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Carbamate Linkers as Latent N-Methylamines in Solid Phase Synthesis

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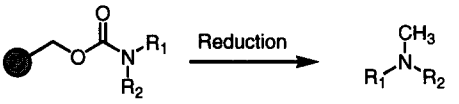
Abstract: A new linker strategy for solid phase synthesis has been developed. It utilizes LAH reduction of a carbamate connection to Wang resin which results in N-methylamines, a useful functionality in medicinal chemistry. © 1997 Elsevier Science Ltd.

Solid-phase synthesis of small organic molecules promises to become a powerful tool in drug research because it offers a number of advantages to working in the solution phase. There is the potential to use a large excess of reagents, since they can be simply washed away from the polymer bound product. In fact, final products are often sufficiently pure to be tested without further purification. Because compounds attached to a solid support are easily manipulated, large numbers of molecules can be synthesized simultaneously, even as purposefully generated mixtures, if so desired. Additionally, the use of automation and robotics in the synthetic process is much more feasible.

However, the attachment of a starting molecule to a solid support and the eventual removal of the ultimate product from the support are two additional and unique steps to solid-phase synthesis. Consequently, this has spawned a search for attachments or linkers to polymeric backbones that would be suitable for a variety of needs and chemistries. Many linkers have been discovered and reported; each has unique features and purposes. The choice of a suitable linker between the growing molecule and the solid support is critical to a successful synthesis. It must allow efficient attachment of a starting molecule, remain unchanged or unaffected by the synthetic sequence, and then allow removal of the final product under conditions which do not affect that molecule. Another important linker consideration is the residual functionality that usually remains on the final product as a result of the point of attachment. The possibilities include acids, amides, hydroxyls, primary and secondary amines.[1] More recently, silicon-based "traceless linkers" for phenyl rings have been reported.[2] An elegant approach based on a Michael addition and a Hofmann elimination to yield a tertiary amine has been published.[3] It requires no additional functional group for linking compounds to the resin other than the amines constructed during the synthesis. Undoubtedly, many new linkers will be developed for small organic molecule syntheses.

Recently, we discovered a series of compounds with interesting biological activity and wanted to carry out an analog program via solid-phase chemistry. Since this particular series did not have a convenient functional group which could be used as an anchoring point, we were required to search for an alternative solution. We have developed what promises to be a convenient and generally useful strategy that uses a carbamate linker as a latent N-methylamine. As pictured, this requires reductive cleavage of compounds from the resin support.

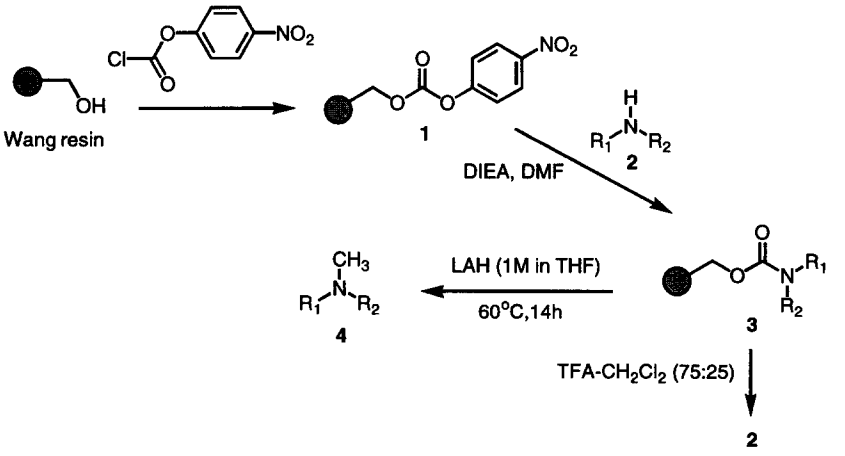


The carbamate linker has been used in solid-phase synthesis and is easily cleaved by trifluoroacetic acid (TFA) to give amines as hydrolysis products.[4] In another application, carbamate linkers have reacted intramolecularly with amide groups to form hydantoins as the product of cleavage from a resin.[5]

We have explored the reduction of carbamates with lithium aluminum hydride (LAH) to give N-methylamines as the linker residue. Our studies show that a variety of carbamates from primary or secondary amines efficiently undergo reduction/cleavage and give the opportunity for a number of different N-methyl amines (see Table 1). Clearly there is the opportunity to carry out a variety of chemistry on other functional groups present in R_1 and R_2 prior to reductive cleavage. The only limitation is that the carbamate, which is a fairly stable functionality, remain unaffected by intermediate transformations.

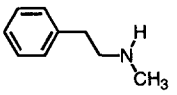
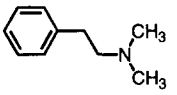
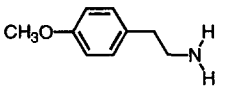
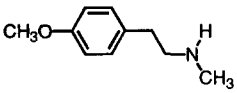
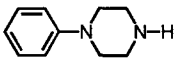
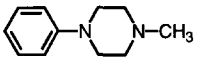
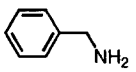
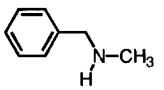
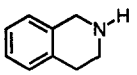
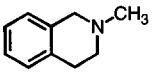
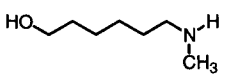
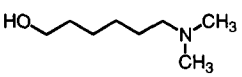
Our synthetic route is outlined in Scheme 1. Wang resin was derivatized to the p-nitrophenyl carbonate **1** according to the literature procedure.[5] Reaction of this carbonate with amine **2** gives the resin-bound carbamate

Scheme 1



3. When **3** is reductively cleaved with lithium aluminum hydride, the N-methyl compound **4** is obtained. Alternatively, hydrolytic cleavage with TFA-DCM (dichloromethane) returns amines **2**. Table 1 shows some examples of N-methylamines prepared by this route. Although the yields are somewhat variable, the purity of the products is good.

Table 1. Synthesis of N-Methylamines from LAH Reduction of Carbamates on Wang Resin.

Amine	Methyl Amine Product	GC Purity	Yield
		>95%	90%
		>95%	59%
		>95%	84%
		84%	67%
		>95%	62%
		94%	48%

All compounds gave satisfactory 300MHz 1HNMR and the correct molecular ion by GC/MS. The yields are isolated crude yields based on the loading of resin.

The general method for the synthesis of N-methylamines follows. Wang resin (Advanced ChemTech) was stirred in a solution of N-methylmorpholine (3 equiv.) and p-nitrophenylchloroformate (3 equiv.) at 0°C for 2 hrs and then at room temperature (RT) overnight. The resin was washed with DMF (6X) , MeOH (1X), and DCM (6X) then dried at RT overnight. The obtained nitrophenyl carbonate resin was mixed with a solution of amine (5 equiv.) and DIEA (5 equiv) in DMF and shaken at RT overnight. The resin was washed with DMF (6X) and DCM (6X), suspended in a solution of LAH/THF (10 equiv.) and heated at 60°C with shaking for 14

hrs. The reaction was quenched by sequential addition of water, 15% NaOH aq.solution, and water (38μL, 38μL, and 114μL, respectively, per mmol of LAH). The solid was washed with DCM and the filtrate was concentrated. The residue was analyzed by NMR and GC/MS, or HPLC. The final products could be passed through a C18 SPE column to remove any trace of aluminum salt by washing first with water and then eluting with acetonitrile-water (80:20) containing 0.1% TFA.

In summary, we have demonstrated that a carbamate attachment to Wang resin can be reduced with lithium aluminum hydride to prepare N-methylamines. This has proven to be a general reaction and we are using this approach to prepare a series of N-methyl compounds for biological testing. These efforts will be reported in future publications.

Acknowledgments

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References

1) For reviews see: (a) Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A., *J. Med. Chem.* **1994**, *37*, 1223-1251, 1385-1401. (b) Fruchtel, J.S.; Jung, G., *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17-42. (c) Hemkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D., *Tetrahedron* **1996**, *52*, 4527-4554.

2) (a) Plunkett, M.J.; Ellman, J.A., *J. Org. Chem.* **1995**, *60*, 6006-6007. (b) Chenera, B.; Finkelstein, J.A.; Veber, D.F., *J. Amer. Chem. Soc.* **1995**, *117*, 11999-12000.

3) Morphy, J.R.; Rankovic, Z.; Rees, D.C., *Tetrahedron Lett.* **1996**, *37*, 3209-3212.

4) (a) Letsinger, R.L.; Kornet, M.J.; Mahadevan, V.; Jerina, D.M., *J. Amer. Chem. Soc.* **1964**, *86*, 5163-5165. (b) Dixit, D.M.; Lenzoff, C.C., *J. Chem. Soc. Chem. Commun.* **1977**, 798-799. (c) Letsinger, R.L.; Kornet, M.J., *J. Amer. Chem. Soc.* **1963**, *85*, 3045-3046. (d) Felix, A.M.; Merrifield, R.B., *J. Amer. Chem. Soc.* **1970**, *92*, 1385-1391. (e) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589-1592.

5) Dressman, B.A.; Spangle, L.A.; Kaldor, S.W., *Tetrahedron Lett.* **1996**, *37*, 937-940.

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