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Solution-Phase Parallel Synthesis of Carbamates Using Polymer-Bound *N*-Hydroxysuccinimide

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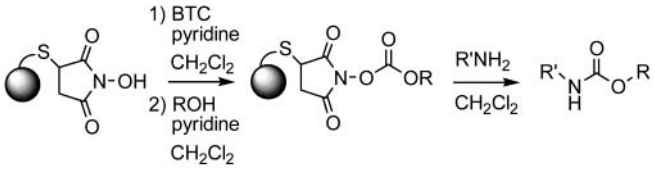
ABSTRACT



A convenient method for the synthesis of carbamates using polymer-supported *N*-hydroxysuccinimide is described. Various carbamates were synthesized in highly pure form without the need for chromatographic purification. This new "catch and release"-type solid-phase synthesis should be useful for combinatorial synthesis of various carbamates.

The carbamate group has reasonable chemical and biological stability, and has been used as a protecting group for the amino group.[1,2] It is also found in various pharmaceuticals and agrochemicals,[3] and a number of procedures for the synthesis of the carbamate group have been reported.[4] Combinatorial chemistry is now becoming a powerful approach in the search for biologically active compounds, and an efficient method for the parallel synthesis of a variety of pure carbamates is required for library synthesis. This would be particularly useful for preparing focused libraries, i.e., groups of compounds having a wide variety of residues connected to a specific "core",[5] for lead optimization, since carbamate would be a good functional group to connect the two parts. Polymer-supported reagents would be useful for this purpose, because both spent and unreacted reagent can be removed by simple filtration. Several syntheses of the carbamate group using polymer-supported reagents have been reported, in which chloroformates were required for the preparation of the reagents.[6] Only a few chloroformates such as Fmoc-Cl and Boc-Cl are commercially available. Thus, these previous methods are useful only for preparation of Fmoc- or Boc-protected amines or amino acids. From the viewpoint of library synthesis, synthetic protocols that enable the use of alcohols are preferred. Here we report a new "catch and release"-type method for the efficient synthesis of

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(2) Henklein, P.; Heyne, H. U.; Halatsch, W. R.; Niedrich, H. *Synthesis* **1987**, 166−167.

(3) (a) Wu, T.; Huang, J.; Arrington, N. D.; Dill, G. M. *J. Agric. Food Chem.* **1987**, *35*, 817−823. (b) Kato, T.; Suzuki, K.; Takahashi, J.; Kamoshita, K. *J. Pesticide Sci.* **1984**, *9*, 489.

(4) (a) Sandler, S. R.; Karo, W. In *Organic Functional Group Preparations*; Academic Press: New York, 1971; Vol. II, pp 223−245. (b) Ghosh, A. K.; Duong, T. T.; McKee, S. P.; Thompson, W. J. *Tetrahedron Lett.* **1992**, *33*, 2781−2784. (c) Morpurgo, M.; Bayer, E. A.; Wilchek, M. *J. Biochem. Biophys. Methods* **1999**, *38*, 17−28. (d) Ghosh, A. K.; McKee, S. P.; Duong, T. T.; Thompson, W. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1308−1310.

(5) (a) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. *J. Med. Chem.* **2001**, *44*, 3216−3222. (b) Sodeoka, M.; Baba, Y. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 1095−1102.

(6) (a) Dendrinos, K. G.; Kalivretenos, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1463−1464. (b) Barrett, A. G.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 261−264. (c) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Tetrahedron Lett.* **2001**, *42*, 7579−7581. (d) Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, J. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1817−1820. (e) Phoon, C. W.; Sim, M. M. *Synlett* **2001**, *5*, 697−699.

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carbamates that should find application not only for protection of the amino group but also for the synthesis of carbamate libraries.

We have reported that polymer-supported *N*-hydroxysuccinimide (NHS) **2** can easily be prepared from commercially available PS-thiophenol resin **1** and *N*-hydroxymaleimide, and we showed that it is useful for the synthesis of various amides.[7] Thus, we planned to use this PS-NHS resin **2** for the synthesis of carbamate libraries. Figure 1 illustrates the idea behind our column-chromatography-free carbamate synthesis. Namely, treatment of **2** with bistrichloromethyl carbonate (BTC)[8,9] would afford the polymer-supported chloroformate **3**. Further treatment of **3** with an alcohol is expected to give the polymer-supported NHS-carbonate **4**. Pure carbamate should be obtained by the reaction of **4** with an amine, followed by filtration and evaporation of the filtrate.

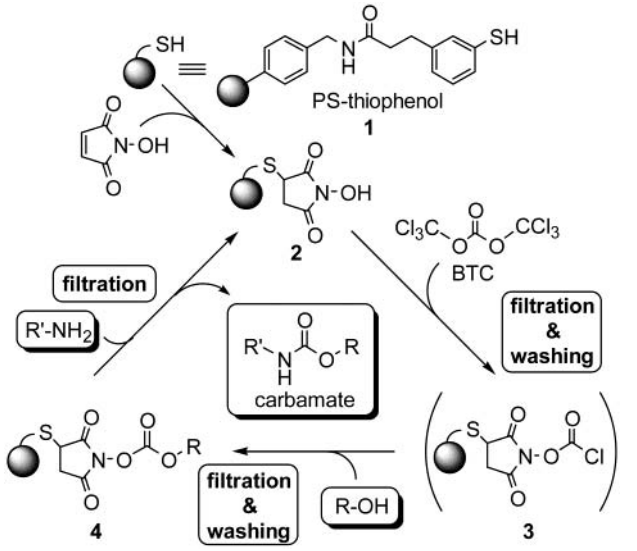
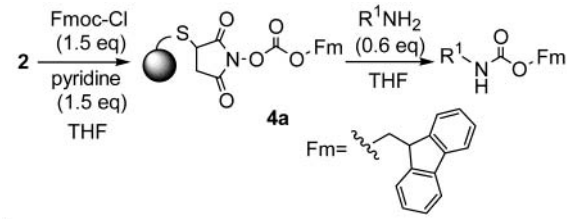
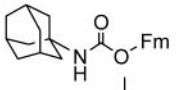
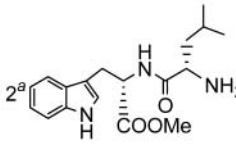
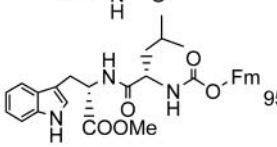
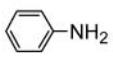
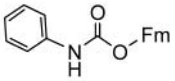
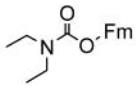


Figure 1. General scheme for the synthesis of carbamates using polymer-bound *N*-hydroxysuccinimide.

To examine the stability and reactivity of **4**, and to compare our procedure with the published protocols,[5] first the polymer-supported Fmoc carbonate resin **4a** was prepared by the reaction of **2** (1.00 mmol/g)[10] with Fmoc-Cl (1.5 equiv) in the presence of pyridine (1.5 equiv) in THF (23 °C, 2 h). Filtration and washing afforded **4a** (0.83 mmol/g),[10] which was sufficiently stable for storage at ambient temperature. The amines (0.6 equiv) were stirred with **4a** in THF at 23 °C, affording the desired products (Table 1). Various amines, including a secondary amine and an aromatic amine, were cleanly converted to the corresponding Fmoc derivatives in good chemical yields. The purity of the product obtained by the simple filtration, washing, and evaporation was confirmed to be >95% by ^{1}H NMR analysis.

Table 1. Synthesis of Carbamates Using Fmoc-Cl



entry	R^1NH_2	product	yield (%)
1[a]			86
2[a]			95
3[b]			90
4[a]			82

[a] Reaction time = 1 h. [b] Reaction time = 7 h.

Next, preparation of polymer-supported NHS-carbonates using various alcohols was examined. Efficient parallel synthesis of carbamates in four-step sequences from **1** was achieved by using a semi-automated apparatus, Quest210 (Argonaut). The PS-NHS resin **2** was first prepared from the PS-thiophenol resin **1** and *N*-hydroxymaleimide in a reaction vessel with a filter, basically according to the reported procedure.[7] It was then treated with BTC (2.0 equiv) and pyridine (1.0 equiv) in dichloromethane (CH_2Cl_2) at 23 °C for 2 h. After removal of excess reagents by filtration, the resin was washed with CH_2Cl_2. The resulting resin was stirred with an alcohol (3.0 equiv with respect to the NHS group) and pyridine (1.0 equiv) in CH_2Cl_2 at 23 °C for 3 h and then washed with CH_2Cl_2 to give the polymer-supported carbonate **4**. Loading of the alcohol was estimated from the recovery of the alcohol.[11] It was found that 43−75% of the thiophenol groups of resin **1** were converted to NHS-carbonate groups. It is possible that a cross-linked disuccinimidyl carbonate was partially formed on the resin, in addition to the chloroformate **3**.

(7) Katoh, M.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 881−884.

(8) Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, 553−576.

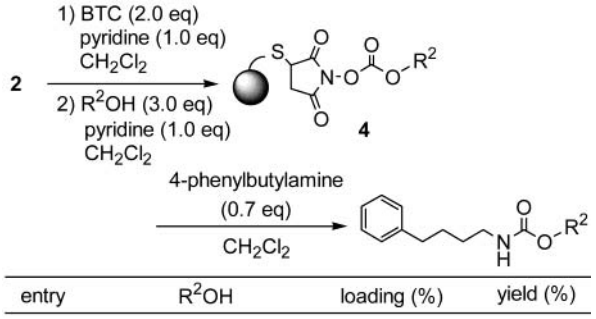
(9) Konakahara, T.; Ozaki, T.; Sato, K.; Gold, B. *Synthesis* **1993**, 103−106.

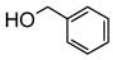
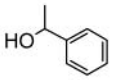
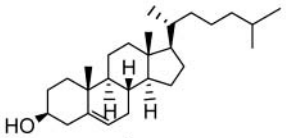
(10) Reaction with *N*-hydroxymaleimide or Fmoc-Cl was assumed to be almost quantitative, and the loading of resin **2** or **4a** was estimated from the original loading of the thiophenol group and the weight of the recovered resin **2** or **4a**.

(11) After the reaction with alcohol, all filtrates were combined and concentrated, and diphenylmethane (3.0 equiv with respect to the NHS group) was added to this mixture as an internal standard. Recovery of the alcohol was quantified by ^{1}H NMR analysis.

Disuccinimidyl carbonate is also known to react with alcohol, but only a half of the NHS groups on the resin could be converted to NHS-carbonate, if disuccinimidyl carbonate were formed. The resulting NHS-carbonates **4b**−**g** were stirred with 4-phenylbutylamine (0.7 equiv with respect to the carbonate) in CH_2Cl_2 at 23 °C. The solution phase was separated, and the resin was washed with CH_2Cl_2. The combined solution was concentrated to give the desired carbamate in good chemical yield, except for the tertiary alcohols (Table 2). It is likely that polymer-supported NHS-carbonate of the tertiary alcohol is sterically hindered, and approach of the amine to the carbonyl carbon might be difficult.

Table 2. Synthesis of Carbamates Using Various Alcohols

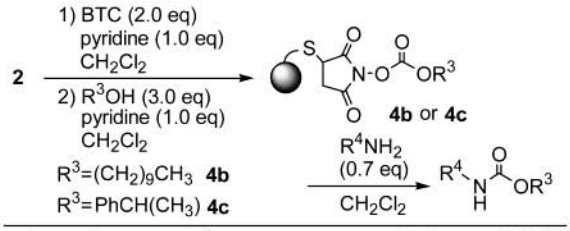


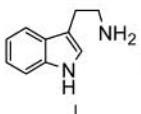
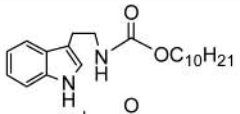
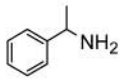
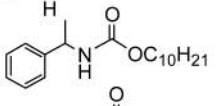
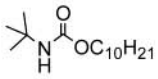
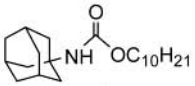
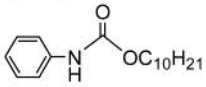
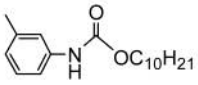
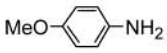
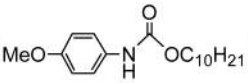
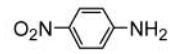
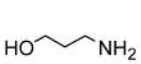
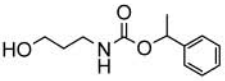
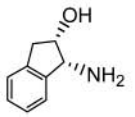
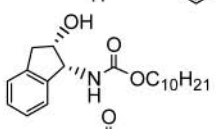
entry	R^2OH	loading (%)	yield (%)
1[a]	$CH_3(CH_2)_9OH$	**4b** (66)	87
2[a]		**4c** (74)	95
3[a]		**4d** (63)	90
4[b]		**4e** (58)	71
5[c]		**4f** (75)	—
6[c]		**4g** (43)	—

[a] Reaction time = 3 h. [b] Reaction time = 12 h. [c] Reaction time = 24 h.

Reactions of the polymer-supported NHS-carbonate **4b** with various amines were also examined. As shown in Table 3, the reaction proceeded smoothly to give the desired carbamate in highly pure form (>95%) without any purification. No significant amount of the starting amine or byproduct was observed in the solution phase. The purity of the product was confirmed by HPLC and/or ^1H NMR. Not only aliphatic amines, but also aromatic amines (except for *p*-nitroaniline) reacted smoothly to give the corresponding carbamates. No reaction occurred for *p*-nitroaniline, probably due to its poor nucleophilicity. It is also noteworthy that the reaction with the amino alcohols proceeded without difficulty, and no O-acylation was observed in any case (entries 10−12). In the case of the reaction of amines with low solubility in CH_2Cl_2 (entries 1, 5, and 11), vigorous shaking was required for the completion of the reaction.

Table 3. Synthesis of Carbamates Using Various Amines



entry	carbonate	R^4NH_2	product	yield (%)
1[a]	**4b**			95
2[b]	**4b**			94
3[b]	**4b**	MeO-Try-Leu-H	MeO-Try-Leu $OC_{10}H_{21}$	98
4[b]	**4b**			65
5[a]	**4b**			83
6[c]	**4b**			65
7[c]	**4b**			75
8[c]	**4b**			71
9[c]	**4b**		—	—
10[b]	**4c**			83
11[a]	**4b**			59
12[b]	**4b**	$HO(CH_2)_5NH_2$	$HO(CH_2)_5NH$ $OC_{10}H_{21}$	89

[a] Conditions: 23 °C, 10 h, vigorous shaking using a shaker for the last step. [b] Conditions: 23 °C, 3 h. [c] Conditions: 40 °C, 24 h.

Finally, the NHS-resin was found to be recyclable. Three successive cycles were run using the same resin in the same reaction vessel. Namely, the reactions of **1** with *N*-hydroxymaleimide, BTC, 1-decanol, and 1-phenylethylamine were carried out in a manner similar to that shown in Table 3, entry 2. After the isolation of the carbamate, the resin that

remained in the reaction vessel was retreated with BTC and 1-decanol in the same sequence to give the carbonate resin **4b**. This recycled resin was used for the second reaction with 1-phenylethylamine. After the second reaction, the resin was retreated with BTC, 1-decanol, and the amine again. Loadings of the alcohol in each cycle, as estimated from the consumption of the alcohol, were 53, 58, and 45%, respectively. The yields of the carbamate were 84, 74, and 87% in the first, second, and third cycles, respectively.

In conclusion, a new method for the facile preparation of various carbamates by utilizing polymer-supported NHS **2** has been developed. The major advantage of this method is the ability to prepare carbamates in highly pure form without any time-consuming purification step such as column chromatography. The whole procedure is suitable for automation. Since alcohols can be used in this method,[12] it should be useful for the synthesis of carbamate libraries.[13] Furthermore, this methodology is useful not only for protection of the amino group in small molecules and for combinatorial chemistry but also for the selective labeling of small molecules or proteins[4b] with biotin, a chromophore, a photoreactive group, a radiolabel, and so on.

Acknowledgment. We thank Argonaut Technologies for the generous gift of the PS-thiophenol resin. This work was supported in part by a grant from Uehara Memorial Foundation, The Naito Foundation, Suzuken Memorial Foundation, and Hoh-ansha Foundation, as well as a Grant-in-Aid for Creative Scientific Research (No. 13NP0401), a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research on Priority Areas (A) from The Ministry of Education, Culture, Sports, Science and Technology.

Supporting Information Available: Experimental details and spectral data for carbamates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026756F

(12) Recently, solid-phase synthesis of carbamates using a large excess of alcohols and amines was reported. However, it requires an acid cleavage step to obtain the final product. See: Fernandez-Forner, D.; Huerta, J. M.; Ferrer, M.; Casals, G.; Ryder, H.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 3543−3546.

(13) **General Procedure.** PS-Thiophenol resin **1** (200 mg, 1.14 mmol/g) was placed in the reaction vessel of a Quest machine and first treated with tri-*n*-butylphosphine to reduce the oxidized thiophenols. The resin was treated with *N*-hydroxymaleimide (0.296 mmol) and diisopropylethylamine (DIPEA) (0.091 mmol) in THF/DMF (2:1, 5 mL) to afford the PS-NHS resin **2**. This resin was then suspended in CH_2Cl_2 (3 mL), and a solution of BTC (0.456 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.228 mmol) were added. The reaction mixture was stirred at 23 °C for 2 h; then, the liquid phase was separated, and the resin was washed with CH_2Cl_2. The resin was treated with an alcohol (0.684 mmol) and pyridine (0.288 mmol) at 23 °C for 2 h to give the carbonate resin **4**. Finally, this resin **4** was treated with an amine (0.7 equiv with respect to the carbonate) in CH_2Cl_2 (5 mL) at 23 °C until all the amine was consumed. The desired carbamate was obtained by simple filtration, washing with CH_2Cl_2, and evaporation of the solvent.