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AMEBA: An Acid Sensitive Aldehyde Resin for Solid Phase Synthesis

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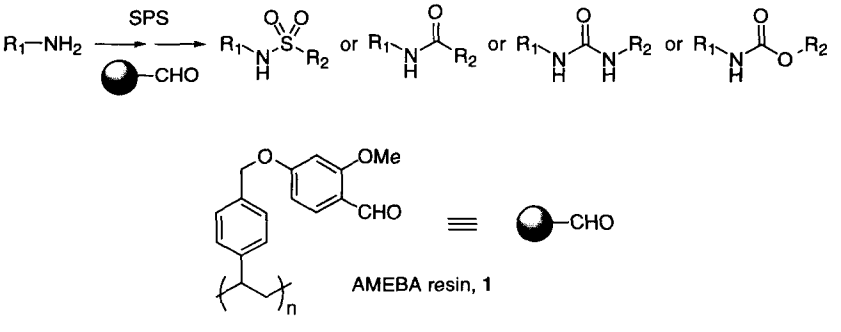
Abstract: Oxidation of 4-(3-methoxy-4-hydroxymethylphenoxy)methyl polystyrene resin produced AMEBA resin **1**, a novel acid sensitive aldehyde resin. Reductive amination of AMEBA resin generated resin bound amines which were derivatized as sulfonamides, amides, ureas, and carbamates. Cleavage of the resin under mild acidic conditions generated the derivatized amines in high purity and moderate yield. © 1997 Elsevier Science Ltd.

Sulfonamides, amides, ureas, and carbamates are important structural elements of many drug molecules. The solution phase synthesis of these functional groups commonly occurs by the combination of an amine with the requisite sulfonylating or acylating agent. By contrast, general methods for the solid phase synthesis (SPS) of these groups are limited because of the requirement for a point of attachment of the reactant to the resin.[1] A practical solution would employ a method for generation of an intermediate resin bound amine through a traceless linker that allowed cleavage of the final product under mild conditions.[2-4] For this purpose, we have developed a novel **A**cid sensitive **ME**thoxy **B**enz**A**ldehyde (AMEBA) polystyrene resin **1** that is useful for the solid phase synthesis of derivatized amines (Scheme 1).



Scheme 1. AMEBA resin for SPS.

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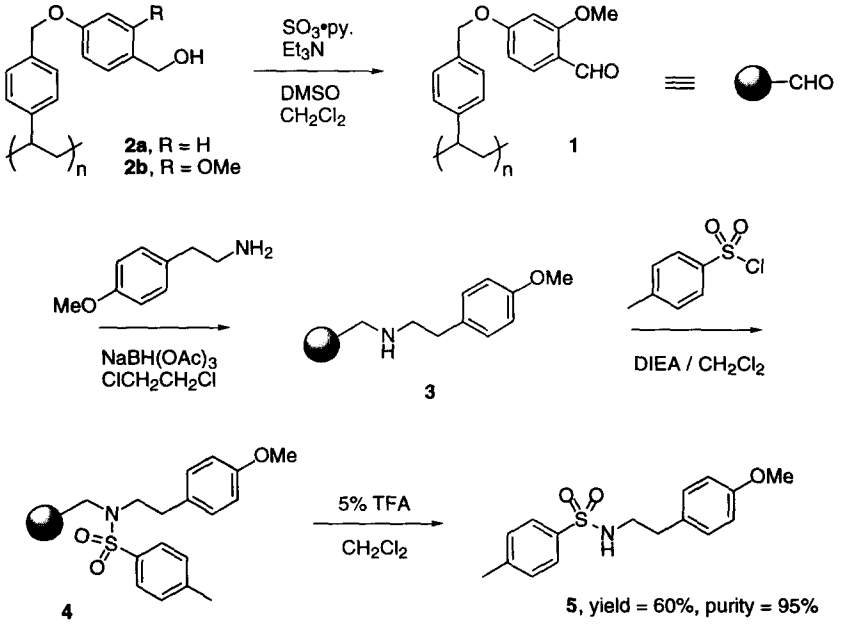
We chose to base our aldehyde resin on a high loading polystyrene resin with an acid cleavable linker. Merrifield polystyrene resin derivatized with a 4-hydroxymethylphenol linker (**2a**) has been used extensively as a trifluoroacetic acid (TFA) cleavable resin for the synthesis of peptide acids (Scheme 2).[5] Addition of an *o*-methoxy substitutent (**2b**) generates a resin which is significantly more acid labile, and is commercially available with a loading of 0.89 mmol/g under the trade name SASRIN™.[6]



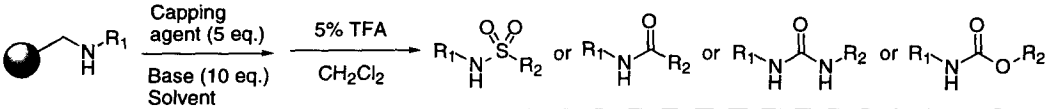
Scheme 2. Synthesis of sulfonamides using AMEBA resin.

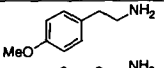
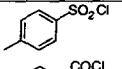
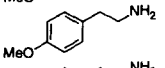
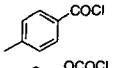
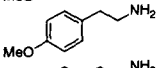
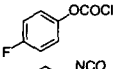
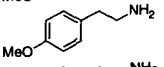
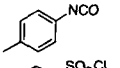
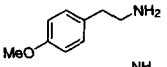
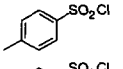
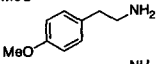
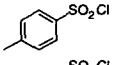
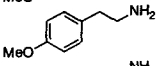
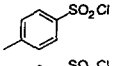
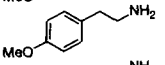
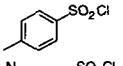
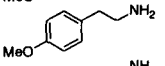
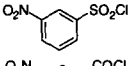
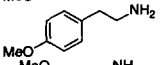
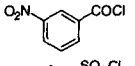
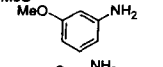
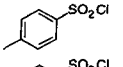
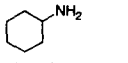
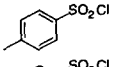
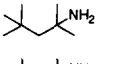
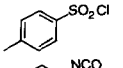
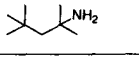
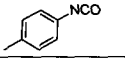
AMEBA resin **1** was generated by oxidation of resin **2b** with 5 equivalents of SO_3•pyridine complex (Scheme 2).[7] It was found that pre-drying of resin **2b** was required for efficient conversion to the aldehyde resin **1**. AMEBA resin **1** gave a diagnostic aldehyde signal at 10.5 ppm by Nanoprobe ^{1}H NMR[8] and was stable to storage at room temperature for several months, unlike the corresponding bromomethyl resin.[4,9] Reductive amination of resin **1** using a two equivalents of 4-methoxyphenethylamine and $NaBH(OAc)_3$ gave the corresponding amine resin **3**. Nanoprobe ^{1}H NMR of resin **3** showed no residual aldehyde signal and combustion analysis indicated 90-95% of the theoretical nitrogen content. Reaction of resin **3** with *p*-toluenesulfonyl chloride generated the sulfonamide resin **4**. Cleavage of the resin **4** with 5% TFA/CH_2Cl_2 produced the sulfonamide **5** in 66% isolated yield and 95% purity by HPLC and ^{1}H NMR analysis. The high purity of the final product was an unanticipated result which prompted additional studies (Table 1). In control experiments, we found that treatment of amine resin **3** with up to 95% TFA/H_2O did not result in any detectable cleavage of the resin. However, when the amine resin **3** was derivatized as a sulfonamide, amide, urea, or carbamate, cleavage of the linker occurred in 5% TFA/CH_2Cl_2 (Table 1; entries 1-4). Thus,

under the final mild acid cleavage conditions, any residual unreacted amine remained bound to the AMEBA resin and only the derivatized amine was released into solution. In practice, the final products were generated in high purity following a simple filtration and evaporation of the CH_2Cl_2 solution.

A series of studies was initiated to optimize the sulfonamide synthesis and to explore the versatility of AMEBA resin **1** for the synthesis of derivatized amines (Table 1). A diverse set of primary amines were loaded onto the AMEBA resin by reductive amination using 2 equivalents of the amine and $NaBH(OAc)_3$. In all cases loss of the aldehyde signal was observed by Nanoprobe ^1H NMR, and the resulting amine resin gave the theoretical nitrogen content by combustion analysis. Highest yields of the sulfonamide **5** were produced when DIEA, pyridine, or NMM were used as a base (entries 1, 7-8). Derivatives of electron deficient capping groups were cleaved from the resin under the strandard conditions (entries 9-10). Anilines and hindered primary amines also reacted efficiently (entries 11-14).[10]

Table 1. SPS of Derivatized Amines.



Entry	R_1-NH_2	Capping agent	Base	Solvent	Yield (%)[a]	Purity (%)[b]
1			DIEA	CH_2Cl_2	66	95
2			DIEA	DMF	79	90
3			DIEA	CH_2Cl_2	48	90
4			—	DMF	73	95
5			DBU	CH_2Cl_2	23	90
6			TMG	CH_2Cl_2	26	85
7			Pyridine	CH_2Cl_2	68	95
8			NMM	CH_2Cl_2	66	95
9			NMM	CH_2Cl_2	80	95
10			NMM	CH_2Cl_2	75	95
11			NMM	CH_2Cl_2	71	95
12			NMM	CH_2Cl_2	63	90
13			Pyridine	CH_2Cl_2	20	85
14			—	DMF	67	95

[a] Isolated yield of final product based on an initial loading of 0.89 mmol/g; [b] Purity determined by HPLC and ^1H NMR. Abbreviations: DIEA, *N,N*-diisopropylethylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TMG, tetramethylguanadine; NMM, *N*-methylmorpholine; DMF, *N,N*-dimethylformamide.

In summary, AMEBA resin **1** is a versatile acid sensitive solid support for the traceless synthesis of secondary sulfonamides, amides, ureas, and carbamates in high purity and moderate to high yield.

Preparation of AMEBA resin 1: SASRIN™ resin **2b** (Bachem Bioscience, 10.0 g, 0.89 mmol/g) was washed with DMF, MeOH, and CH_2Cl_2, and dried in a vacuum oven at 70 °C overnight. To a suspension of the dried resin **2b** in DMSO (100 ml) and CH_2Cl_2 (25 ml) was added Et_3N (12.4 ml, 10 eq.) followed by SO_3•pyridine complex (7.1 g, 5 eq.). The suspension was stirred at room temperature overnight, filtered, washed with CH_2Cl_2, DMSO, CH_2Cl_2, and THF, and dried under vacuum to give 10.0 g of aldehyde resin **1**. AMEBA resin **1** was stable to storage at room temperature for several months.

SPS of sulfonamide 5: AMEBA resin **1** (75 mg) was suspended in dichloroethane (2 ml). 4-Methoxyphenethylamine (20 mg, 2 eq.) and $NaBH(OAc)_3$ (30 mg, 2 eq.) were added. The resin was shaken for 1h, filtered and washed with CH_2Cl_2, DMF, MeOH, and CH_2Cl_2. The resulting resin was suspended in CH_2Cl_2 (1 ml). DIEA (0.12 ml, 10 eq.) and *p*-toluenesulfonyl chloride (60 mg, 5 eq.) were added. The resin was shaken for 2 h, filtered and washed with CH_2Cl_2, DMF, MeOH, and CH_2Cl_2. The resulting resin was suspended in 5% TFA/CH_2Cl_2 (1 ml). After 10 min, the resin was filtered and the filtrate was concentrated to yield 13.5 mg (66%) of the sulfonamide **5**.

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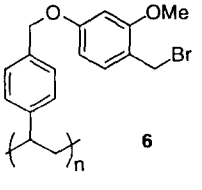
References and Notes:

1. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643-5678.
2. Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999-12000.
3. Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006-6007.
4. Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973-976.
5. Wang, S. W. *J. Am. Chem. Soc.* **1973**, *95*, 1328-1333.
6. Mergler, M.; Nyfeler, R.; Gostelli, J.; Grogg, P. *Chem. Biol., Proc. Am. Pept. Symp. 10th* **1988**, 259-260.
7. Chen, C; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661-2662.
8. Keifer, P. A. *J. Org. Chem.* **1996**, *61*, 1558-1559.
9. Bromination of resin **2b** with Ph_3P:Br_2 generated the corresponding bromomethyl resin **6** (c.f. reference 4). In our hands, resin **6** was not stable to storage at room temperature and reaction with 4-methoxyphenethylamine gave variable results.



6

10. In contrast to anilinosulfonamides, cleavage of anilinoamides from the AMEBA resin required 50% TFA/CH_2Cl_2. Similar observations have prompted the generation of "super" acid labile linkers for traceless synthesis of secondary anilinoamides: a) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742-5743. b) Holmes, C. P., Presented at the 213th National Meeting of the American Chemical Society, San Francisco, CA, April 1997; paper ORGN 383.

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