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Carbamates from alcohol diversity: a simple solution phase library method

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Abstract—A simple one-pot, solution phase method for the parallel synthesis of carbamates from amines and alcohols is described. The high-yielding method does not require support-bound reagents, extractions or resin washing steps and should be broadly applicable to the manual or automated generation of carbamate libraries.

In efforts to prepare carbamate libraries from a variety of amine-bearing cores to support lead development projects in metabolic disease research, existing methods were found to be somewhat limited. Library strategies that utilize support-bound scavengers and bases with amines and chloroformates to give carbamates are well established.[1] Unfortunately, few chloroformates are commercially available. Thus, these methods are most useful when chloroformate-bearing cores can be prepared for library synthesis. It would be advantageous to utilize alcohols as a diversity unit, given the large number that can be purchased. Library methods that employ alcohols and a polymer-bound *N*-hydroxysuccinimide[2] or nitrophenol[3] to prepare carbamates have recently appeared.

We sought a simple solution phase strategy for the preparation of carbamate libraries that does not require the use of polymer supports, multiple synthesis and resin washing steps or in situ purifications such as liquid–liquid extraction. Appealing strategies would allow for the addition of all reagents as stock solutions to give product solutions suitable for direct submission to high throughput purification platforms without additional clean-up steps. We were drawn to the mild *N*,*N*-disuccinimidyl carbonate (DSC)-mediated carbamate synthesis of Ghosh et al.[4] in which alcohols are treated with DSC in the presence of triethylamine to give mixed carbonates. The carbonate-containing mixtures are concentrated, purified with liquid–liquid extraction and reconstituted in solvents for displacement with amines to provide carbamate products. While effective as a serial method, the number of manipulations involved makes this process difficult to perform in parallel.

We set out to adapt this method to parallel synthesis (Fig. 1). In a typical experiment, an alcohol in acetonitrile (1 M stock solution) was added to a 4 ml vial fitted with a magnetic stir bar. DSC in acetonitrile (0.3 M stock solution with 3 equiv of triethylamine vs alcohol) was added and the formation of the mixed carbonate

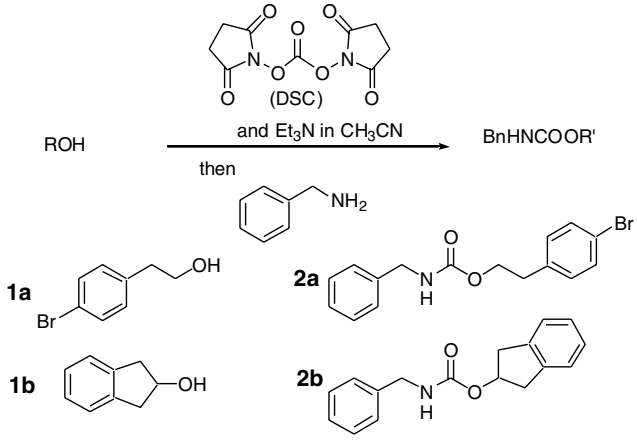

Figure 1. Solution phase, one-pot carbamate synthesis employing stock solutions.

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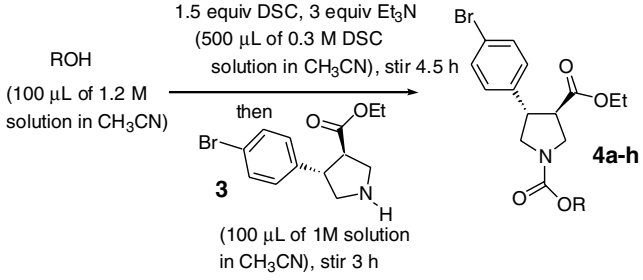
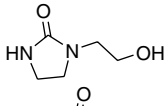
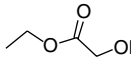
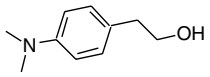
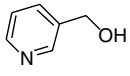
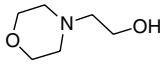
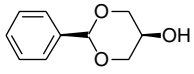
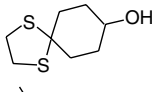
was monitored periodically by LC/UV over an 8 h period. The amine in acetonitrile (1 M stock solution) was added to form carbamate products and the reaction mixture was concentrated and chromatographed to determine yield based upon the amount of amine employed. The use of 1:1:1 alcohol/DSC/amine gave modest yields of **2a** (64%) and **2b** (75%). Analysis showed that alcohol remained after 8 h, suggesting that the formation of the mixed carbonate was inefficient. Raising the ratio of alcohol did not improve mixed carbonate formation, nor did the profiling of several bases. Interestingly, in all of our trials, including trials using a greater ratio of amine, no byproducts resulting from the reaction of residual DSC with the amine, such as symmetrical urea, were identified. Thus, we speculated that DSC was decomposing during the mixed carbonate formation step. By using an excess of DSC in the ratio of 1.2:1.5:1 alcohol/DSC/amine, efficient mixed carbonate formation was seen in <4.5 h, and superior yields of **2a** (93%) and **2b** (82%) were observed upon amine addition.[5] It should be noted that the major byproducts of this process, triethylamine and *N*-hydroxysuccinimide, are easily managed with normal or reverse phase chromatography.

We applied our method to the derivatization of the amine scaffold **3** (Table 1).[6] Primary alcohols, including electron poor alcohol ethyl glycolate, worked well giving **4a** and **4b** in 80% and 86% yield, respectively. Alcohols bearing basic functionalities such as anilines, pyridines and 3° amines were viable substrates providing **4c** (82%), **4d** (93%) and **4e** (84%). In addition, the reaction of secondary alcohols gave **4f** (90%) and **4g** (82%) efficiently. As is observed with the aforementioned serial method, the use of 3° alcohols results in only a trace amount of carbamate products (entry 8).

Table 1. Parallel carbamate synthesis



Entry	Alcohol	Carbamate	Yield[a]
1		**4a**	80
2		**4b**	86
3		**4c**	82
4		**4d**	93
5		**4e**	84
6		**4f**	90
7		**4g**	82
8		**4h**	Trace

[a] Yields of analytically pure material based upon amine equivalent.

In conclusion, a simple, one-pot parallel synthesis method has been developed to prepare carbamate libraries from alcohol diversity partners. Using these methods, both 1° and 2° alcohols featuring a variety of functional groups provide carbamate products in good yields. Although designed to be compatible with automated synthesis stations in which all reagents are added from stock solutions with solvent handling, this method can be performed on the bench top in capped vials or in microtitre plates, without the need for specialized equipment.

Acknowledgements

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Supplementary data

Supplementary data including analytical data for **4a–g** is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.139.

References and notes

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4. Ghosh, A. K.; Duong, T. T.; McKee, S. P.; Thompson, W. J. *Tetrahedron Lett.* **1992**, *20*, 2781–2784.
5. Yields for this one-pot process were comparable to those obtained using the serial method in which an extractive purification of the mixed carbonate was employed, followed by amine addition.
6. General procedure for the synthesis of **4a–h**: A DSC stock solution was prepared by dissolving DSC (390 mg, 1.5 mmol, DSC was pulled down overnight over P_2O_5) in CH_3CN (4.6 mL) and adding triethylamine (420 μL, 3.0 mmol). To a solution of alcohol (0.12 mmol) in anhydrous CH_3CN (100 μL) was added the DSC stock solution (0.5 mL). The reaction was stirred at room temperature for 4.5 h, at which time 100 μL of a 1 M solution of **3** (0.1 mmol) in CH_3CN was added. The reaction was stirred for 3 h, concentrated and purified over silica gel to provide the products in analytically pure form.