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5-(4'-Chloromethylphenyl)pentylpolystyrene Resin (CMPP resin). A New Linker Resin for Solid-Phase Organic Synthesis Under Lewis Acidic Conditions

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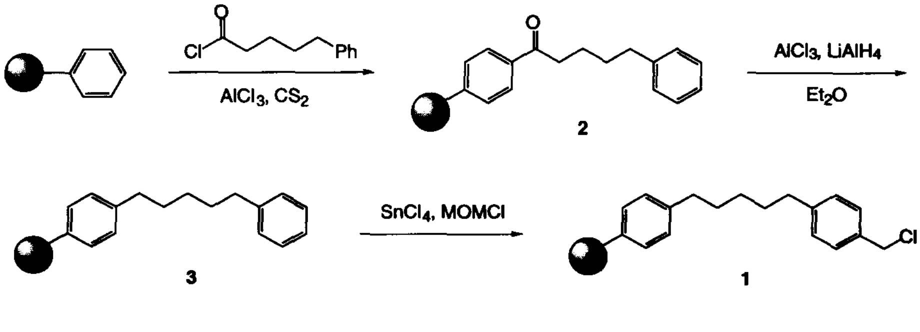
Abstract: *A new linker resin for solid-phase organic synthesis under Lewis acidic conditions has been developed. The resin, 5-(4'-chloromethylphenyl)pentylpolystyrene resin (CMPP resin), has no oxygen or nitrogen atoms in its spacer moiety. Imino aldol reactions of polymer-supported silyl enol ethers using the new resin with imines were demonstrated in the presence of a Lewis acid, and it was shown that the yields using CMPP resin were much higher (ca. 10-30%) than those using Merrifield resin.* © 1997 Elsevier Science Ltd.

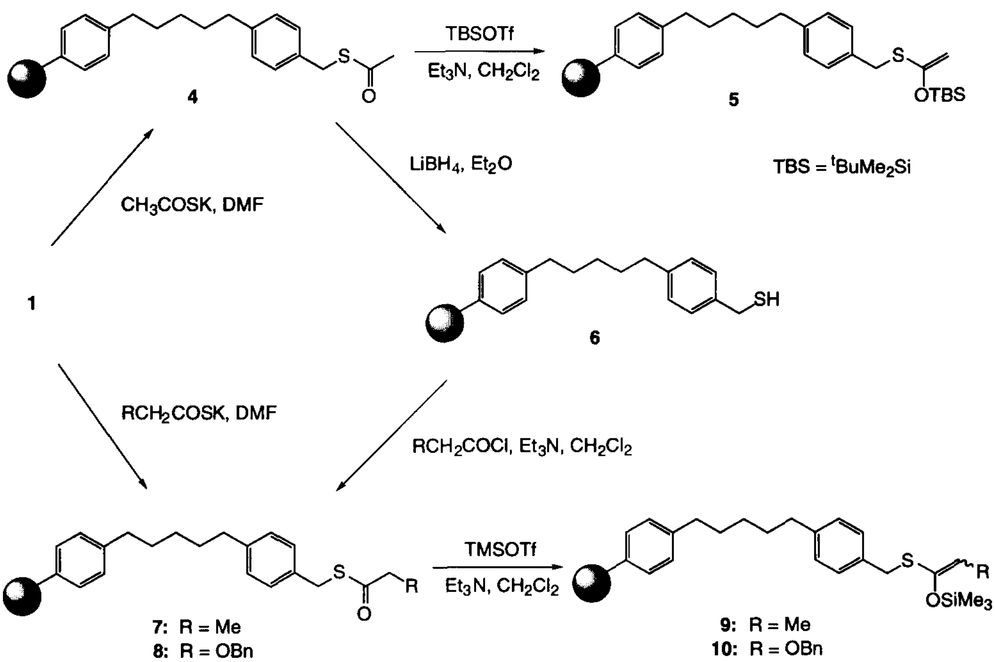
The proper choice of supports and linker groups is among the most important factors in the success of organic synthesis on solid supports.[1] Although several linkers have already been developed, these are mostly optimized for biopolymer synthesis such as peptides and oligonucleotides, and unsatisfactory results are sometimes obtained in the reaction sequences possible on supports. For example, almost all linkers developed contain oxygen and/or nitrogen atoms including ether, ester, and amide functional groups, which coordinate Lewis acids to be decomposed or deactivated.[2] Hence, these linkers can not be used in Lewis acid-promoted reactions, which provide numerous useful transformations in liquid-phase organic synthesis.[3] In the course of our program on the development of Lewis acid-catalyzed reactions on solid-phase,[4] we were confronted with the above problem. In this paper, we describe a new linker resin, 5-(4'-chloromethylphenyl)pentylpolystyrene resin (CMPP resin), which can be successfully used in Lewis acid-promoted reactions on solid-phase.[5]



Scheme 1. Preparation of New Linker Resin 1

We chose carbon atoms instead of nitrogen or oxygen atoms in the new linker, and methylene groups were used as a spacer. The synthetic scheme of the new linker, CMPP resin (**1**), is shown in Scheme 1. Friedel-Crafts acylation[6] of copoly-(styrene-1%-divinylbenzene) resin (200-400 mesh) with 5-phenylvaleryl chloride was carried out using aluminum chloride in carbon disulfide. The resulting acylated resin **2** was reduced using $AlCl_3$-LAH[7] in ether to afford 5-phenypentyl resin **3**. Finally, **3** was chloromethylated under standard conditions to afford CMPP resin (**1**).

The evaluation of the new linker resin was carried out by the imino aldol reactions of polymer-supported silyl enol ethers with imines.[4a] The polymer-supported silyl enol ethers of CMPP resin were prepared according to Scheme 2. The results of the imino aldol reactions of the silyl enol ethers derived from the polymer-supported thioacetate (**4**) with *N*-benzylideneaniline are summarized in Table 1. CMPP resin gave higher yields than Merrifield and Wang resins.[8] The loading levels of the enolate moieties in CMPP resin were also examined, and it was found that the best results were obtained by using CMPP resin having a 0.96 mmol/g loading level, which was prepared by using 2.0 mmol/g of the acylating reagent in the Friedel-Crafts acylation (Scheme 1).



Scheme 2. Synthesis of Polymer-Supported Silyl Enol Ethers Using Novel Linker Resin **1**

We then tested several examples of the $Sc(OTf)_3$-catalyzed imino aldol reactions using CMPP resin, and the results are shown in Table 2. In all cases, the yields of the desired adducts (amino alcohols) using CMPP resin were much higher (ca. 10-30%) than those using Merrifield resin. These results indicate the effectiveness of the new linker resin.

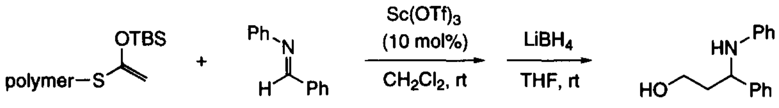
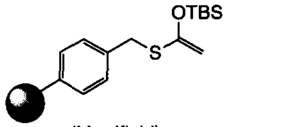
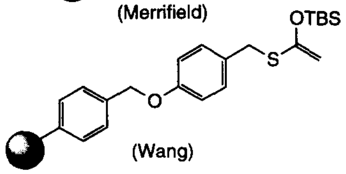
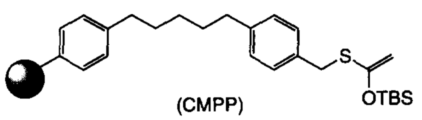


Table 1. Effect of Linker Resin

Polymer-supported Silyl Enol Ether	Loading Level /mmol/g	Yield/%
 (Merrifield)	1.15	53
 (Wang)	0.71	57
 (CMPP)	1.82[a]	62
	1.15[a]	67
	0.96[b]	74
	0.83[b]	71

a) 5.1 mmol/g of 5-phenylvaleryl chloride was used in Scheme 1. b) 2.0 mmol/g of 5-phenylvaleryl chloride was used in Scheme 1.

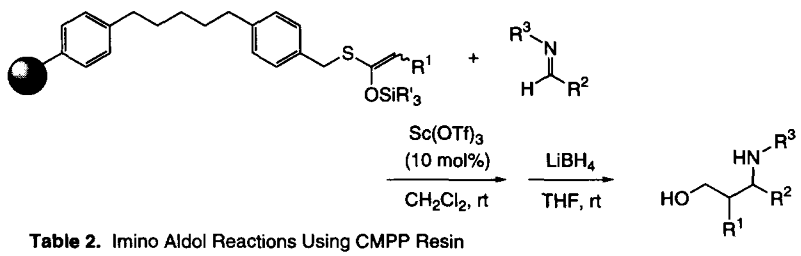


Table 2. Imino Aldol Reactions Using CMPP Resin

R^1	R^2	R^3	SiR'_3	Yields/% (CMPP)	(Yield/% (Merrifield))[a]
H	Ph	Ph	TBS	**74**	(53)
H	p-ClPh	Ph	TBS	**72**	(60)
Me	Ph	Ph	$SiMe_3$	**90**	(78)
Me	Ph	p-MeOPh	$SiMe_3$	**96**	(64)
Me	2-furyl	Ph	$SiMe_3$	**quant.**	(68)
OBn	Ph	Ph	$SiMe_3$	**96**	(67)
OBn	Ph	p-MeOPh	$SiMe_3$	**93**	(66)
OBn	2-furyl	Ph	$SiMe_3$	**90**	(77)

a) Cf. Ref. 4 (a).

In summary, we have developed a new linker resin, CMPP resin, for solid-phase organic synthesis under Lewis acidic conditions. $Sc(OTf)_3$-catalyzed imino aldol reactions of polymer-supported silyl enol ethers using the new resin with imines were demonstrated. CMPP resin is readily prepared and will be useful for many organic reactions on solid-phase.

Preparation of CMPP resin

To copoly-(styrene-1%-divinylbenzene) resin (200-400 mesh, 5.0 g) and $AlCl_3$ (10.0 mmol) in carbon disulfide (30 ml) was slowly added 5-phenylvaleryl chloride (10.0 mmol) at 0 °C. The mixture was heated under reflux for 8 h to afford 2-oxo-5-phenylpentyl resin **2**. **2** (5.0 g) was then treated with $AlCl_3$ (40.0 mmol) in ether (100 ml) at rt and then cooled to 0 °C. $LiAlH_4$ (10.0 mmol) and ether (60 ml) were carefully added at rt and the mixture was reacted at the same temperature for 15 h to give 5-phenypentyl resin **3**. Finally, chloromethyl methyl ether (MOMCl, 5.5 ml) and tin (IV) chloride (0.12 mmol) in MOMCl (0.5 ml) was added to **3** (1.0 g) at rt. The mixture was reacted for 2 h to afford CMPP resin (**1**) (0.96 mmol/g).

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