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Secondary Amide-based Linkers for Solid Phase Organic Synthesis

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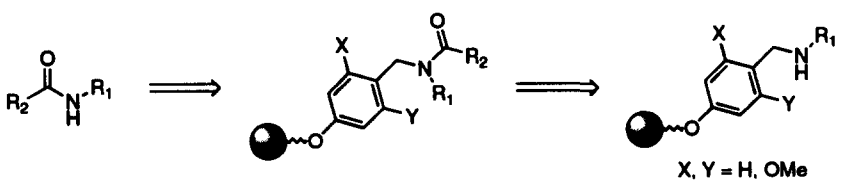
Abstract: The electron rich benzaldehyde derivatives 4-hydroxybenzaldehyde and 2-methoxy-4-hydroxybenzaldehyde have been investigated for use as linkers for solid phase organic synthesis. Reductive amination of these aldehydes attached to ArgoGel resins with a model primary amine gave the corresponding benzylic secondary amines. These compounds were then converted to the corresponding ureas, sulfonamides, aryl amides, and alkyl amides by derivatization with an appropriate electrophile. The desired secondary amide derivative was then cleaved from the support by treatment with trifluoroacetic acid to provide essentially quantitative yields of products in high purity.

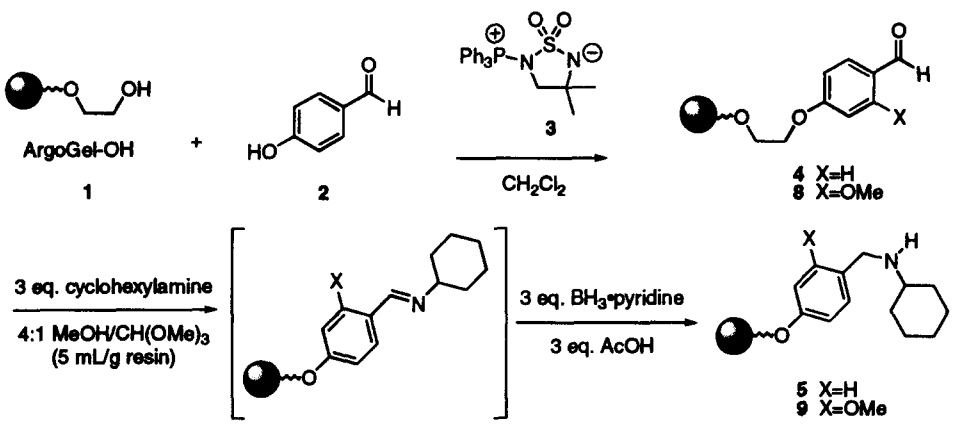
The growing use of combinatorial chemistry strategies as powerful tools in the drug discovery process has resulted in an explosion if interest in the synthesis of small organic molecules on solid supports.[1] This necessitates the efficient attachment, derivatization, and cleavage of the desired compound from the support. A great many successful strategies for accomplishing this task exist, however, the bulk of these methods result in the release of a molecule bearing a defined group (NH_2, OH, CO_2H, $CONH_2$, etc.), which therefore limits the diversity that can be achieved. To help overcome this problem, we have investigated the possibility of utilizing electron rich benzyl derivatives as functionalizable,[2] traceless[3] linkers for solid phase synthesis.

A linking strategy reported for the synthesis of a series of benzodiazepines[4] utilizes the highly acid labile 2,6-dimethoxy-4-alkoxybenzyl (Figure 1, X=Y=OMe) moiety which results in the release of a secondary amide, but reports difficulty of substitution at the very hindered 2,6-dimethoxybenzyl nitrogen. Related approaches have described the use of the Rink amide,[5] 4-alkoxybenzyl and 2-methoxy-4-alkoxybenzyl[6] linkers as a starting point for the synthesis of secondary sulfonamides. While the latter study employed a variety of amines, there has been no investigation of the variety of amides that can be prepared using electron rich benzylic linkers. Toward our goal of preparing diverse libraries on solid support, we wished to employ a variety of electrophilic reagents to functionalize amine-containing scaffolds at the point of attachment to the support as substituted ureas, sulfonamides, and a variety of aryl and alkyl amides. Using cyclohexylamine as a model primary amine scaffold, we have examined the suitability of the commonly employed 4-alkoxyl (Figure

Figure 1



Scheme 1



1, X=Y=H) and 4-alkoxy-2-methoxy benzylic (Figure 1, X=OMe, Y=H) linkers for the synthesis of a series of secondary amides.

To prepare the support, we employed a Mitsunobu reaction of the acid stabile ArgoGel™-OH[7] solid support **1** with 4-hydroxybenzaldehyde (**2**, Scheme 1). Using standard Mitsunobu conditions reported to effect coupling of hydroxybenzaldehydes to alcohols on solid support[8] gave very impure product, apparently containing ethyl groups by ^{13}C NMR.[9] This contaminant presumably arises due to the formation of adducts of the reduced DEAD by-product with the resin-bound aldehyde. Employing DIAD in place of DEAD reduced the problem, but still provided slightly impure material, even upon washing of the product with acetone and/or aqueous acid in an attempt to convert the presumed adduct back to the desired aldehyde. Reaction using the sulfonamide betaine **3**[10] in CH_2Cl_2, however gave complete conversion and very clean aldehyde resin **4**.

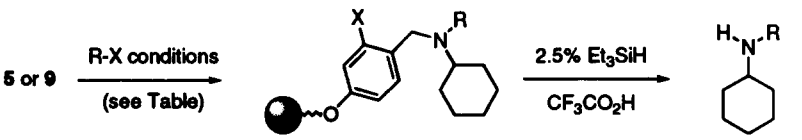
This aldehyde was then reductively aminated with cyclohexylamine to provide **5**. BH_3•pyridine[11] was found to be the most efficient reagent for this reductive amination, and gave significantly cleaner products than did the commonly employed $NaBH_3CN$[12] or $NaBH(OAc)_3$.[13] We have subsequently found that complete functionalization of the resin can be obtained by reaction of **4** with as little as 1.15 eq. of amine overnight in order to effect pre-formation of the imine, followed by reduction with 2 eq. of BH_3•pyridine/AcOH.

The resin bound benzylic amine **5** was then functionalized appropriately to provide sulfonamide **6a**, urea **6b**, and amides **6c-e** (Scheme 2). Substitution of the relatively unhindered support bound benzylamine **5** with carboxylic acids was easily effected using the coupling agent HATU,[14] which was reported to give poor coupling to the more sterically hindered 2,6-dimethoxy-4-alkoxybenzyl linker.[4] Cleavage of the desired product from the support was effected with trifluoroacetic acid containing 2.5% Et_3SiH as a scavenger to provide the amides **7a-d** in excellent yields and purity. Cleavage of compounds **6a** and **6b** was complete within 0.25 h, however the amides took substantially longer, requiring 6 h and 18 h for complete cleavage to **7c** and **7d**, respectively. The amino acid derivative **6e** proved resistant to cleavage, affording only 10-20% yields of **7e** even after 24 h of reaction. This is presumably due to rapid BOC removal to provide the corresponding protonated amine, which retards protonation and homolysis of the benzyl amide bond. It should be noted that no resin by-products or detached polyethylene glycol material was present in the ^1H NMR spectra of **7c** or **7d** despite the long cleavage reaction, presumably due to the excellent acid stability of the ArgoGel support used.

In order to expand the scope of this linkage method, we investigated the use of the more acid labile 2-methoxybenzaldehyde derivative **8**, which is now commercially available (ArgoGel-MB-CHO).[7] Reductive

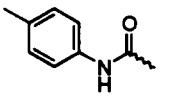
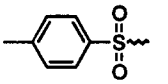
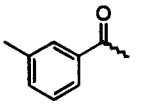
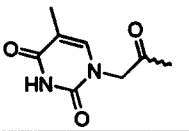
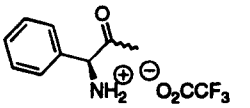
amination of **8** with cyclohexylamine proceeded cleanly to provide **9**, which was functionalized to provide **10a** and **10e** in the same manner as for **6a** and **6e**. Interestingly, despite the increased steric bulk imparted by the 2-methoxy group of **9**, complete conversion to **10e** was observed utilizing a HATU-mediated coupling. This indicates that the steric requirements of **9** are more similar to those of **5** than the corresponding 2,6-dimethoxy derivative. In contrast to **6e**, however, the 2-methoxybenzyl derived support **9e** was readily cleaved with 2.5% Et_3SiH/TFA to provide an 86% yield of the amino acid amide **7e** at 4 h, and a nearly quantitative yield upon cleavage overnight. In all cases purity of the products **7** was judged to be greater than 90% by ^1H NMR, and the stated yields are calculated based upon the theoretical loading of the resin, reflecting 3 steps in the case of **7a-7d** and 2 steps for **7e**. The synthesis of **7e** also serves to illustrate the use of *t*-butyl based protecting groups for functionalities having reactive side chains, which allows a one step cleavage and deprotection. The volatile nature of the by-products allows isolation of the desired products free from protecting group contamination without any purification steps, which in turn facilitates rapid synthesis of libraries using automated processes.

Scheme 2



6 X=H
10 X=OMe

7a-e

Resin	Functionalization Conditions	Product[a]	Yield[b]	R
6a	5/0.2 M tolyl isocyanate/NMP/12 h	**7a**	92 %	
6b	5/0.1 M tosyl chloride/0.15 M DIPEA/CH_2Cl_2/12 h	**7b**	93 %	
6c	5/5 eq. m-toluic acid/5 eq. HATU/10 eq. DIPEA/1:1 CH2Cl2/NMP/12 h	**7c**	90 %	
6d	5/5 eq. thymine acetic acid/5 eq. HATU/10 eq. DIPEA/1:1 CH2Cl2/NMP/12 h	**7d**	88 %	
10e	9/5 eq. BOC-Phe-OH/5 eq. HATU/10 eq. DIPEA/1:1 CH_2Cl_2/NMP/12 h	**7e**	99 %	

[a]Product identity was determined by ^1H NMR and HRMS analysis. In all cases the purity was >90% by ^1H NMR. [b]By dry weight of product after cleavage from support, based on theoretical available functionality of the starting resin (0.43 mmole/g for **1** and 0.41 mmole/g for **8**).

In conclusion, a solid support linking strategy has been investigated which employs an acid labile, electron rich benzylic linker. This methodology has proven applicable to the synthesis of substituted ureas,

sulfonamides and amides, and allows functionalization from an immense pool of commercially available reagents including sulfonyl chlorides, isocyanates, aryl acids, carboxylic acids, and amino acids. It is also straightforward to envision the use of amines as diversity reagents *via* initial activation of the support bound amine to the corresponding activated carbonyl derivative and subsequent conversion to the corresponding ureas. While this preliminary investigation has focused exclusively on using cyclohexylamine as a model scaffold, it should be noted that more complex amines can readily be employed. The use of amines bearing suitable functionality for further derivatization allows the synthesis of complex molecules on solid support, while retaining the ability to introduce diverse functionalities at the site of attachment.[15]

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REFERENCES AND NOTES

[1] a) *Annual Reports in Combinatorial Chemistry and Molecular Diversity, Vol. 1*; Moos, W. H.; Pavia, M. R.; Kay, B. K.; Ellington, A. D., Eds.; ESCOM: Leiden, 1997, and references cited therein. b) *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*; Chaiken, I. M.; Janda, K. D.; Eds. ACS, **1996**.

[2] For examples of functionalizable linkers see: a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172. b) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3056. c) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 211-214.

[3] For examples see: a) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006-6007. b) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1996**, *117*, 11999-12000. c) Boehm, T. L.; Showalter, H. D. D. *J. Org. Chem.* **1996**, *61*, 6498-6499. d) Zhao, X.-Y.; Jung, K. W.; Janda, K. W. *Tetrahedron Lett.* **1997**, *38*, 977-980.

[4] Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240-1256.

[5] Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tetrahedron Lett.* **1996**, *37*, 1145-1148.

[6] Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973-976.

[7] Argonaut Technologies, Inc. San Carlos, CA, (888) 598-1350.

[8] a) Devraj, R.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 9368-9373. b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671.

[9] All resin-bound products were characterized by gel-phase ^{13}C NMR. The yield was assumed to be quantitative based upon the stated loading of the resin if all starting material had disappeared, and only products were evident.

[10] Castro, J. L.; Matassa, V. G. *J. Org. Chem.* **1994**, *59*, 2289-2291. We have found that 3 is particularly well suited for Mitsunobu-like reactions on solid supports, especially when performing reactions using automation equipment. The addition procedure is simplified, as only two components (3/acid or alcohol) need to be added in place of the usual three (DEAD/Ph_3P/acid or alcohol), and the exotherm generated upon addition of DEAD to a Ph_3P solution is avoided.

[11] a) Khan, N. M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822. b) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996.

[12] Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720-6722.

[13] a) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47-50. b) Abdel-Magid, A. F.; Carson, K.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.

[14] Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397-4398.

[15] In our initial library synthesis efforts employing this linkage strategy, we have prepared bi-functional amines, and used them to construct small heterocycles having combinatorial sites. These studies will be reported in due course.

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