

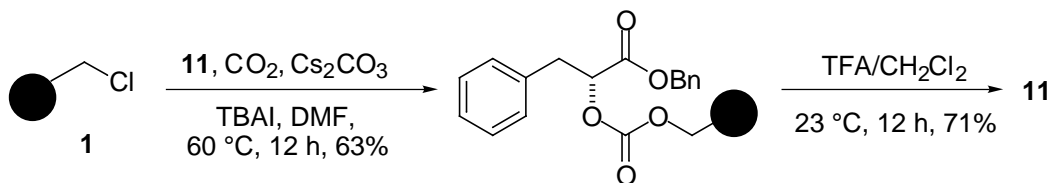
Cs₂CO₃ Promoted Efficient Carbonate and Carbamate Synthesis on Solid Phase

Ralph N. Salvatore, Vincent L. Flanders, Dang Ha, and Kyung Woon Jung*

Department of Chemistry (SCA 400), University of South Florida and Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute 4202 E. Fowler Avenue, Tampa, Florida 33620-5250

kjung@chuma.cas.usf.edu

Supporting Information



Preparation of carbonate bound resin of 11: (*S*)-Benzyl 2-hydroxy-3-phenylpropionate (1.54 g, 6 mmol, 3 eq) was dissolved in anhydrous *N,N*-dimethylformamide (20 mL) to make a clear solution. Into the solution, were consecutively added cesium carbonate (1.95 g, 6 mmol, 3 eq.) and tetrabutylammonium iodide (2.22 g, 6 mmol, 3 eq.). The suspension was stirred at room temperature while passing carbon dioxide gas through for 1 hour before Merrifield's peptide resin (1 g, 2 mmol) was added to the solution. Carbon dioxide gas was continuously bubbled through the solution and the reaction was allowed to proceed overnight at 60 °C. The mixture was then cooled to room temperature, and diluted with water. The resin was washed successively with MeOH/H₂O, H₂O, 0.2 *N* HCl, H₂O, THF, CH₂Cl₂, and MeOH. After drying *in vacuo* for 24 hours, 1.33 g of resin bound carbonate of **11** was obtained (63% yield): **IR** (KBr pellet) 3071, 3035, 2921, 2846, 1943, 1874, 1611, 1495, 1462, 1394, 1253, 1172, 1036, 765, 700 cm⁻¹.

The loading and yield for the carbonate resin of **11** was determined by gravimetric analysis as follows. (See the Supporting Information: Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998.) The basic assumptions are: (1) that the change in the mass of the resin corresponds to the mass of the

carbonate loaded minus the mass of the Cl⁻ displaced, and (2) that the number of moles of carbonate loaded equals the number of moles of Cl⁻ displaced.

Loading:

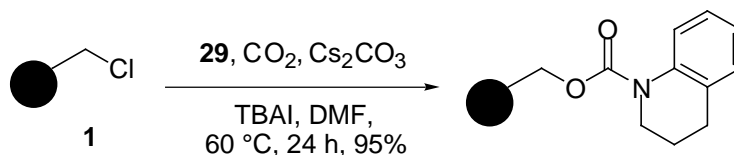
$$\begin{aligned} 1.33 \text{ g of carbonate bound resin of } \mathbf{11} - 1.0 \text{ g Merrifield's resin} &= 0.33 \text{ g mass loaded} \\ 0.33 \text{ g} &= (255.3 + 44) (\text{mol of carbonate added}) - (35.45 \text{ g/mol})(\text{mol Cl}^-) \\ &\text{assuming that mol carbonate loaded} = \text{mol Cl}^- \text{ displaced.} \\ 0.33 \text{ g} &= 299.3 (x) - (35.45 \text{ g/mol})(x) \\ 0.33 \text{ g} &= 263.85 (x) \\ 1.25 \text{ mmol} &= x \\ 1.25 \text{ mmol of carbonate loaded/1.0 g resin} &= 1.25 \text{ mmol/g} \end{aligned}$$

The yield of the reaction is calculated from the loading of the starting material (Merrifield's resin) and the moles of carbonate loaded; thus, the yield is 63% in this example.

Yield:

$$(1.25 \text{ mmol loaded} / 2 \text{ mmol}) \times 100 = 63\%$$

The resulting resin bound benzyl 3-phenylpropionate carbonate of **11** was converted back to the starting alcohol **11** (1.5 g; 70%) by hydrolytic cleavage using TFA/CH₂Cl₂ (75:25, v/v) after stirring at room temperature for 12 hours (see: Ho, C. Y.; Kukla, M. J. *Tetrahedron Lett.* **1997**, 38, 299). The product was spectroscopically (¹H NMR) compared with the authentic sample and the optical rotation was taken and compared with the starting material, as well as with the reported value. The observed value was -53° (c=2, CH₂Cl₂) whereas the reported value is -55° (c=1.8, CH₂Cl₂), respectively.



Preparation of carbamate bound resin of 29: 1,2,3,4-Tetrahydroquinoline (0.67 g, 5 mmol, 2.5 eq.) was dissolved in *N,N*-dimethylformamide (40 mL). Cesium carbonate (2.44 g, 7.5 mmol, 3.75 eq.) and tetrabutylammonium iodide (2.77 g, 7.5 mmol, 3.75 eq.) were added to the solution under vigorous stirring. The temperature of reaction was then raised to 60 °C, after which carbon dioxide was allowed to pass into the stirred suspension at the same temperature for 10 hours. Merrifield's resin (1 g, 2 mmol, 1 eq.) was added and the reaction was continually stirred at 60 °C for 12 hours with constant carbon dioxide bubbling. The reaction mass was then cooled to room temperature and filtered through a coarse fritted filter disc. The resin was subsequently washed with 20 mL aliquots of water, methanol/water (1:1 v/v), water, tetrahydrofuran, dichloromethane and methanol in the given order and then dried *in vacuo* for 24

hours to yield the desired carbamate bound resin of **29** (1.27 g, 95%) as a solid. Data for carbamate bound resin of **29**: IR (KBr pellet) 3440, 3075, 3045, 2920, 2850, 1900, 1875, 1740, 1695, 1590, 1560, 1505, 1450, 1395, 1320, 1250, 1220, 1170, 1115, 1010, 950, 905, 830, 820, 740, 695, 530 cm⁻¹.

Loading:

$$1.27 \text{ g of carbamate bound resin of } \mathbf{29} - 1.0 \text{ g Merrifield's resin} = 0.27 \text{ g mass loaded}$$

$$0.27 \text{ g} = (132.19 + 44) (\text{mol of carbamate added}) - (35.45 \text{ g/mol})(\text{mol Cl}^-)$$

assuming that mol carbamate loaded = mol Cl⁻ displaced.

$$0.27 \text{ g} = 176.19 (x) - (35.45 \text{ g/mol})(x)$$

$$0.27 \text{ g} = 140.74 (x)$$

$$1.9 \text{ mmol} = x$$

$$1.9 \text{ mmol of carbamate loaded}/1.0 \text{ g resin} = 1.9 \text{ mmol/g}$$

The yield of the reaction is calculated from the loading of the starting material (Merrifield's resin) and the moles of carbamate loaded; thus, the yield is 95% in this example.

Yield:

$$(1.9 \text{ mmol loaded}/ 2 \text{ mmol}) \times 100 = 95\%$$