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Polystyrylsulfonyl chloride resin: an efficient solid-supported condensation reagent for the solution phase synthesis of esters

N. Zander and R. Frank*

AG Molecular Recognition, GBF (German Research Center for Biotechnology) Mascheroder Weg 1, D-38124 Braunschweig, Germany

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Abstract—We describe the use of the readily available polystyryl sulfonyl chloride resin in the solution-phase synthesis of esters from carboxylic acids and alcohols or phenols in high yields and purity. All byproducts can be removed by filtration.

Although solid-supported reagents and scavengers have been used in organic synthesis for decades, it was the development of combinatorial and parallel high throughput synthesis techniques that brought this class of reagents to a wider attention. The first compound collections were based on peptides and oligonucleotides, that were stepwise assembled on a solid support,[1] following the concept developed by Merrifield.[2] Despite the success of adapting this method to the general organic synthesis in recent years, there are also severe limitations to this approach. Especially, the development of a suitable reaction scheme is often a time-consuming process. The limitations of the different solid-supports and linkers have to be taken into account and the available techniques to monitor solid-supported reactions are not as convenient and rapid as the solution-phase methods. The application of solid-supported reagents and scavengers for the solution-phase organic synthesis on the other hand combines the simple work up by filtration with a fast reaction optimization. Their use in multi-step organic synthesis has been recently reviewed.[3]

While there are numerous applications of solid-supported reagents and scavengers only a few examples for the formation of esters were described. Solid-supported acids were used as catalysts in the esterification of carboxylic acids with alcohols.[4] Carboxylates, generated with solid-supported organic bases, were alkylated with alkyl halides.[5] However, in an automated parallel alkylation of α-bromo ketones with carboxylic acids described by Warmus et al., solid-supported bases were inferior to soluble ones and the use of polystyrene-bound thiols as scavenger resin for bromo ketones failed.[6] Solid-supported organic bases were also used as scavenger resins in the esterification of benzyl alcohol with benzoyl chlorides, giving clean benzyl esters in high yields.[7] This approach requires the acid chloride to be available. A modification of the Mitsunobu reaction with resin-bound triphenylphosphine and soluble di-*t*-butylazodicarboxylate was described, that allowed for the isolation of pure products without chromatography.[8] The work-up process is rather lengthy, involving a filtration and an aqueous extraction step and the required pretreatment with TFA restricts the range of possible compounds accessible by this approach. A polymer-supported carbodiimide has been used so far for the esterification of carboxylic acids with the more reactive *N*-hydroxysuccinimide or pentafluorphenol only.[9] A very recent report describes the alkylation of carboxylic acids with carbenium ions, generated from polymer-supported triazines, for the ester-formation.[10] The necessary acid catalysis is provided by the carboxylic acids itself, so no further catalysts have to be added and removed from the product. This approach, however, requires the preformation of the polymer-supported triazine for each alkyl group to be transferred and a relatively high excess of the alkylating resin. No examples for the formation of aryl esters are given.

We report here a convenient and general procedure for the synthesis of esters from carboxylic acids and alco-

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* Corresponding author. Fax: +49 (0)531 6181795; e-mail: rfr@gbf.de

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hols employing the commercially available polystyrylsulfonyl chloride resin[11] as the solid-supported condensation reagent. Although the base-catalyzed ester formation by sulfonyl chlorides was described long ago.[12,13] the polymer-supported equivalent of *p*-toluenesulfonic chloride has been applied primarily as scavenger resin for nucleophiles and as the activating reagent for alcohols in the 'Catch and release' synthesis of secondary and tertiary amines, thioethers and *N*-alkylimidazoles.[14] We found only one brief note by Patchornik on the preparation of carboxylic acid -OBt esters.[15]

Dichloromethane (DCM) was the solvent most compatible with the reagents and resin. *N*-Methylimidazole (MeIm) was chosen as the base. This combination was found superior for the esterification of Fmoc-amino acids to solid supported alcohols by MSNT, a reactive sulfonic acid azolide.[16] Table 1 shows the influences of the excess of base and sulfonyl chloride resin on the esterification of Fmoc-glycinol **2** with acetic acid **1** (Scheme 1a, R = Me). The reaction rate is strongly influenced by the excess of base used. At least 3 equiv. of base are necessary for a complete conversion after 1 h (entries 1–5), while only a slight excess of resin is sufficient (entries 6–8). Independent of the reaction conditions, the ester **3** is formed without any traces of byproducts. For all the following experiments, 4 equiv. of MeIm and 1.3 equiv. of resin were used.

Table 1. Influences of the excess of base and sulfonyl chloride resin[a]

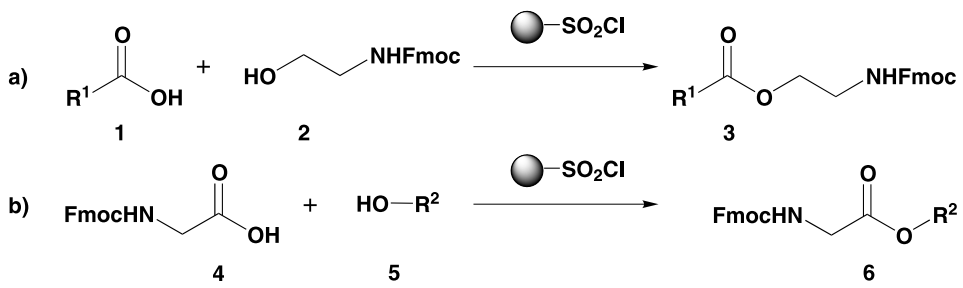
Entry	Equiv. of MeIm	Equiv. of resin[b]	Conversion[c,d]
1	0.75	2	91+9
2	1.3	2	77+23
3	2	2	30+70
4	3	2	0+100
5	5	2	0+100
6	4	1.1	1+99
7	"	1.3	0+100
8	"	1.5	0+100

[a] 0.0706 mmol Fmoc-Gly-ol, 1.5 equiv. acetic acid, 1 ml abs. DCM.
[b] Based on the loading given by the supplier.
[c] Crude product: percent alcohol and percent product by HPLC after 60 min.
[d] All compounds were characterized by HPLC-ESI-MS.

We examined the scope of our procedure by reacting six carboxylic acids **1** with Fmoc-glycinol **2** (Scheme 1a) and seven alcohols **5** with Fmoc-glycine **4** (Scheme 1b). The results are summarized in Table 2. The purity of all the different esters **3** derived from Fmoc-glycinol (entries 1–6) was very good (>93%), while the reaction time necessary for a complete conversion varied considerably. The sterically hindered pivalic acid and the electron rich 4-acetamidobenzoic acid did not react completely even after 22 h. The electron poor 3-nitrobenzoic acid was the fastest to react. All products **6** of the esterification of Fmoc-glycine (entries 7–13) with different alcohols and donor or acceptor substituted phenols were essentially 100% pure, except for *tert*-butanol, which reacted only after the addition of 0.25 equiv. of DMAP. The conversion was slow, but the resulting ester was of good purity.

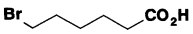
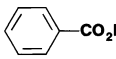
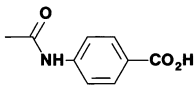
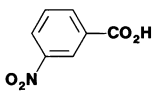
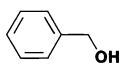
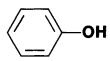
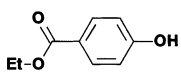
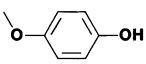
To establish a simple work-up procedure, we applied an excess of carboxylic acid to drive the esterification reaction to completion.[17] When HPLC analysis showed complete conversion of the Fmoc-glycinol, aminomethylated polystyrene resin was added to remove the excess of Fmoc-glycine. After filtration, the base was removed with the acidic ion-exchange resin Amberlyte 15 to give the expected ester in 93% isolated yield and 100% purity by HPLC. ^{1}H NMR showed the ester to be accompanied by only 5 mol% of remaining *N*-methylimidazole.

In summary, we demonstrated the use of polystyrylsulfonyl chloride resin as an efficient dehydration reagent for the formation of esters from carboxylic acids. The reaction works equally well with alcohols and phenols. The method uses only commercially available supported reagents and scavengers and allows compounds to be obtained in excellent yields and high purity by simple filtration. Exploitation of this reagent to improve the performance of other dehydration reactions is under investigation.



Scheme 1.

Table 2. Scope of the reaction

Entry	Carboxylic acid	Alcohol	Purity[c, d]	Reaction Time
1		Fmoc-Gly-ol[a]	100	60 min
2		"	98 (2)	22 h
3		"	100	30 min
4		"	94	60 min
5		"	93 (7)	22 h
6		"	100	15 min
7	Fmoc-Gly-OH[b]		100	30 min
8	"		100	30 min
9	"		87	22 h[e]
10	"		100	30 min
11	"		100	30 min
12	"		98	30 min
13	"		100	30 min

a) 0.0706 mmol Fmoc-Gly-ol, 1.3 eq. carboxylic acid, 1.3 eq sulfonyl chloride resin, 4 eq. MeIm 1 ml abs. DCM; b) 0.0673 mmol Fmoc-Gly-OH, 1.3 eq. alcohol, 1.3 eq sulfonyl chloride resin, 4 eq. MeIm 1 ml abs. DCM; c) HPLC of the crude product, percent starting material in parenthesis; d) all compounds were characterised by HPLC-ESI-MS or ^{1}H-NMR, e) 0.25 eq. DMAP added

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17. Typical procedure: To a mixture of 20 mg (0.0706 mmol) Fmoc-glycinol, 27.3 mg (1.3 equiv.) Fmoc-glycine and 61.6 mg (1.3 equiv.) of polystyrylsulfonyl chloride resin (1.49 mmol/g) in 1 mL abs. DCM, 22.5 μl *N*-methylimidazole were added. After 2 h 138 mg (2 equiv.) aminomethylated polystyrene resin and 1 mL DCM were added and the suspension was shaken for 30 min. After filtration through a syringe equipped with a polypropylene frit, the resin was rinsed thoroughly with DCM and the combined eluents were concentrated to roughly 3 ml. Amberlyte 15 (176 mg) was added and the suspension was shaken again for 30 min and filtered as described. After evaporation of the solvent the pure product was obtained as a colorless foam in 93% yield (37.1 mg).