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New Synthesis of SASRIN™ Resin

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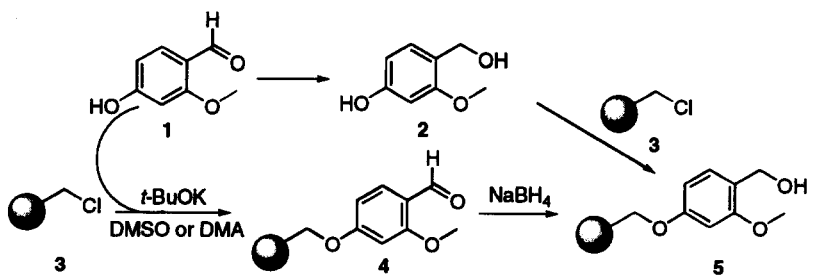
Abstract: SASRIN™ resin is synthesized by a two step sequence involving linking 4-hydroxy-2-methoxybenzaldehyde to Merrifield resin, followed by reduction with sodium borohydride.

Solid phase organic synthesis has become a powerful tool for the synthesis of small molecule libraries.[1,2] The development of new organic reactions on solid phase is dependent on the properties of the linker.[2] SASRIN™ (Super Acid Sensitive Resin) **5**,[3a] a highly acid labile polystyrene-based resin has evolved as a versatile anchor for a wide variety of transformations.[3b,4] The molecules anchored on SASRIN™ can be released under very mild conditions by treatment with 1%,[3a] 2%[4a,d] or 3%[4c,e] (v/v) TFA in CH_2Cl_2.

The synthesis of SASRIN resin **5**, as described a decade ago, comprised the reduction of 4-hydroxy-3-methoxybenzaldehyde **1** to the corresponding benzyl alcohol **2** and coupling to Merrifield resin **3**.[3a] In our hands, free alcohol **2** from the reduction of aldehyde **1** was found to be highly unstable and to polymerize easily even upon storage at 4 °C in the refrigerator. This behavior is most likely due to the fact that *p*-hydroxybenzyl alcohols are known for their instability.[5]



Scheme 1

Aldehyde **1** was expected to be stable under strong basic conditions (for example resistant to Canizzaro reaction).[6] Indeed, the potassium salt of **2** was obtained by treatment with potassium *tert*-butoxide in dry DMSO or DMA. Displacement of chlorine in Merrifield resin by the resulting phenolate afforded resin **4**[8](Scheme 1) which was characterized by gel phase ^{13}C NMR.[7] Cleavage of the resin **4** with HF(l) afforded **1** with trace amount of the corresponding acid as indicated by LC-MS of the cleaved material. Reduction of the resin aldehyde **4** with sodium borohydride in THF/NMM/ethanol = 2.5/1/1 (v/v) at room temperature for 24 hours afforded the SASRIN™ resin **5**.[9] The OH loading of resin **5** was determined to be 0.96 mmol/g.[9] An authentic sample of SASRIN™ (purchased from BACHEM) was identical to the one we synthesized in terms of spectroscopic characteristics.

Full details are now provided for the preparation of SASRIN™ resin **5** using stable reagents and intermediates which should alleviate the limitation on its use caused by the high cost of the commercial resin.

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8. *Preparation of Resin 4.* *t*-BuOK (1.12 g, 0.01 mol, ACROS) was charged to an oven-dried glass flask under argon. 4-Hydroxy-2-methoxybenzaldehyde (1.52 g, 0.01 mol) was added, the air was replaced with argon and dry DMA (20 mL) was added *via* a syringe. The yellow solution was stirred for 10 min. Merrifield resin (1.1 mmol/g, 100-200 mesh, 3 g, 0.0033 mol, NovaBiochem) was charged to an oven-dried glass flask with a magnetic stirring bar. The resin was swollen in DMA (14 mL) under argon for 20 min. The yellow solution was transferred *via* canula to the reaction flask. During addition, the solution was gently stirred. The reaction flask was immersed into a silicon oil bath heated at 90 °C. A complete rotation of the stirring bar was performed every 30 min. After 4 hours the temperature was lowered to 50 °C in 40 min and the reaction mixture was kept without stirring for additional 10 hours. The resulting slurry was cooled to rt, and filtered through a frit-glass funnel. The resin was washed on the frit with: water (2 × 30 mL), MeOH (2 × 30 mL), THF (2 × 30 mL), water-THF (2:1) (2 × 30 mL), water (2 × 30 mL), THF (2 × 30 mL) and MeOH (2 × 30 mL). The remaining resin was dried under high vacuum for 8 hours at rt. to afford 3.35 g white resin. ^{13}C NMR ($CDCl_3$) δ (ppm) 55.5 (CH_3), 70.3 (CH_2O), 98.7, 106.4, 119.1, 130.6, 163.5, 165.3, 188.1 (CHO). FT-IR (KBr, cm^{-1}): 1680 (CHO).
9. *Preparation of SASRIN™ Resin 5.* Resin **4** (2.50 g, 0.0024 mol) was charged to an oven-dried 50 mL Erlenmeyer flask. Dry THF (16 mL), NMM (7 mL) and ethanol (7 mL) were added and, after shaking for 20 min, sodium borohydride (0.378 g, 0.01 mol) was added and the flask was shaken under argon (with a balloon), at rt for 24 hours. The contents of the flask were filtered through a frit-glass funnel. The resin was treated on the frit with water (5 × 30 mL) then washed with: MeOH (2 × 30 mL), twice with THF (2 × 30 mL), water (2 × 30 mL), THF (2 × 30 mL) and MeOH (2 × 30 mL). The resulting white resin was dried under high vacuum at rt overnight to give 2.48 g white resin. ^{13}C NMR ($CDCl_3$) δ (ppm) 55.2 (CH_3O), 61.3 (CH_2OH), 70.0 (CH_2O), 99.2, 104.6, 121.8, 129.6, 158.5, 159.9. FT-IR (KBr, cm^{-1}): 3588 (OH). The OH loading of the resin was determined by linking Fmoc-β-alanine with DIC/DMAP and UV spectrophotometric (λ = 290 nm) quantitative determination of Fmoc release upon treatment with piperidine/DMF = 1/4 (v/v) and the adequate mass correction: 0.96 mmol/g.
10. *Abbreviations*: DMA: *N,N*-dimethylacetamide; NMM: *N*-methylmorpholine; DIC: diisopropylcarbodiimide; DMAP: *N,N*-dimethyl-4-aminopyridine.

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