



Facile Preparation of Chloromethylaryl Solid Supports Using Methanesulfonyl Chloride and Hunig's Base

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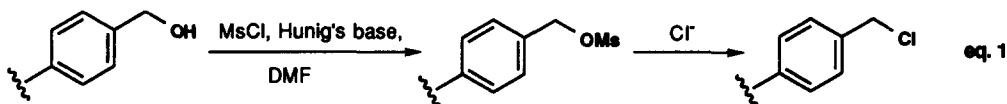
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Abstract: Several commercially available hydroxymethylaryl resins were converted to their corresponding chloromethyl analogs by simple treatment with methanesulfonyl chloride and Hunig's base in DMF at 25 °C over 3 days. This mild method gave quantitative conversions as determined by elemental analysis and ¹³C NMR.

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The use of solid-phase organic chemistry has become routine in many research settings. There is a constant search for adapting different types of chemistry to solid-supports.¹ One approach to this goal is expanding the limited supply of commercially available solid-supports. A previous report by Mergler² disclosed a method for converting Wang³ and SASRIN⁴ resins to their corresponding chloromethylaryl analogs. This allowed loading amino acids onto the resin and subsequently coupling the amino acids with minimal racemization. Employing triphenylphosphine dichloride⁵ to perform this conversion gave variable results and only in one case quantitative conversion to the desired chloromethylaryl resin. We wish to disclose a superior method of preparing chloromethylaryl resins which consistently gives quantitative conversions.

The method involves treating a suspension of the resin in DMF with methanesulfonyl chloride pretreated with diisopropylethylamine as shown in eq. 1. The starting benzylic alcohol is initially converted to the intermediate mesylate which is subsequently displaced by chloride ion to give the desired benzyl chloride in quantitative yield.




A typical procedure using Wang resin is as follows: Wang resin (3.0 g, 0.9 mmol/g, 2.7 mmol) was suspended in dry DMF (25 mL) to which diisopropylethylamine (1.9 mL, 10.8 mmol) was added in one portion at room temperature. After 5 min., methanesulfonyl chloride (0.78 mL, 8.1 mmol) was added via syringe over 1 min. The addition causes an exothermic reaction. After 3 days, the resin was filtered and washed with DMF (2 X 20 mL), methanol (2 X 20 mL), and dichloromethane (2 X 20 mL). The resin was then dried in a vacuum oven at 60 °C overnight. The amount of resin recovered was 2.95 g. Elemental analysis calculated for chlorine: 3.19; found: 3.27. Elemental analysis did not detect any nitrogen indicating all the chlorine observed came from the resin.⁶ The IR spectrum showed no OH stretch indicating complete disappearance of the benzylic alcohol. The ¹³C NMR showed the complete disappearance of the hydroxymethyl benzylic carbon at 64.5 ppm with a new signal at 46.3 ppm corresponding to the newly formed chloromethyl benzylic substituent. The resin is stable at room temperature and can be stored indefinitely in a closed container.

Table 1 shows the method's versatility across several solid-support types. Care must be taken to dry the Tentagel resin by lyophilization for 24 hours prior to subjecting it to the reaction conditions.⁷ In the examples shown, quantitative conversions were obtained as determined by elemental analysis⁸ and ¹³C NMR. The mild reaction conditions are most evident by the quantitative conversion of SASRIN resin to its corresponding

chloromethyl derivative. The use of DMF was critical to the success of this procedure. The reaction did not proceed at all when CH_2Cl_2 or THF was employed. Stopping the reaction at less than 3 days showed incomplete conversion. This was not detrimental as the resin could be resubjected to the reaction conditions, driving the reaction to completion.

Table 1.



Resin	reaction time (hr)	conversion (%) ^a	¹³ CNMR shift (ppm) ^b
Wang	72	100	46.3
SASRIN	72	100	48.1
Photocleavable AM ^c	24	90	44.3
Photocleavable AM	72	100	
Photocleavable TG ^d	72	100	43.7

^a Determined by elemental analysis for chlorine and nitrogen. ^b Corresponds to the chemical shift of the chloromethyl carbon determined by magic angle solid-phase NMR. ^c Hydroxymethyl-Photolinker AM resin.⁹ ^d Hydroxymethyl-Photolinker NovaSyn[®] TG resin.⁹

In conclusion, we have presented a simple and efficient method for converting hydroxymethylaryl-based resins to their corresponding chloromethylaryl derivatives using methanesulfonyl chloride and Hunig's base. This method should expand the utility of available hydroxymethylaryl resins. We are in the process of using these resins for nucleophilic displacement reactions and those results will be reported in due course.

References and notes.

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- Inefficient removal of diisopropylethylamine hydrochloride would result in erroneous chlorine content determination. The lack of any elemental nitrogen indicates these salts were efficiently removed in the washing process.
- No reaction was observed without prior drying of the resin.
- Chlorine analysis allowed for conversion determination based on the initial resin loading level.
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