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A practical synthesis of carbamates using an 'in-situ' generated polymer-supported chloroformate

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Abstract—A versatile method for the synthesis of carbamates from an 'in-situ' generated polymer-supported chloroformate resin is presented. BTC (bis-trichloromethyl carbonate) is used as phosgene equivalent to afford a supported chloroformate, which, by sequential 'one-pot' reaction with a variety of alcohols and amines, furnishes the corresponding carbamates in high yields and purities.

Carbamate is a widespread functional group in organic synthesis. In general, carbamates are found as protecting groups for the amino function, especially in the chemistry of peptides and peptidomimetics.[1] Moreover, carbamates also play an important role in drug design, as hydrolytically resistant ester[2] or phosphate[3] surrogates. In this context, we are currently exploring the development of combinatorial libraries of phospholipid analogues in which the more robust carbamate group is used as phosphodiester surrogate. Based on these premises, we wish to report on an efficient synthetic protocol for the solution-phase parallel synthesis of carbamates by means of a polymer supported 'in-situ' generated chloroformate.[4,5]

Our approach relies on the nitrophenol resin **1**, easily prepared from an inexpensive polystyrene-type resin,[6] as described in the literature.[7,8] To check the feasibility of this strategy, we first reacted resin **1** with a series of commercially available chloroformates to afford intermediate carbonates **2a**–**d**. Gratifyingly, carbamates **3a**–**e** were obtained in good isolated yields upon treatment of the above carbonates with different amines, as shown in Table 1.[5,9]

Since the number of commercially available chloroformates is rather limited and preparation of individual chloroformates may be cumbersome, these results prompted us to develop a more versatile procedure for the generation of carbamates **3**, based on the 'in-situ' generation of a supported chloroformate (**4**)[10] followed by sequential reaction with the required alcohols and amines. Among the commercially available safer phosgene equivalents, we found that reaction of resin **1** with bis-trichloromethyl carbonate (BTC)[11,12] followed by sequential treatment of the putative chloroformate **4** with excess (5 equiv) isobutyl alcohol and benzylamine afforded carbamate **3e** in comparable yield to that found in the above two-step procedure.[13,14] This method also proved efficient for other amines, as indicated in Table 2. In all cases, with the exception of the aniline derivative shown in entry 9, the corresponding carbamates **3e**–**m** were obtained in good overall yields. Interestingly, chloroformate **4** reacts chemoselectively with amino alcohols, as shown in entries 5 and 6.

The intermediate chloroformate **4** was also challenged against a series of alcohols (Table 3) and the intermediate carbonates **2a**,**e**–**i** were next reacted with benzylamine to afford the corresponding carbamates **3n**–**s** in good yields.

The method is straightforward, since excess alcohol and coupling reagents can be removed by simple filtration of

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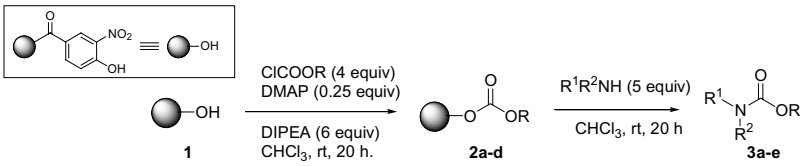
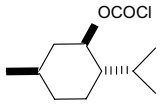
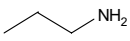
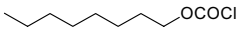
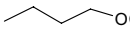
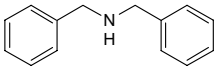
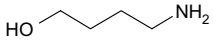
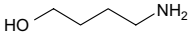
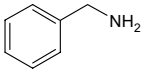
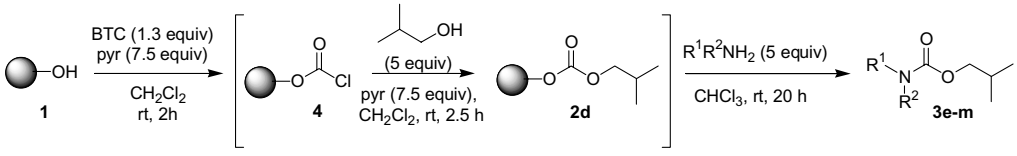
Table 1.

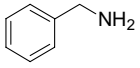
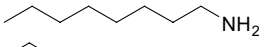
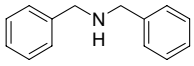
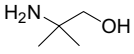
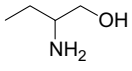
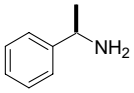
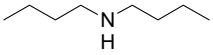
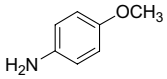


Entry	Chloroformate	Carbonate	Amine	Carbamate	Yield[a] (%)
1		**2a**		**3a**	95
2		**2b**		**3b**	97
3		**2c**		**3c**	75
4		**2d**		**3d**[b]	99
5		**2d**		**3e**	80

[a] Isolated yields.
[b] Reaction was run in THF due to low solubility of amino alcohol.

Table 2.

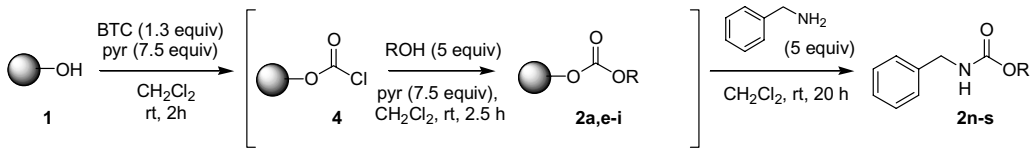


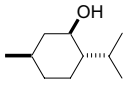
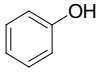
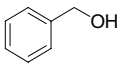
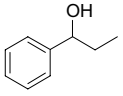
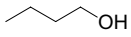
Entry	Amine	Carbamate	Yield[a]
1		**3e**	88
2		**3f**	75
3		**3g**	89
4		**3h**	69
5		**3i**	99
6		**3j**	94
7		**3k**	81
8		**3l**	88
9		**3m**	40

[a] Yields were calculated from the ^{1}HNMR crude in the presence of dimethyl terephthalate as internal standard.

the resin, whereas excess amine can be efficiently removed from the final product by aqueous acidic washings.[15] In all cases, the resulting carbamates showed homogeneous chromatographic (HPLC) and spectro-

Table 3.



Entry	Alcohol	Carbonate	Carbamate	Yield[a]
1		**2a**	**3n**	53
2		**2e**	**3o**	56
3		**2f**	**3p**	66
4		**2g**	**3q**	70
5		**2h**	**3r**	76
6		**2i**	**3s**	98

[a] Yields were calculated from the ^{1}H NMR crude in the presence of dimethyl terephthalate as internal standard.

scopic (^{1}H and ^{13}C NMR) patterns, and no further purification was required.

Finally, the intrinsic 'catch and release' nature of this methodology allows the recovery of the resin at the end of the process. Interestingly, exploratory assays with reused resin **1** showed no substantial loss of efficiency on the synthesis of carbamates **3g–j** (Table 2).

In summary, a simple and straightforward procedure for the solution-phase synthesis of carbamates in high yields and purities from a nitrophenyl derived polymer-supported chloroformate is reported. The supported reagent can be easily prepared from an inexpensive commercial PS resin.[6] The method allows the easy removal (or recycling, if required) of the excess alcohols and amines at the end of each cycle.[15] In addition, the nitrophenyl resin can be reused with no significant loss of efficiency. This method is suitable for application in combinatorial synthesis, taking into account the wide repertoire of commercially available alcohols and amines as building blocks.

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9. Synthesis of carbamate **3e** is representative: An agitated suspension of nitrophenol resin **1** (200 mg, 0.75 mmol/g) in anh. $CHCl_3$ (1.0 mL) was treated with a solution of DMAP (4.5 mg, 0.037 mmol) in $CHCl_3$ (0.5 mL) and neat DIPEA (160 μL). After 15 min agitation, a solution of isobutyl chloroformate (78 μL, 0.6 mmol) in $CHCl_3$ (1.5 mL) was added and the reaction mixture was agitated for 20 h at room temperature. The resin was next filtered and successively washed with $CHCl_3$ (3 × 2 mL), DMF (3 × 2 mL) and $CHCl_3$ (3 × 2 mL). The resin was next taken up in $CHCl_3$ (3 mL) and a solution of benzylamine (81.5 μL, 0.75 mmol) in $CHCl_3$ (1.5 mL) was added. After agitation for 20 h at room temperature, the resin was filtered and washed with $CHCl_3$ (3 × 2 mL). The combined filtrates were washed with aqueous 1 N HCl (3 × 1.5 mL), dried, and evaporated to furnish carbamate **3e** (24.8 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 6H, J = 6.6 Hz, CH_3), 1.91 (m, 1H, CH), 3.88 (d, 2H, J = 6.6 Hz, CH_2O), 4.37 (d, 2H, J = 6 Hz, CH_2N), 5.06 (br, 1H, NH), 7.27–7.36 (m, 5H, CH arom); ^{13}C NMR (75 MHz, $CDCl_3$) 19.1, 28.1, 45.1, 71.3, 127.5, 127.6, 128.7, 138.7, 157.0; IR (film) 3335, 2961, 1698, 1558, 1521, 1248.
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13. Initial experiments showed, in some cases, a nonnegligible formation of the corresponding symmetrical ureas. We have attributed this side reaction to the incomplete formation of carbonates **2** from chloroformate **4**, which depends on the intrinsic reactivity of the alcohol used. In agreement with this assumption, ureas were not observed from the sequential reaction of resin **1** with chloroformates and amines (Table 1), a process that does not imply the formation of chloroformate **4**. The use of DMAP as catalyst for the synthesis of carbonates **2** from chloroformate **4** was crucial to avoid the formation of the urea byproducts.
14. Synthesis of carbamate **3e** is representative: A suspension of nitrophenol resin **1** (200 mg, 0.75 mmol/g) in HPLC-grade CH_2Cl_2 (1.0 mL) was treated with dry pyridine (85 μL, 1.05 mmol) and agitated at room temperature for 10 min. A solution of bis-trichloromethyl carbonate (BTC, 60 mg, 0.20 mmol) in CH_2Cl_2 (0.5 mL) was next added and the reaction mixture was agitated for 2.5 h, filtered, and washed with CH_2Cl_2 (5 × 3 mL). The resin was suspended in CH_2Cl_2 (1.0 mL) and treated with pyridine (85 μL, 1.05 mmol), DMAP (5 mg), and a solution of the corresponding alcohol (5 equiv/mol) in CH_2Cl_2 (1.0 mL). After agitation at room temperature for 2.5 h, the resin was filtered and washed with CH_2Cl_2 (5 × 3 mL). The resin was next suspended in CH_2Cl_2 (1.0 mL), treated with a solution of the amine (5 equiv/mol) in CH_2Cl_2 (1.0 mL) and agitated for 20 h at room temperature. The resin was next filtered and washed with CH_2Cl_2 (5 × 3 mL). The combined filtrates were washed with aqueous 1 N HCl (3 × 1.5 mL), dried, and evaporated to furnish carbamate **3e** (27.3 mg, 88%). For NMR data, see Ref. 9.
15. In a single case, carbamate **3a** (Table 1) was obtained in comparable yield by using only 1.1 equiv of the corresponding amine. However, the generality of this modification has to be confirmed. Usually, excess reagents are recommended for parallel synthesis protocols.