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Cs_2CO_3-Promoted Efficient Carbonate and Carbamate Synthesis on Solid Phase

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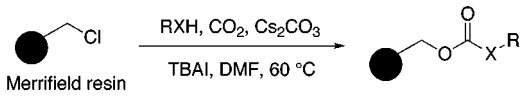
ABSTRACT



Mild and efficient preparation of alkyl carbonates and carbamates on solid supports is described herein. Alcohols or amines were coupled with Merrifield's resin through a CO_2 linker in the presence of cesium carbonate and tetrabutylammonium iodide (TBAI).

Organic reactions on solid phases have played an important role in combinatorial and medicinal chemistry.[1] Preparation of small molecule libraries on polymer supports has emerged as a powerful method for the development of new lead compounds in the field of drug discovery.[2] The synthetic targets include peptidomimetics,[3] oligonucleotides,[4] and oligosaccharides.[5] Because of new interesting structural features, artificial biomolecules containing new scaffoldings have become popular synthetic targets. In this Letter, we describe an efficient and practical solid-phase synthesis of carbonates and carbamates that can be utilized as a framework in further syntheses.[6]

The carbonate and carbamate linkers are usually prepared by utilizing haloformates or carbonate exchange.[7] These methods are often costly, and the employed reagents are toxic; therefore, alternative approaches are in demand.

Recently, we reported a highly efficient cesium base-promoted solution-phase synthesis of alkyl carbonates that

(1) (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Fruchtel, J. S.; Jung, G. *Angew. Chem.* **1996**, *108*, 19. (d) Balkenhohl, F. O.; Bussche-Hunnefeld, C. v. d.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2437. (e) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643. (f) Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry*; Wiley-Interscience: New York, 1997, and references therein.

(2) (a) See refs 1a and 1b. (b) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144. (c) Patel, D. V.; Gordon, E. M. *Drug Discovery Today* **1996**, *1*, 134.

(3) For reviews on solid-phase peptide synthesis and its derivatives, see: (a) Atherton, E.; Sheppard, R. C. *Solid-phase peptide synthesis; a practical approach*; IRL Press: Oxford, 1989. (b) Stewart, J. M.; Young, J. D. *Solid-Phase Peptide Synthesis*, 2nd ed.; Pierce Chemical Co.: Rockford, IL, 1984. (c) Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367. (d) Pavia, M. R.; Sawyer, T. K.; Moos, W. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 387. (e) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Foder, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233.

(4) For reviews on solid-phase oligonucleotide synthesis, see: (a) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223. (b) Montserrat, F. X.; Eritja, A. G.; Pedroso, E. *Tetrahedron* **1994**, *50*, 2617.

(5) For recent reviews on oligosaccharides, see: (a) Frechet, J. M.; Schuerch, C. *Carbohydr. Res.* **1972**, *22*, 399. (b) St. Hilaire, P. M.; Meldal, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1162. (c) Osborn, H. M. I.; Khan, T. H. *Tetrahedron* **1999**, *4*, 481. (d) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (e) Sofia, M. J. In *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Jr., Eds.; Wiley-Liss; New York, 1998; pp 243−269.

(6) For carbonate scaffoldings, see: (a) Mertes, M. P.; Coats, E. A. *J. Med. Chem.* **1969**, *12*, 154. (b) Jones, D. S.; Tittensor, J. R. *Chem. Commun.* **1969**, 1240. (c) Tittensor, J. R. *J. Chem Soc.* **1971**, 2656. For carbamate scaffoldings, see: (d) Cho, C. Y.; Moran, E. J.; Chery, S. R.; Stevens, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303. (e) Paikoff, S. J.; Wilson, T. E.; Cho, C. Y.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5653.

(7) For a recent review on linkers for solid-phase organic synthesis, see: (a) James, I. W. *Tetrahedron* **1999**, *55*, 4855. For selective examples, see: (b) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922. (c) Greenburg, M. M.; Matray, T. J.; Kahl, J. D.; Yoo, D. J.; McMinn, D. L. *J. Org. Chem.* **1998**, *63*, 4062. (d) Alsina, J.; Rabanal, F.; Chiva, C.; Giralt, E.; Albericio, F. *Tetrahedron* **1998**, *54*, 10125. (e) Veerman, J. J. N.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 6079. (f) Raju, B.; Kogan, T. P. *Tetrahedron Lett.* **1997**, *38*, 3373.

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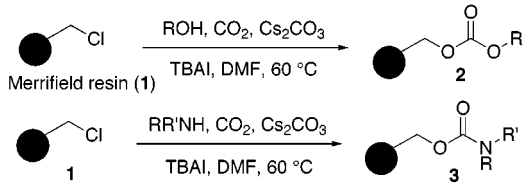
utilized nontoxic reagents under mild conditions.[8] As a complementary approach, this protocol has been extended to solid-phase synthesis of both carbonates and carbamates, which is the theme of the current report.

In the presence of cesium carbonate and tetrabutylammonium iodide (TBAI), various alcohols and amines were ligated to Merrifield resin **1** via a CO_2 bridge to exclusively produce carbonates **2** and carbamates **3**, respectively (Scheme 1). Carbon dioxide was supplied by bubbling it into the

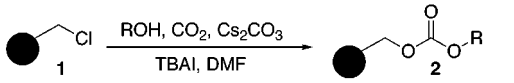
Scheme 1

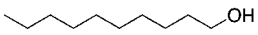
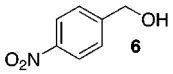


reaction suspension, where *N*,*N*-dimethylformamide was the choice of solvent. In our solution-phase carbonylations and carbamations, the desired conversions were achieved at ambient temperatures, whereas the solid-phase syntheses required elevated reaction temperatures, still allowing for clean transformations.

In a comparative study (Table 1), 1-decanol (entry 1), benzyl alcohol (entry 3), and *p*-nitrobenzyl alcohol (entry

Table 1. Conditions for Solid-Phase Synthesis of Carbonates at Various Temperatures

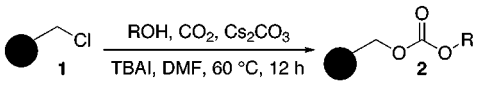


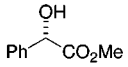
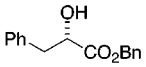
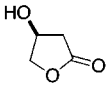
entry	alcohol (ROH)	conditions	yield
1		23 °C, 20 h	55%
2	**4**	60 °C, 12 h	70%
3	BnOH (**5**)	23 °C, 17 h	63%
4		60 °C, 12 h	97%
5		23 °C, 24 h	35%
6	**6**	60 °C, 12 h	81%

5) smoothly conjugated with CO_2 at room temperature to give the intermediate carbonate anion in DMF. Upon addition of polystyrene resin **1**, carbonate-bound resin **2** was obtained in moderate yields over a 24 h time period. On the other hand, after screening several reaction temperatures including reflux temperature, the optimum reaction temperature was found to be 60 °C, which offered shortened reaction times and increased yields significantly (entries 2, 4, and 6, respectively).[9]

Under these conditions,[10] we applied our technology to solid-phase carbonate synthesis using sterically crowded unreactive alcohols and chiral templates particularly prone to racemization. (Table 2).[11] Using secondary alcohols such

Table 2. Solid-Phase Synthesis of Carbonates Using Secondary Alcohols and Chiral Templates

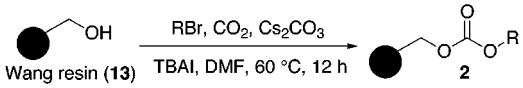


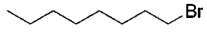
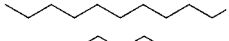
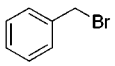
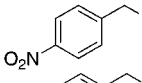
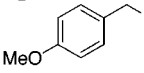
entry	alcohol (ROH)		yield
1		(**7**)	98%
2		(**8**)	98%
3	Menthol	(**9**)	83%
4		(**10**)	76%
5		(**11**)	63%
6		(**12**)	58%

as cyclohexanol **7** and 3,3-dimethyl-2-butanol **8**, similar trends were observed to deliver the resin-bound carbonates in excellent yields (entries 1 and 2). Subsequently, using chiral alcohols containing a small degree of sterics, such as menthol **9**, the desired chiral carbonate formed in high yield (entry 3). As depicted in entries 4−6, α-hydroxy esters and lactones encompassing lactate **10**, phenyllactate **11**, and γ-butyrolactone **12** underwent carbonylations to deliver their corresponding carbonates in moderate yields without any loss of stereochemical sense.[12]

Carbonylations were also successful upon switching reaction partners, as illustrated in Table 3. Using the polymeric Wang resin **13** and various bromides, unsymmetrical carbonates formed smoothly in high yields, making this method complementary to the aforementioned route (Table 3).[13]

Table 3. Solid-Phase Synthesis of Carbonates Using Wang Resin and Bromides



entry	bromide (RBr)		yield
1		(**14**)	97%
2		(**15**)	99%
3		(**16**)	91%
4		(**17**)	83%
5		(**18**)	83%

(8) For our cesium-promoted carbonylations, see: (a) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem.* **1999**, *64*, 4578. (b) Chu, F. Dueno, E. E.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1847.

Reaction of **13** with lipophilic primary bromides **14** and **15** gave rise to the exclusive synthesis of carbonate resin **2** in excellent yields (entries 1 and 2). Using a reactive bromide such as benzyl bromide **16**, the desired carbonate was generated in 91% yield (entry 3). In comparison, regardless of electron-withdrawing or -donating substituents at the 4-position of benzyl bromide, the carbonate formations were highly efficient (entries 4 and 5).

As shown in Table 4, the newly developed techniques were applicable with various amines, also offering efficient carbamate synthesis.[14] Allylic amines **19** and **20** gave polymer-bound carbamates in high yields, whereas the carbamate analogue of tryptamine **21** formed in 60% yield after the same duration. Saturated primary alkylamines, encompassing 2-methoxyethylamine **22** and tetrahydrofufurylamine **23**, exhibited similar reactivities using the same conditions, and cycloalkylamines **24** and **25** were also found to couple with **1** efficiently. With chiral auxiliaries in mind, methylbenzylamine **26** and aminoester **27** were examined, and the desired resin-bound organic carbamates formed exclusively in good yields. In addition, various secondary amines also proved to be facile and pragmatic (**28**−**31**).[15]

Since aromatic amines and nitrogen heterocycles are extensively used as building blocks in numerous syntheses, we next directed our attention toward the formation of aromatic carbamates on a solid support (Table 5). Using our cesium base-promoted carbamate methodology, aniline **32** reacted smoothly under the standard conditions with complete conversion. Comparatively, its electron rich derivatives **33** and **34** and electron deficient anilines **35** and **36** all reacted efficiently. In addition, 2- and 3-aminopyridines reacted smoothly, offering moderate yields (entries 6 and 7). Likewise, a secondary aromatic amine, *N*-ethylaniline **39**, led to the corresponding carbamate in 86% yield.[15]

Table 4. Solid-Phase Synthesis of Carbamates Using Merrifield Resin with Primary and Secondary Amines

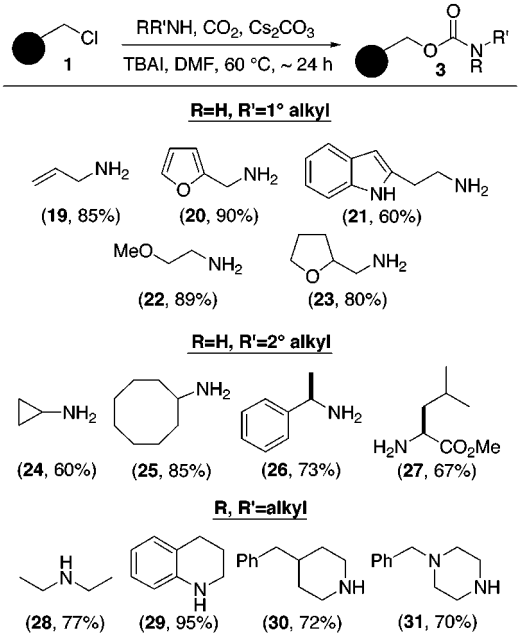
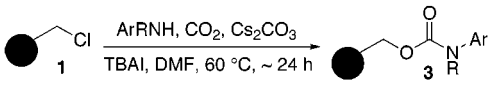
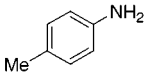
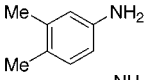
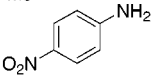
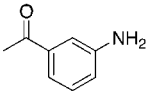
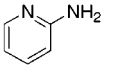
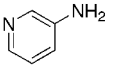


Table 5. Solid-Phase Synthesis of Carbamates Using Aromatic Amines and Merrifield Resin



entry	amine (ArRNH)		yield
1	Aniline	(**32**)	70%
2		(**33**)	81%
3		(**34**)	97%
4		(**35**)	55%
5		(**36**)	62%
6		(**37**)	66%
7		(**38**)	72%
8	*N*-Ethylaniline	(**39**)	86%

(9) Infrared spectra of all resin-bound carbonates were taken as KBr pellets and showed the indicative carbonyl stretching band in the appropriate locations for carbonates. The yield for the reactions were calculated on the basis of resin loading from gravimetric analysis after drying in vacuo over a 24 h time period. For a similar calculation, see the Supporting Information from the following reference: Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998.

(10) **Representative experimental procedure for carbonates:** Benzyl alcohol (0.61 mL, 6 mmol, 3 equiv) was dissolved in anhydrous *N*,*N*-dimethylforamide (20 mL) to make a clear solution. Into the solution were consecutively added cesium carbonate (1.95 g, 6 mmol) and tetrabutylammonium iodide (2.22 g, 6 mmol, 3 equiv). The suspension was stirred at room temperature while passing carbon dioxide gas through the solution for 1 h 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/H_2O, H_2O, 0.2 N HCl, H_2O, THF, CH_2Cl_2, and MeOH. After drying under vacuum for 24 h, 1.22 g of resin was obtained (97% yield): IR (KBr pellet) 3061, 3020, 2918, 2851, 1945, 1870, 1816, 1744, 1605, 1499, 1448, 1361, 763, 698, 546 cm^{-1}.

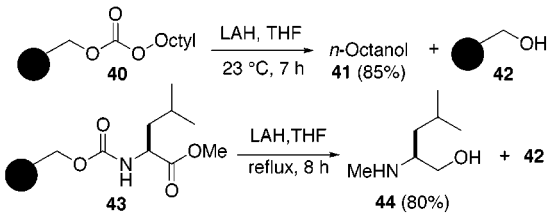
(11) Under basic conditions, α-hydroxy esters and lactones racemize easily; therefore, alkylations of such moieties are usually carried out under acidic conditions. So far, silver-catalyzed alkylations seem to be the most popular alkylation method, which is a costly process. (a) McKenzie, A.; Wren, H. *J. Chem. Soc.* **1919**, *115*, 602. (b) Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.

(12) The stereochemistry of the products was confirmed by spectroscopically comparing the products with the authentic samples. Also, the resulting carbonates were converted to the starting alcohols by cleavage with TFA/CH_2Cl_2, and the optical rotations of the produced products were compared with starting materials as well as those reported. If any sterochemical sense was lost, it was to a negligible extent.

(13) Carbonate products using Wang resin **13** were verified using infrared analysis (KBr pellet) showing the absence of the hydroxyl band. Also, the products were cleaved from the resin using triethylamine (10 equiv) in methanol, to yield the appropriate corresponding alcohols cleanly, which were compared to authentic samples by proton NMR analysis.

To address issues of selectivity utilizing our solid-phase protocol, the resulting carbonates and carbamates were further verified by cleavage from the Merrifield resin using two different conditions.[16] As delineated in Scheme 2, resin-

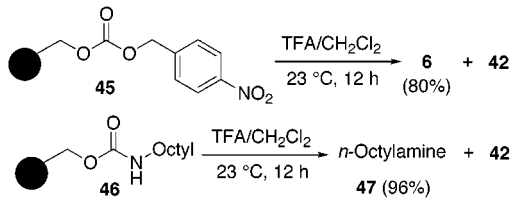
Scheme 2



bound octyl carbonate **40** was cleaved using LAH reduction at room temperature to give *n*-octanol **41** after 7 h. However, carbamate **43** required elevated temperatures, such as reflux, which gave rise to the *N*-methylated amino alcohol **44** in 80% yield after 8 h.

Alternatively, hydrolytic cleavage of carbonate **45** or carbamate **46** with TFA/CH_2Cl_2 (75:25, v/v) at room temperature returned the starting alcohol **6** or amine **47** in high yields. In all cases, crude NMR spectra exhibited clean products and no other side products were noticed within our detection limits. Furthermore, IR spectra of all cleaved resins yielded only the corresponding polymer-supported benzyl alcohol **42** exclusively (Scheme 3).

Scheme 3



In summary, a one-step three-way coupling was performed uniting Merrifield resin, carbon dioxide, and various alcohols or amines, which led to the exclusive synthesis of mixed alkyl carbonates or carbamates, respectively. Our reaction conditions offered easy purification procedures and complete conversions. Furthermore, isolation techniques allow for the generation of large combinatorial libraries for rapid screening in order to determine the pertinent activity of molecules having new or interesting properties. The procedures discussed herein were mild enough to avert side reactions such as hydrolysis or elimination commonly found using similar methods. Chiral substrates encompassing α-hydroxy esters, susceptible to racemization, survived the conditions. Our solid-phase synthetic methodology provides alternative procedures for the preparation of carbonates and carbamates efficiently as linkers on polymeric supports as well as scaffoldings for novel artificial biomolecules.

Acknowledgment. We acknowledge financial support from the H. Lee Moffitt Cancer Center & Research Institute and the American Cancer Society (IRG #032). We thank Chemetall for generous supply of cesium bases.

Supporting Information Available: Additional experimental procedures and method for determining yields are illustrated for examples **11** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Representative experimental procedure for carbamates:** 1,2,3,4-Tetrahydroquinoline (0.67 g, 5 mmol, 2.5 equiv) was dissolved in *N*,*N*-dimethylformamide (40 mL). Cesium carbonate (2.44 g, 7.5 mmol, 3.75 equiv) and tetrabutylammonium iodide (2.77 g, 7.5 mmol, 3.75 equiv) 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 h. Merrifield's resin (1 g, 2 mmol, 1 equiv) was added, and the reaction was continually stirred at 60 °C for 12 h 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 h to yield the desired carbamate (1.27 g, 95%) as a solid. 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}.

(15) All carbamate products were verified by IR analysis, which indicated the appropriate carbonyl stretching band as well as the corresponding amide stretches.

(16) For similar cleavage examples, see: Ho, C. Y.; Kukla, M. J. *Tetrahedron Lett*. **1997**, *38*, 2799.