 g) in CH₂Cl₂ (5 ml). The mixture was stirred for 12 h and then diluted with CH₂Cl₂ (20 ml). The resulting mixture was washed with 10% aqueous citric acid (10 ml), sat'd NaHCO₃ (10 ml) and dried over Na₂SO₄. Removal of the solvent, followed by chromatography over silica gel (25% EtOAc-hexanes) afforded carbamate **6** (0.28 g, 81%) as a white solid: mp 68–70°C; IR (neat) 1702 cm⁻¹; ¹H NMR (CDCl₃) δ 5.2 (br s, 1H), 5.0 (s, 1H), 4.6 (m, 3H), 4.3 (t, 1H, J=6.1 Hz), 3.35 (s, 3H), 3.31 (m, 2H), 1.85–2.1 (m, 2H), 1.0–1.7 (m, 7H), 1.48 (s, 3H), 1.32 (s, 3H), 0.9 (d, 6H, J=7.0 Hz), 0.82 (d, 3H, J=6.9 Hz).

Preparation of Carbamate 19 (method B):

To a stirred suspension KH (1.2 mmol, 0.05 g, pre-washed) in THF (2 ml) at 0°C was added a solution of alcohol **17** (0.83 mmol, 0.11 g) in THF (2 ml) dropwise over 5 min. The mixture was stirred (0°C to 23°C) for 1 h and DPC (1.2 mmol, 0.27 g) was added. The mixture was stirred for 4 h and the reaction was cautiously quenched with sat'd NH₄Cl solution. The solvent was removed under reduced pressure, and the residue was diluted with

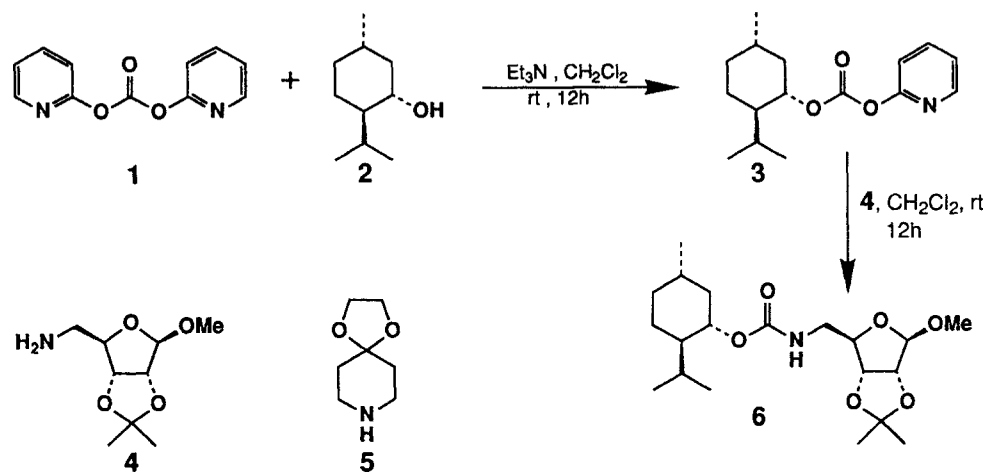
sat'd NaHCO₃ (5 ml) and extracted with EtOAc (2×10 ml). The combined extracts were dried over Na₂SO₄ and concentrated. The residue was then dissolved in CH₂Cl₂ (2 ml) and added to a stirred solution of amine **5** (1.0 mmol, 0.14 g) in CH₂Cl₂ (3 ml). After stirring for 12 h (23°C), the reaction mixture was worked-up and purified according to above procedure to afford **19** (0.17 g, 68%) as a white solid: mp 76–78°C; IR (neat) 1695 cm⁻¹; ¹H NMR (CDCl₃) δ 3.98 (s, 4H), 3.52 (t, 4H, J=5.8 Hz), 2.85 (m, 2H), 2.35–2.61 (m, 4H), 1.7 (m, 6H), 1.51 (s, 3H).

Acknowledgement:

The authors thank Dr. Wayne J. Thompson for helpful discussions and acknowledge the encouragement and support of Dr. Joel R. Huff and Dr. Paul S. Anderson.

References and Notes:

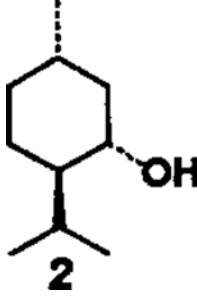
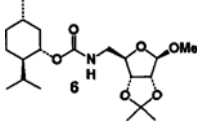
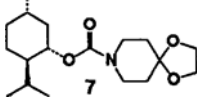
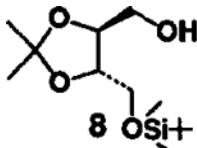
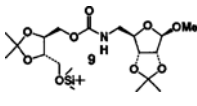
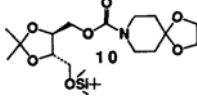
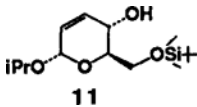
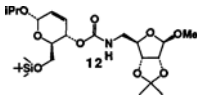
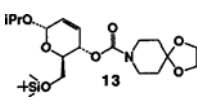
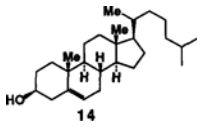
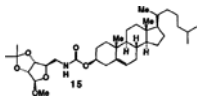
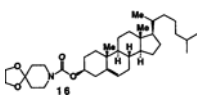
1. (a)Matassa VG, Maduskuie TP, Shapiro HS, Hesp B, Snyder DW, Aharony D, Krell RD and Keith RA; J. Med. Chem, 1990,33, 1781; [PubMed: 2342072] (b)Firestone RA, Pisano JM, Falck JR, McPhaul MM and Krieger M; J. Med. Chem, 1984,22,1037.
2. (a)Eckert H and Forster B; Anaew Chem Int Ed, 1987, 26, 894;(b)Denarie M, Grenouillat D, Malfroot T, Senet J-P, Sennyey G and Wolf P; Tetrahedron Letters, 1987, 28,5823;(c)Pedersen U; Weyl Houben, Methoden der Organischen Chemie 1983, E4, 144;(d)Takeda K, Tsuboyama K, Yamaguchi K, Ogura H; j. Org. Chem, 1985,50, 273;(e)Shute RE and Rich DH; synthesis, 1987, 346.
3. Kim S, Lee JI and Ko YK; Tetrahedron Letters, 1984, 25, 4943.
4. This reagent has been known in the literature by a variety of names:(a)O,O'-Carbonylbis(α-hydroxypyridine); Cramer F, CA 64:6625d;(b)O,O'-Carbonyldihydroxypyridine; Kampe W, Angew Chem,1963, 75(13), 641;(c)Di(2-pyridyl) carbonate; Kampe W, Chem. Ber,1965, 98(4) 1031.
5. (a)Levene PA and Stiller ET; J. Biol. Chem, 1934, 106, 421;(b)Leonard NJ and Carraway KL; J Het. Chem, 1966,3,485.
- 6 (a). Alcohol **11** was prepared by Ferrier rearrangement (ref. 8) of tri-O-acetyl-D-glucal with isopropanol, hydrolysis of the resulting acetates with aqueous methanol and triethylamine, followed by selective protection of primary alcohol as TBDMS ether (63%, overall yield):for alcohol **8**, see: lida H, Yamazaki N and Kibayashi C; J. Org. Chem, 1987,52, 3337.;
7. Alcohol **17** was obtained by reaction of methylmagnesium bromide and tetrahydrothiopyran-4 one in dry tetrahydrofuran at 23°C for 12h (51% isolated yield).
8. Ferrier RJ and Prasad NJ; J. Chem. Sot. (C), 1969,570.
9. Mixed carbonate often undergoes rearrangement to the corresponding alkoxy carbonyl 2-pyridone derivative (5-10%), which imposes no complication to subsequent reaction.
10. All new compounds gave satisfactory spectroscopic and analytical results.

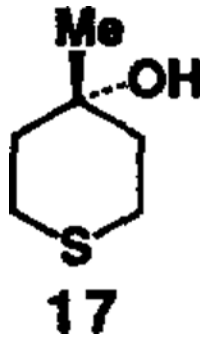
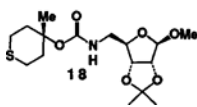
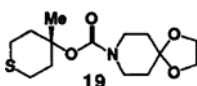


Scheme 1.

Table I:

Synthesis of carbamates with DPC^a

Entry	Alcohols	Amines	Carbamates	Method	Yields(%) ^b
1.		4		A	81
2.	2	5		A	70
3.		4		A	79
4.	8	5		A	87
5.		4		A	77
6.	11	5		A	83
7.		4		A	81
8.	14	5		A	83

Entry	Alcohols	Amines	Carbamates	Method	Yields(%) ^b
9.	 17	4	 18	B	72
10.	17	5	 19	B	68

^aAll reactions were carried out under N₂

^bYield of pure products after silica gel chromatography (0.5–4.0 mmol scale)