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# Solid-phase syntheses of *N*-substituted carbamates. Reaction monitoring by gel-phase $^{13}C$ NMR using a $^{13}C$ enriched BAL-linker†

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**Abstract**—The solid-phase synthesis of *N*-substituted carbamates using the tris(alkoxy)benzyl (BAL) resin is reported. The incorporation of the primary amine was carried out by reductive amination, which was followed by reaction with an alkyl succinimidyl carbonate prepared in situ from the alcohol and *N*,*N*′-disuccinimidyl carbonate (DSC). Final cleavage with trifluoroacetic acid rendered the target compounds. Scope and limitations of these methods are discussed. The reactions were controlled by gel-phase $^{13}C$ NMR using a $^{13}C$ enriched BAL resin. 

A well-known method of carbamate preparation in solution phase is through a one-step reaction of an isocyanate and an alcohol.[1] Nevertheless, depending on the precise chemical structures of the reaction components, there are two significant problems in the application of this method to parallel synthesis. The first is the availability/instability of the corresponding isocyanate and the second is the often-needed purification to eliminate urea by products.

Therefore, the advantages inherent to solid-phase synthesis make this an appealing strategy for carbamate preparation.[2] Herein, we report the optimisation of a very simple, efficient, and straightforward solid-phase synthesis of *N*-substituted carbamates process which allows the preparation of highly pure compounds for lead optimisation (Scheme 1).

In particular, the optimised conditions for obtaining quinuclidinyl carbamate analogues is detailed. This class of compounds have been described in the literature as muscarinic M3 antagonists.[3]

The backbone amide linker (BAL) was chosen as a traceless linker for the attachment of the carbamate function to the solid support. BAL-resin was prepared by incorporation of the BAL-linker [5-(4-formyl-3,5-dimethoxyphenoxy) butyric acid] to a polyethylene glycol-polystyrene based resin (NovaSyn TG amino resin LL, 0.28 mmol/g) by HBTU–DIEA mediated coupling.[4a] The incorporation of the primary amine was carried out by on-resin reductive amination.[4a,5] In a first round of experiments, both the amine and $NaBH_3CN$ were used in considerable excess (10 equiv. of each) over resin-bound aldehyde. DMF containing enough HOAc to reach an apparent pH of approx. 5, was used as a solvent. The reaction was carried out for 18 h at room temperature. Although the reductive amination on solid support is a well documented reaction, there are only few examples in the literature of solid-phase carbamate formation.[6] As may been anticipated, carbonylation of the rather hindered secondary amino group attached to the BAL-resin proved to be the key step of this process. Based on previous work carried out during the preparation of carbamate *pseudo*peptides,[7] the use of alkyl succinimidyl carbonate was investigated. This mixed carbonate was prepared by reaction of the corresponding alcohol (20 equiv.)

*Abbreviations:* BAL, backbone amide linker; trisalkoxybenzyl, 5-(4-formyl-3,5-dimethoxyphenoxy) butyric acid; DIEA, *N*,*N*-diisopropylethylamine; DMAP, 4-*N*,*N*-dimethylaminopiridine; DMF, *N*,*N*-dimethylformamide; DSC, *N*,*N*′-disuccinimidyl carbonate; HBTU, *N*-[(1*H*-benzotriazol-1-yl) (dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HOAc, acetic acid; MeOH, methanol; TFA, trifluoroacetic acid.

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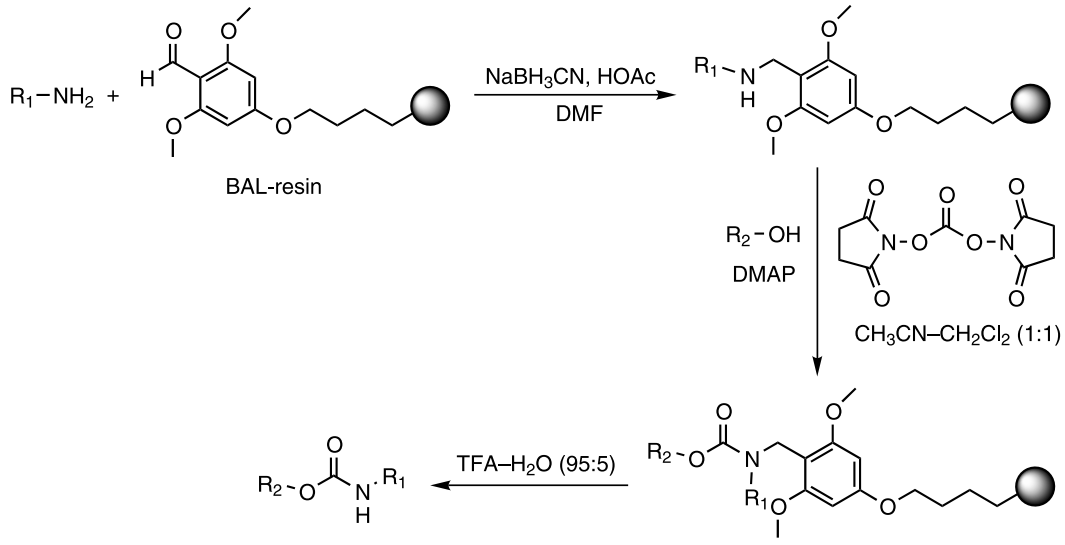


**Scheme 1.** Solid-phase synthesis of *N*-substituted carbamates

with DSC (18 equiv.) in the presence of DMAP (9 equiv.) in $CH_3CN$–$CH_2Cl_2$ (1:1) for 0.5 h, at room temperature. The reaction mixture, without isolation of the intermediate, was added to the resin and left to react with the resin bound secondary amine for 18 h at room temperature. The use of an excess of the alcohol should help to assure that no free DSC reacts with the resin giving internal ureas and/or other side products. Using these conditions carbamates derived from phenyl and benzyl amines and *N*-benzyl 4-hydroxypiperidine were obtained with good yields (60–70%) and purities (75–85%).

When these conditions were applied to more hindered amines and/or alcohols the yields were reduced. Therefore, a systematic study was carried out in order to optimise reaction conditions. The reactions were followed by gel-phase $^{13}C$ NMR,[8] first with regular BAL-resin and then with a BAL-resin prepared from $^{13}C$ enriched linker.[9,10] Gel-phase $^{13}C$ NMR is a powerful technique that provides a clean and non-destructive analytical method for the characterisation of functionalised solid supports. The method has the advantage of not requiring any special instrumentation besides a conventional FT-NMR spectrometer and a conventional $^{13}C$ probe.[8] One of the main drawbacks of this technique for monitoring the reactions is the long acquisition time needed to obtain a good signal to noise ratio. The presence of the $^{13}C$ label is very useful because only 20% of enriched $^{13}C$-resin allows a 50-fold reduction acquisition time. Furthermore, in this work, it had the additional advantage of simplifying the interpretation of the spectrum because the labelled carbon is that of the aldehyde function, and hence is spatially close to the chemical modifications, and therefore, exhibits a clear change of chemical shift in the $^{13}C$ NMR spectra. The combination of a polyethyleneglycol–polystyrene based resin, such as NovaSyn TG resin, and $CD_3OD$ as a solvent is particularly suitable from a practical point of view, as the resin does not float and swells well. These characteristics favour both manipulation of the resin in the NMR tube (see the experimental) and the quality of the spectra.

Benzhydrylamine was chosen as an example of a hindered and lipophilic amine for the optimisation of the synthetic protocol. Fig. 1 shows the gel-phase $^{13}C$ NMR spectrum corresponding to the reductive amination product. This reaction was carried out with a 0.25 M solution of amine and $NaBH_3CN$ (4.2 equiv. each) in MeOH–DMF (8:2) containing HOAc at an apparent pH of 5 for 18 h at room temperature. We have observed from different experiments that the adjustment of pH to around 5 with HOAc, as well as the use of MeOH as a solvent, gave the cleanest resin bound secondary amine. In spite of this, to avoid precipitation problems with bulky amines, MeOH–DMF (8:2) was finally used as preferred solvent.

Fig. 2 shows the gel-phase $^{13}C$ NMR for the optimisation of the carbonylation step using a 0.5 M solution of quinuclidinol (20 equiv.), DSC (18 equiv.), and DMAP (9 equiv.) in $CH_3CN$–$CHCl_3$ (1:1). $CHCl_3$ was used instead of $CH_2Cl_2$ due to the detection of some chloromethylated quinuclidinol by-products, presumably arisen from the presence of $CH_2Cl_2$. The spectra obtained after the different experiments show that the bound resin benzhydrylamine hardly reacted when the standard room temperature conditions were used. Heating to 70°C was required to push the production of carbamate to completion.

Finally, TFA–$CHCl_3$–$H_2O$ (50:50:1) proved to be an excellent cleavage cocktail resulting in cleaner crude products than TFA–$H_2O$ (95:5).

Using these conditions some quinuclidinyl carbamates were obtained with 40–75% yield and 85–99% purity. The further exploitation of the solid-phase parallel synthesis of carbamates as potential muscarinic antagonists will be published elsewhere.

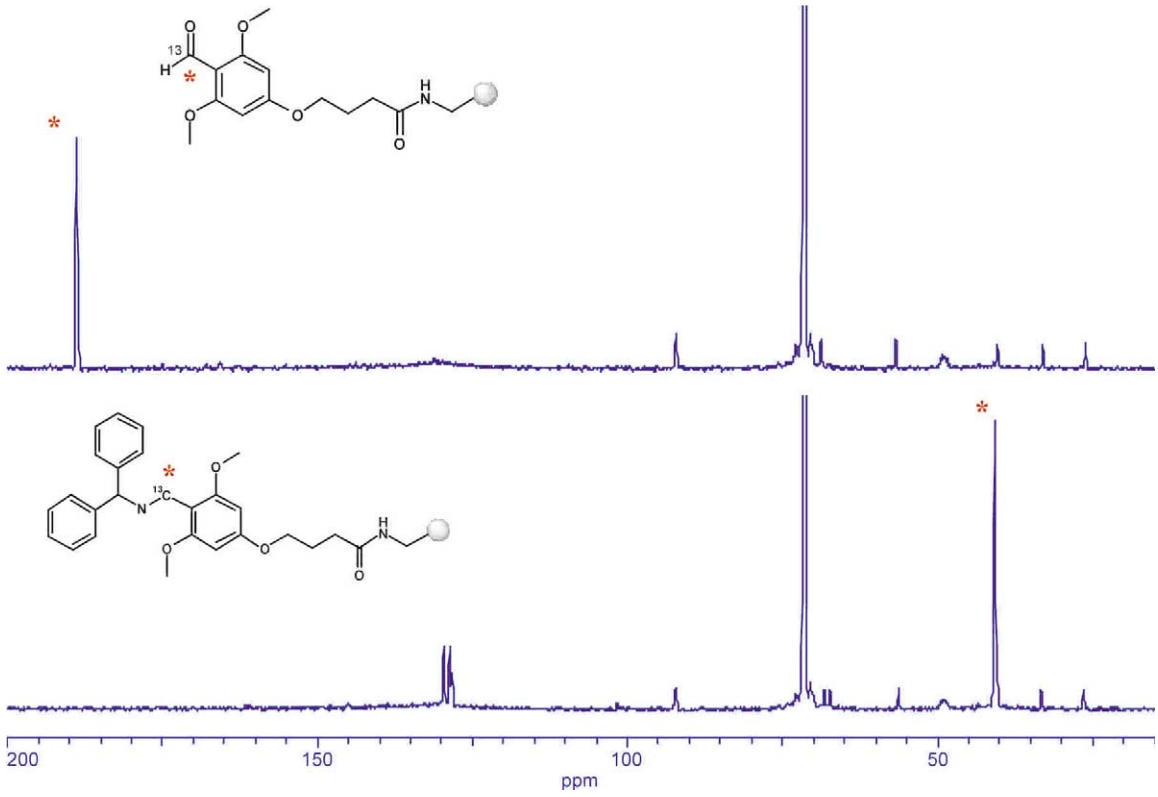


**Figure 1.** Gel-phase $^{13}C$ NMR monitoring of reductive amination reaction (see conditions in experimental).

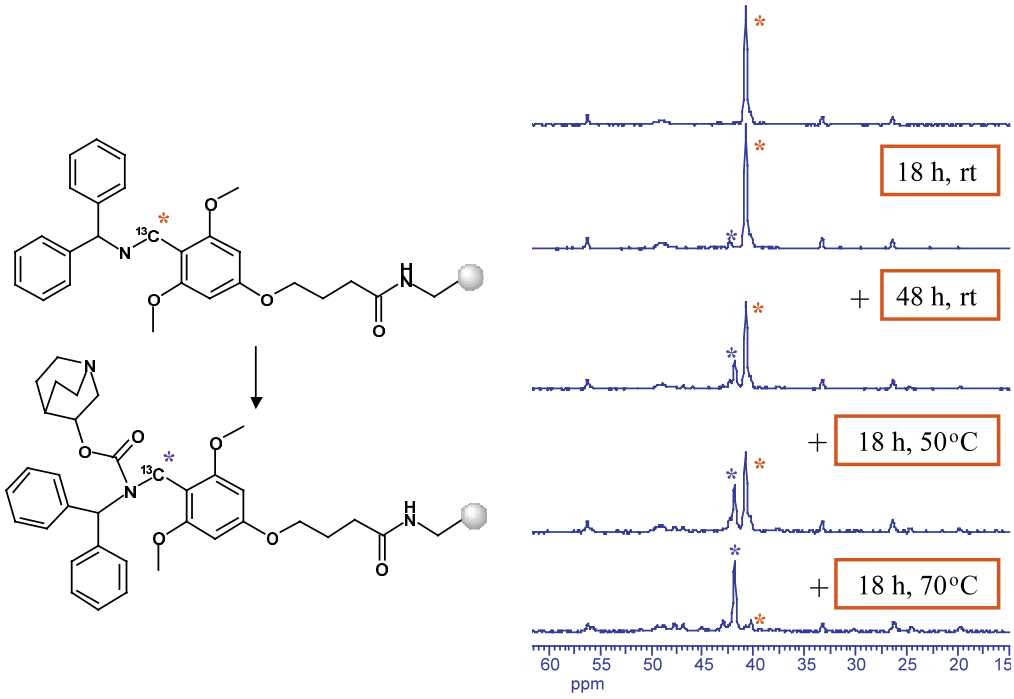


**Figure 2.** Gel-phase $^{13}C$ NMR monitoring of the carbonylation reaction (see conditions in experimental).

## Experimental

Solid-phase reactions were carried out in either polypropylene syringes (5 ml) fitted with a polyethylene porous disc or glass column reaction vessels. For the carbonylation reaction, the reaction vessel was heated and agitated by an orbital shaker.

**$^{13}C$ enriched BAL resin**. $^{13}C$ enriched BAL linker was synthesised following the protocol previously

described[4a] but using 20% of enriched $^{13}$C-DMF obtained from Cambridge Isotope Laboratories for the formylation. This linker was incorporated to a NovaSyn®TG amino resin (NovaBiochem, 0.25 mmol/g) by a HBTU/DIEA mediated coupling.[4a]

**Reductive amination**. 1.25 ml (4.2 equiv.) of a 0.25 M solution of the corresponding amine in DMF–MeOH (8:2) containing HOAc up an apparent pH of 5 was added to the pre-swelled BAL-TG-amino resin (300 mg, 0.075 mmol) followed by the addition of 0.31 ml of a 1 M solution of $NaBH_3CN$ (4.2 equiv.) in DMF–MeOH (8:2) and the mixture was left to stir for 18 h at room temperature. Resin was then washed with MeOH, DMF, and $CHCl_3$.

**Carbonylation**. A solution of 1.5 mmol (20 equiv.) of the corresponding alcohol and 0.67 mmol (9 equiv.) of DMAP in 1 ml of $CHCl_3$, was added to a suspension of DSC (18 equiv.), in 0.6 ml of $CH_3CN$. The mixture was left to stand at room temperature for 0.5 h and added to the secondary amine bonded resin (300 mg, 0.075 mmol). The reaction vessel was stirred for 18 h at 70°C. After filtration, resin was then washed with $CH_3CN$–$CHCl_3$, MeOH, DMF and $CHCl_3$.

**Cleavage**. Carbamate bounded resins were treated with 1 ml of TFA–$CHCl_3$–$H_2O$ (50:50:1) for 1 h at room temperature, and the resins were filtered. The cleaved resins were washed with 2×2 ml of MeOH, and the combined filtrates and washings were evaporated to dryness. In average, 10–25 mg of expected carbamates were obtained. Products were analysed by HPLC-MS.

**Gel phase $^{13}$C NMR**. 100–200 mg of dried resins were swelled in 1.5 ml of deuterated methanol (SDS >99.80% of deuterium) in a 10 ml vial. Capped vial was placed in an ultrasonic bath for 2 minutes in order to achieve a good swell of the resin. The resin-methanol-$d_4$ slurry was introduced in a 5 mm OD NMR tube with a Pasteur pipette. Once the resin was in the bottom of the tube, the extra solvent was removed. $^{13}$C NMR spectra were obtained at 75.45 MHz on a VARIAN GEMINI 2000 spectrometer equipped with a dual $^1$H/$^{13}$C probe. The 90° pulse with was 25 μs. Typical conditions were 0.1 s acquisition time, 0.2 s delay time, 23.5 μs pulse width, and 150.000 transients for regular BAL-resin and 0.15 s acquisition time, 0.2 s delay time, 23.5 μs pulse width and 2048 transients for $^{13}$C enriched BAL-resin. All spectra were processed using weighting parameters larger than those currently used with solution samples: 16 Hz line broadening, 0.024 s sinebell, and 0.1 s gaussian function.

In conclusion, we have reported a useful and efficient solid-phase method for the parallel synthesis of *N*-substituted carbamates. The utilisation of gel-phase $^{13}$C NMR using a $^{13}$C enriched resin was shown to be very useful for the monitoring and/or optimisation of solid-phase reactions. Optimised conditions for this pathway of reactions involve: (i) reductive amination with $NaBH_3CN$ in DMF–MeOH (8:2) containing HOAc at an apparent pH of 5 for 18 h at room temperature; (ii) carbonylation with DSC and DMAP in $CH_3CN$–$CHCl_3$ for 18 h at 70°C; and cleavage with TFA–$CHCl_3$–$H_2O$ (50:50:1) for 1 h at room temperature.

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