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Use of Halomethyl Resins to Immobilize Amines: An Efficient Method for Synthesis of Sulfonamides and Amides on a Solid Support

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Abstract: Methods for the synthesis of chloromethyl and bromomethyl equivalents of Wang's resin are described. To explore the utility of this acid cleavable resin, amines were immobilized through the nitrogen atom, further functionalized, and then cleaved under acid conditions.
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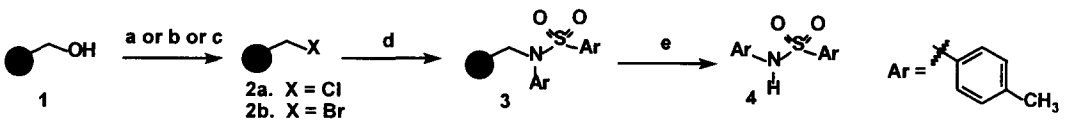
The methodology developed by Merrifield for amide bond formation on a solid support[1] has triggered organic chemists to develop various organic reactions on solid supports.[2] Although the growth in this area was stagnant for almost a decade, recently there has been a rapid growth in the development of new linkers and organic reactions on solid supports for the synthesis of organic molecules as individual entities or as a mixture of compounds to develop molecular diversity.[3] As a result of this, combinatorial and parallel organic synthesis have been the latest tools used to identify nonpeptide leads, and for further optimization of these leads against a protein target.

The vast majority of solid phase synthesis of organic molecules reported to date has used heteroatoms such as O, N, or S as anchoring points for attachment to a solid support, while other linkers have been developed to use a carbon atom as an anchoring point.[3] In a continuation of our effort to develop focused libraries of small molecules, we utilized a nitrogen atom as a site for the attachment to a solid support, followed by functionalization of the resin bound substrate.[4] Further investigations in this area have resulted in the use of acid cleavable linkers to synthesize amides and sulfonamides as described in this letter.

Scheme I



1 2a. X = Cl 2b. X = Br 3 4

Reagents: (a) $SOCl_2$, CH_2Cl_2, 0 °C, 45 min;[5] (b) $SOBr_2$, CH_2Cl_2, 0 °C, 45 min; (c) CH_3SOCl_2, CH_2Cl_2, DIEA, 24 h; (d) $ArNHSO_2Ar$, NaH, DMF, rt, 24 h; (e) TFA:H_2O (95:5), rt, 24 h.

Treatment of Wang's resin **1** with either thionyl chloride or thionyl bromide gave the corresponding halomethyl derivatives[6] **2a** and **2b** (Scheme I), as evidenced by the absence of an hydroxyl stretching band in the IR spectra of the products. The use of inexpensive thionyl halide reagents, and avoidance of the solubility problems of triphenylphosphine oxide make this new method more attractive than those reported recently. Due to the acidic nature of conditions used for this transformation, and literature precedent,[7] we speculated that the ether linkage present in Wang resin (Figure 1, **5a**) may be cleaved resulting in Merrifield resin or its bromomethyl equivalent. An alternative mild approach was undertaken to prepare the chloromethyl Wang resin in which the resin was treated with excess methanesulfonyl chloride in the presence of DIEA for 24 h to give **2a**. The selection of longer time was to permit the initially formed mesylate[8] to be displaced by the chloride ion present in the medium. Under these conditions, there was clear indication of functionalization of the hydroxyl group as evidenced by the absence of an hydroxyl stretching in the IR spectrum, which was identical to that obtained by the above thionyl chloride method.

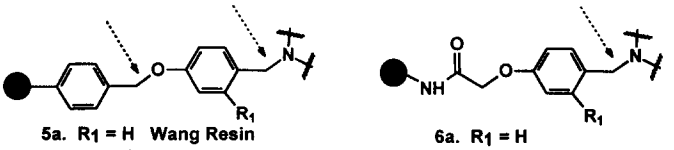
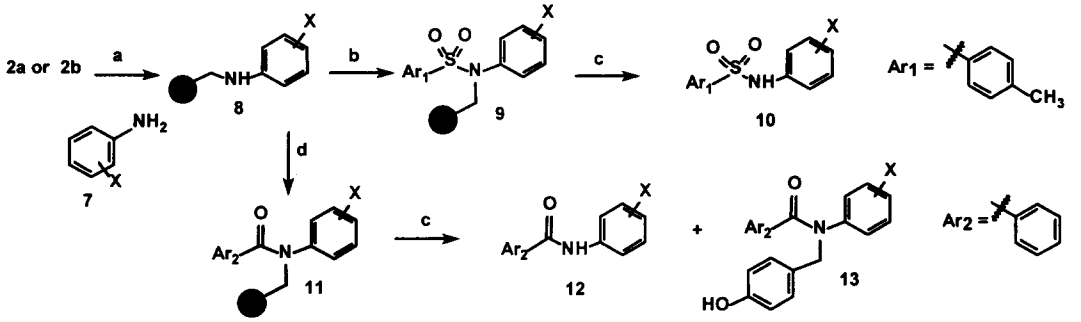


Figure 1

The next critical question in this synthetic approach was to investigate the cleavage pattern of the amino derivatized Wang linker (Figure 1). Towards this end, the resins **2a** and **2b** were coupled to a sulfonamide and subsequently cleaved using a mixture of TFA:H_2O (95:5) to release the sulfonamide (Scheme I). The yield of sulfonamide obtained from either of the above resins **2a** and **2b** was similar, and further NMR analysis of the product showed an absence of N-benzylic protons indicating cleavage had occured at the desired N-benzylic position. Encouraged by the cleavage of the resin bound sulfonamide in a desired fashion, the resins **2a** or **2b** were coupled with the aniline derivatives **7a-f** using proton-sponge[9] as a base to afford **8a-f** (Scheme II). The resin bound anilino derivatives **8a-f** were converted into sulfonamides by treatment with *p*-toluenesulfonyl chloride in the presence of DMAP and pyridine. Cleavage of the resin bound sulfonamides **9a-f** were effected using 95:5 (TFA:H_2O) at room temperature and the products were isolated in good yield and high purity[10] except in the case of **8d** which gave 2-nitroaniline and no sulfonamide detected.

Scheme II



Reagents: (a) Proton-sponge, DMF, NaI, $ArNH_2$(**7a-f**), 90 °C, 24 h; (b) Ar_1SO_2Cl, DMAP, 50 °C, 12 h; (c) TFA:H_2O (95:5), rt 24 h; (d) Ar_2COCl, DIEA, THF, rt, 8 h.

Table 1

		Sulfonamides (**10**)		Amides (**12**)	
Compound (**7-13**)	X	% Yield[a]	Purity[b]	% Yield[a]	Purity[b]
a	-H	56	96	53	95
b	-*p*-CH_3	70	98	76	95
c	-*p*-NO_2	76[d]	84	61	90
d	-*o*-NO_2	**[d]	--	33	100[e]
e	-*o*-CO_2CH_3	72[d]	83	71	95
f	-*o*-CH_3	55	92	30:60 (**12f** and **13f**)[c]	

[a]Yields of the cleaved product are based on the theoretical loading of commercial Wang resin; [b]Analytical HPLC of the products after cleavage using a C18 reverse phase column (250 mm X 4.6 mm) eluting with a water/acetonitrile mixture containing 0.1 % TFA from 5% to 95% acetonitrile (linear gradient) over 30 minutes. [c]Ratio of the products were determined by analytical HPLC. [d]Crude product was passed through a small plug of silica gel and then the PMR was recorded. [e]After purification by column chromatography (Hexane/EtOAc). **Sulfonamide was not detected and the isolated product was 2-nitroaniline.

To extend the scope of this methodology the resin bound anilines **8a-f** were treated with benzoyl chloride in the presence of DIEA, and the resins were cleaved using TFA:H_2O(95:5) (Scheme II). ^{1}HMR analysis of the products showed the presence of the desired amides[10] **12a-e** in good yield and purities except in the case of *o*-toluidine which gave N-benzylated amide **13f** as a major product and **12f** as a minor product

(2:1 ratio). The resin bound 2-nitroaniline derivative **8d** gave the desired amide **12d** and unreacted 2-nitroaniline[11] (1:1 ratio). Formation of the resin bound 2-nitroaniline derivative **8d** and either no reaction with *p*-toluenesulfonyl chloride or incomplete reaction with benzoyl chloride indicates that the steric and electronic properties of anilines affect functionalization of the resin bound secondary nitrogen more than the ability of anilines to react with the solid support. To increase structural diversity in the final products, (amides and sulfonamides) the functional groups present on the resin bound substrates may be transformed under a variety of reaction conditions previously established for solid phase synthesis, since the Wang linker is stable under many reaction conditions.

In conclusion, an efficient and general method for the solid phase synthesis of amides and sulfonamides using a Wang linker through tethering the nitrogen of an amine substrate has been developed. The cost of the functionalized Wang resin used in this methodology is less expensive than the 5-(4-aminomethyl-3,5-dimethoxyphenoxyvaleric acid handle (PAL handle) that has been used earlier.[12a,b] Also, the reagents used for the preparation of chloromethyl or bromomethyl are reasonably inexpensive compared to $P(Ph)_3:X_2$, reported previously.[6] The fact that a sterically crowded amide, such as in **11f**, resulted in cleavage of the benzylic ether giving **13f** as well as cleavage between the amide nitrogen atom and benzyl group (Figure 1, **5a**) is consistent with earlier observations.[12a] This result suggests that the use of polymers such as **6a** or **6b** (Figure 1), in which the ether linkage is further stabilized by the presence of an alkoxy linkage instead of a benzyloxy ether as present in **5a** or **5b** (in **6b** the presence of an additional methoxy group makes this polymer more acid labile), appear to be methods of choice to synthesize amides and ureas. The less expensive Wang resin can be used to construct a sulfonamide library. The presence of functional groups such as amides, ureas and sulfonamides,[13] as critical pharmacophoric feature in various biologically active molecules, enzyme inhibitors and receptor antagonists, prompted us to develop a variety of libraries which are currently in progress and will be the subject of future communications.

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5. Prolonged treatment (24 h, rt) of Wang resin in methylene chloride with 20 equivalents of thionyl chloride and its further use in the synthesis of sulfonamides did not significantly affect the yield of sulfonamide.
6. (a) While this manuscript was in preparation an alternative method was reported for the preparation of halomethyl derivatized Wang resin which was further utilized in the synthesis of sulfonamides. Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973. (b) Resin bound benzylic alcohol was converted to the corresponding benzyl chloride using thionyl chloride and pyridine complex. Wong, J. Y.; Manning, C.; Leznoff, C. C. *Angew. Chem. Internat. Edit.* **1974**, *13*, 666.
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9. Procedure: (a) Chloromethyl Wang resin (Method A) **2a**: To a suspension of the Wang resin **1** (9 g, 0.92 mmol/g, 8.28 mmol) in dry methylene chloride (85 mL) at 0 °C was added thionyl chloride (3.02 mL, 41.4 mmol) dropwise which was stirred at 0 °C for 40 min. The resin was filtered and washed successively with CH_2Cl_2 (500 mL), then MeOH (200 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (b) Chloromethyl Wang resin (Method B) **2a**: To a stirred suspension of resin **1** (2 g, 0.92 mmol/g, 1.82 mmol) in methylene chloride (18 mL) at 0 °C was added DIEA (1.59 mL. 9.1 mmol) followed by methanesulfonyl chloride (1.04 g, 9.1 mmol) dropwise. After complete addition, the reaction mixture was gently stirred for 24 h at rt. The resin was filtered and washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (c) Bromomethyl Wang Resin **2b**: This was prepared using 4 equivalents of thionyl bromide and Wang resin as described in reference (9a) except that the resin was washed only with methylene chloride; (d) Resin bound aniline derivative **8**: To a stirred suspension of resin **2a** (250 mg, 0.92 mmol/g, 0.23 mmol) in dry DMF (3 mL) at rt was added an aniline (5 equivalent), sodium iodide (100 mg), and proton-sponge (123 mg, 2.5 mmol) and the resulting reaction mixture was gently stirred at 90 °C for 24 h. The resin was filtered (hot DMF was filtered and extensive washing with DMF was necessary to remove proton-sponge), then washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (e) Resin bound sulfonamide derivative **9**: To a stirred suspension of resin (250 mg, 0.92 mmol/g, 0.23 mmol) in dry pyridine (3 mL) at rt was added p-toluenesulfonyl chloride (219 mg, 1.15 mmol) and DMAP (50 mg). The resulting reaction mixture was gently stirred at 60 °C for 14 h. The resin was filtered and washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (f) Resin bound amide derivative **11**: To a suspension of the resin (200 mg, 0.92 mmol/g, 0.184 mmol) in dry THF (3 mL) at 0 °C was added DIEA (0.352 mL, 11 mmol) followed by benzoyl chloride (0.288 mL, 1.84 mmol) dropwise. After complete addition, the resulting reaction mixture was vortexed at rt for 8 h. The resin was filtered and washed successively with DMF (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (5 mL), and MeOH (10 mL). The resin was dried under vacuum and the IR spectrum recorded (NaCl); (g) Cleavage of resin bound products: A suspension of resin (200 mg, 0.184 mmol/g) in TFA/H_2O (95:5, 2.5 mL) was vortexed for 24 h at rt. The resin was filtered and washed with methylene chloride (1 mL) and methanol (2 mL). The filtrate was concentrated under reduced pressure to obtain the products.
10. All the final products gave satisfactory high resolution ^1H NMR spectra as well as Fab mass spectra on a subset of samples.
11. Prompted by the cleavage of unreacted 2-nitroaniline, resin **8a** and **8c** (Scheme II) were cleaved using 95:5 (TFA:H_2O). Resin **8a** gave the N-(4-hydroxybenzyl)benzene as a major product (NMR & HPLC). However, the resin bound aniline derivative **8c** bearing an electron withdrawing group on the phenyl ring gave 4-nitroaniline as the only product (NMR & HPLC).
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