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Preparation of Acid-labile Resins with Halide Linkers and their Utility in Solid Phase Organic Synthesis

Khehyong Ngu and Dinesh V. Patel*

Versicor Inc, 270 East Grand Avenue, South San Francisco, CA 94080, USA.

Abstract: *Mild and efficient preparation of acid-labile resins with displaceable halide linkers (3 and 4, X = Br and I) is described. These resins can be used in combinatorial organic synthesis of numerous drug-scaffold libraries. Their synthetic utility is exemplified by high yielding N-alkylations with structurally and electronically diverse sets of aliphatic and aromatic amines. Amongst the various resins modified and evaluated in this study, Wang resin derived bromo resin (3, X = Br) offers the best practical choice with respect to loading, stability, and chemical reactivity.* © 1997, Elsevier Science Ltd. All rights reserved.

Combinatorial organic synthesis (COS) is becoming an increasingly important tool in drug discovery.[1] While the conceptual validation of this technology came through early examples of peptide libraries, a critical prerequisite for its practical application to drug discovery is the ability to synthesize diverse sets of small sized, non-peptidic, drug-like molecules in good yields and purity. A consequence of this goal is the rapid development of methods for solid phase synthesis (SPS) of such chemical entities. This in turn has created a need for new types of resins and linkers with different physical and chemical properties to accommodate a wide range of reagents and reactions. Traditionally, the most common application of SPS has been the synthesis of peptides with an amide or carboxylic acid group at the C-terminus, achieved through acylation with an amino (H_2N-resin) or hydroxyl (HO-resin) group of the linker on resin. To synthesize diverse sets of molecules not restricted to terminating in an amide or acid group, linkers with different functionalities are needed. This has been an area of considerable interest and has recently provided several new examples, such as the ones based on the concept of traceless and safety-catch linkers.[2]

In our efforts aimed at application of COS to drug discovery, we required *an acid labile linker resin with a good leaving group (LG).* Substitution reactions on these resins with various nucleophiles such as amines, thiols, and alcohols followed by further chemical derivatization can lead to a highly diverse set of potentially bioactive molecules. Rather surprisingly, the choices of such resins from commercially available sources is very limited.[3] An ideal resin bearing a good LG should possess an adequate balance of stability and reactivity, i.e. it should have a reasonable shelf-life for convenient and repetitive use, and yet the LG should be reactive enough to be displaceable by a host of nucleophiles under mild reaction conditions.

We commenced our studies with both the 95% TFA labile Wang resin **1** (Calbiochem-Novabiochem Intl.)[4a] as well as the milder 5% TFA labile Tentagel S AC resin **2** (Rapp Polymere)[4b] to derive more flexibility in subsequent synthetic transformations. The terminal hydroxyl group of these two resins was converted to five

different leaving groups [bromo, iodo, mesyl, tosyl, and nosyl] by treatment with appropriate reagents (Table, Scheme 1).[5] The modified resins **3** and **4** were evaluated in the following manner (Scheme 1). Each of the 10 resin aliquots was alkylated individually with n-butylamine, sulfonylated with 2-napthalenesulfonyl chloride (NMM, CH_2Cl_2), and cleaved with TFA. A successfully derivatized resin batch with good stability and reactivity would yield n-butyl-(2-napthyl)-sulfonamide **5** whereas untransformed or unstable and hydrolyzable resin will fail to N-alkylate and instead form 2-naphthalene sulfonic acid **6** resulting from O-sulfonylation (Scheme 1). Relative formation of **5** versus **6** as determined by HPLC would reflect the quality of these modified resins.[6] Of all the ten modified resins tested,[7] the Wang resin derived bromo and iodo resins **3** (X = Br, I) gave the best results (>90%). Yields with halide resins **4** (X = Br, I) derived from the more acid labile Tentagel S AC resin **2** were also comparable (87% for Br, and 79% for I).

Scheme 1: Preparation of acid labile resins 3 and 4 with various leaving groups

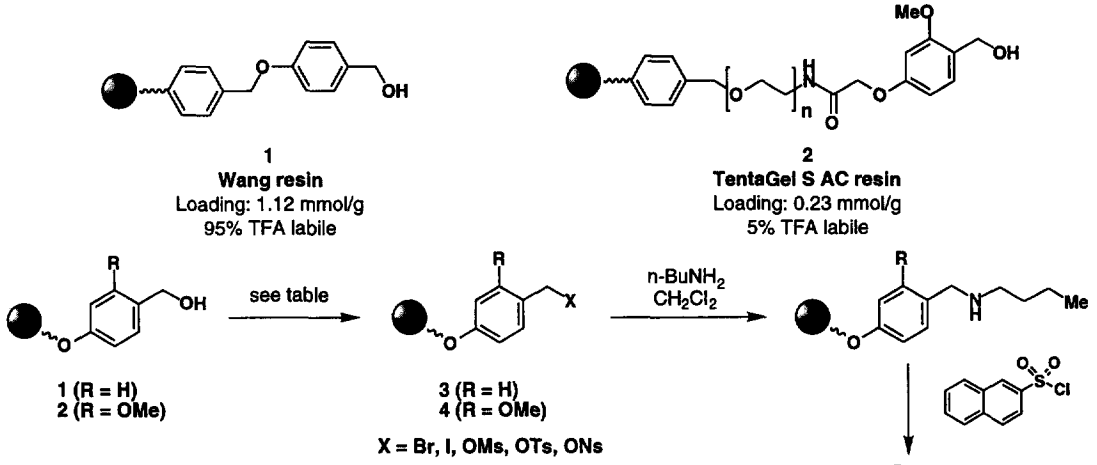


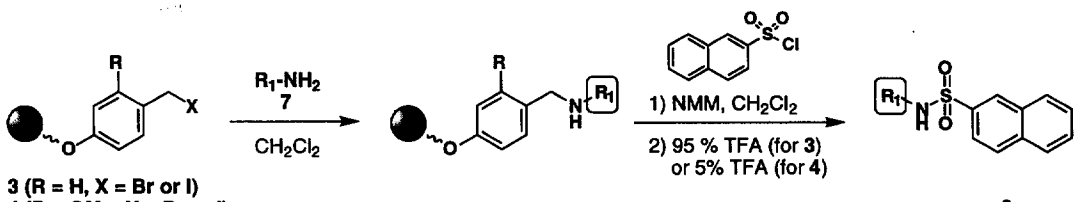
Table 1

#	Reagents	X	5 (from 3)	5 (from 4)
a	Ph_3PBr_2 or Ph_3P/CBr_4	Br	99%	87%
b	Ph_3PI_2 or $Ph_3P/DIAD/CH_3I$	I	93%	79%
c	$MeSO_2Cl$, NMM	OMs	21%[7a]	54%[7a]
d	TsCl, NMM	OTs	0%[7b]	NA[7c]
e	p-NO_2-$PhSO_2Cl$, NMM	ONs	0%[7b]	NA[7c]

The synthetic scope of these four resins (**3** and **4**, X = Br, I) was further explored by N-alkylations with a variety of amines **7** (Scheme 2). Derivatization of resin bound amines **8** with 2-naphthalene sulfonyl chloride followed by TFA cleavage gave sulfonamides **9**,[8] which were characterized by MS and ^1H NMR, and their relative yield and purity was assessed by HPLC. The various amines chosen for this study represent a wide range of relative basicity (pKa = 1 to 11), nucleophilicity, and general steric parameters. To prepare combinatorial libraries

with adequate structural and functional diversity, it is critical to have solid supports and connection chemistries that can accommodate such diversity in the corresponding building blocks. As evident from the data (Table in Scheme 2), the reaction proceeds in excellent yield and purity with acyclic, cyclic, and aromatic amines. Noteworthy is the fact that alkylation with highly electron deficient *p*-nitroaniline (pKa = 1.0) also proceed in good yields (63-78%). In general, Wang resin derived halide resins **3** consistently gave slightly superior yields (78-100%) in comparison to the corresponding Tentagel S AC resin derived halide resins **4** (63-98%). Within each type of resin (Wang or Tentagel S AC), the bromo and iodo derivatives were essentially indiscriminatory in performance. For practical purposes, the bromo resins are preferred because of their superior stability, and the low cost of corresponding reagents required for their preparation (Aldrich: Ph_3PBr_2, \$15.35/5g vs. Ph_3PI_2, \$40.00/5g). Wang bromo resin (**3**, X = Br) bears the additional advantage that it is high loading (1.12 mmol/g vs. 0.23 mmol/g for Tentagel S AC), less hygroscopic, and can be stored at 0 °C for several months and used without any significant deterioration in performance.[9]

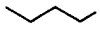
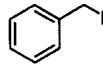
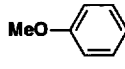
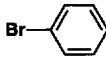
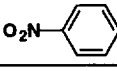
Scheme 2: Reaction of Halide Resins with different Amines



3 (R = H, X = Br or I)
4 (R = OMe, X = Br or I)

8

9

#	R_1-NH_2 7	Amine 7 pKa	Wang derived Resin 3		Tentagel S AC derived Resin 3	
			Bromo (X = Br)	Iodo (X = Br)	Bromo (X = Br)	Iodo (X = Br)
a		10.77	99%	93%	87%	79%
b		10.66	100%	97%	89%	85%
c		9.33	97%	100%	97%	92%
d		NA	92%	95%	71%	80%
e		5.34	98%	100%	97%	98%
f		4.63	99%	100%	92%	93%
g		3.86	100%	100%	97%	95%
h		1.0	78%	78%	67%	63%

In summary, mild and efficient procedures for the preparation of acid-labile resins with halide linkers is described, and their synthetic utility is exemplified by high yielding (63-100%) N-alkylations with a wide variety of sterically and electronically diverse aliphatic and aromatic amines. Acid labile (95% TFA cleavable) Wang resin derived bromo resin (**3**, X = Br) is an ideal high loading (1.12 mmol/g) solid support with a good balance of chemical stability and reactivity that will find good use in the field of solid phase and combinatorial organic synthesis.[10] Tentagel S AC resin derived bromo resin (**4**, X = Br) is a good alternative where milder cleavage conditions (5% TFA) are required.

Preparation of Wang bromo resin (3, X = Br): A suspension of PPh_3Br_2 (1.42 g, 3 equiv, 3.36 mmol) in CH_2Cl_2 (15mL) was slowly added to a stirred suspension of hydroxymethyl Wang resin (1 g, 1 equiv, 1.12 mmol) in CH_2Cl_2 (10 mL) at RT under argon. After stirring for 3 h at RT, the reaction mixture was filtered, and the resin was washed with CH_2Cl_2 (4 x 15 mL), and dried *under vacuo* (1.066 g, 99.5%). The resin is stored at 0 °C, and found to be stable for several months.

The iodo resin was prepared in a similar manner by substituting PPh_3I_2 for PPh_3Br_2 in the above experiment. The Tentagel S AC halide resins were similarly prepared by following the above procedure.

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Notes and References:

1 a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. c) Gordon, E. M.; Gallop, M. A., Patel , D.V. *Acc. of Chem Res.* **1996**, *29*, 144-154. d) Patel D. V., Gordon, E. M. *Drug Discovery Today* **1996**, *1*, 134-144.

2 a) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006. b) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3056.

3 Simple chloromethyl polystyrene-divinylbenzene (Merrifield) resin or bromomethyl polyethyleneglycol polystyrene (Tentagel S Br) resin do not possess a cleavable linker and are therefore unsuitable. The 2-chlorotrityl resin is too labile and too bulky for practical utility in the current study.

4 a) S.W.; Wang. *J. Am. Chem. Soc.* **1973**, *95*, 1328. b) A. Florsheimer et al. "Peptides 1990, Proc. 21st European Peptide Symposium", E. Giralt & D. Andreu (Eds), ESCOM, Leiden, 1991, pp 131.

5 Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B.* (1990, 3rd Edition), Chapter 3, Functional group interconversion by nucleophilic substitution, pp 121-128.

6 HPLC conditions : Dynamax analytical column (C_{18}, 5 μ particle size, 15 cm L, 4.6 mm ID). Solvent A : 0.1% TFA in H_20. Solvent B : 0.1% TFA in MeCN. Running program : 0% B to 100% B in 30 min; flow rate = 1 ml/min. Compound **5**, R_t = 20.37 min; compound **6**, R_t = 9.05 min. All compounds were typically characterized by HPLC, MS, and ^{1}H NMR.

7 a) The mesyl resin (**3** or **4**, X = OMs) gave a mixture of **5** and **6**, suggesting that it reacts well with $nBuNH_2$, but has limited stability and is probably getting partially hydrolyzed to the alcohol. b) The tosyl and nosyl Wang resins (**3**,.X = OTs or ONs) gave no desired sulfonamide product **5**, indicating that most probably they are formed but are rather too stable and unreactive. c) NA = not attempted. Based on the results obtained in 7b, the Tentagel S Ac tosyl and nosyl resins (**4**, X = OTs or ONs) were not included in the study.

8 A sulfonamide group has recently been desribed as an anchoring group on solid support. Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tet. Lett.* **1996**, *37*, 1145-1148.

9 Tentagel S AC derived bromo resin **4** (R = OMe, X = Br) has also been found to be stable at 0 °C for 1 month, and further stability studies are currently in progress.

10 Numerous applications of these halide resins (**3** and **4**, X = Br, I) for synthesis of non-peptidic, drug-like scaffold libraries are under investigation, and will be reported in the near future.

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