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PhFl Polystyrene: A New Resin for Solid Phase Organic Synthesis

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Abstract: *A 9-phenylfluoren-9-yl polystyrene based resin is described for the attachment of nitrogen and oxygen nucleophiles. Higher acid stability compared to standard trityl resins makes this solid support an interesting alternative in solid phase organic synthesis (SPOS). Several applications are shown and the results concerning yield and crude product purity are discussed below.* © 1998 Elsevier Science Ltd. All rights reserved.

With the growing impact of combinatorial chemistry in the drug discovery process, solid phase organic synthesis is increasingly becoming a routine technology in pharmaceutical research laboratories.[1] Pioneered by peptide and oligonucleotide chemists, this technique has been used for over three decades but the potential for synthesizing small organic molecules has been mostly overlooked until recently. Therefore, most of the resins used in solid phase organic synthesis originate from solid phase peptide synthesis (SPPS) and result in carboxy modified compounds like carboxylic acids (e.g. Wang resin) or primary amides (e.g. Rink resin). The 2-chlorotrityl resin is widely used in SPPS due to convenient loading without racemization of the first amino acid and very mild cleavage conditions making the synthesis of protected peptide fragments possible.[2] The attachment of other nucleophiles like alcohols[3] and amines[4] are also described with this resin type making it very interesting for solid phase combinatorial chemistry. For small molecule organic synthesis the acid lability of the trityl resins is often a drawback since even mildly acidic synthetic conditions are often incompatible with the linkage to the support. We were interested in a resin type that shows the broad applicability of the trityl resins for the attachment of different nucleophiles, high protecting group efficiency and ease of synthesis but possessing higher acid stability than the trityl supports.

The 9-phenylfluoren-9-yl group (PhFl) has been described by Rapoport[5] as a protecting group for primary and secondary amines. While the efficiency as a protecting group is comparable to the trityl group, its acid stability is about 6000 times higher than trityl due to the antiaromatic character of the fluorenyl cation produced upon acid cleavage.[6] The similarity of the PhFl group to the trityl group lead us to develop a phenylfluorenyl based polystyrene resin as a new support for solid phase organic synthesis and combinatorial chemistry. The preparation of the resin and some applications are described herein.

Based on the fundamental work on polystyrene resin modifications by Fréchet[7] PhFl polystyrene was synthesized in analogy to the procedure for the trityl resin preparation using 9-fluorenone as the ketone instead of benzophenone. Starting from a 2% crosslinked polystyrene resin the PhFl derived support was obtained using the 'direct lithiation strategy' as shown in Scheme 1.[8] A loading of 1.4-1.6 meq/g was obtained as determined by the weight increase of compound **1** and elemental analysis of the corresponding activated compound **2**. This activated resin was loaded with several nitrogen and oxygen nucleophiles. The immobilized compounds were then chemically modified and cleaved under appropriate conditions depending on the stability of the linkage to the solid support.

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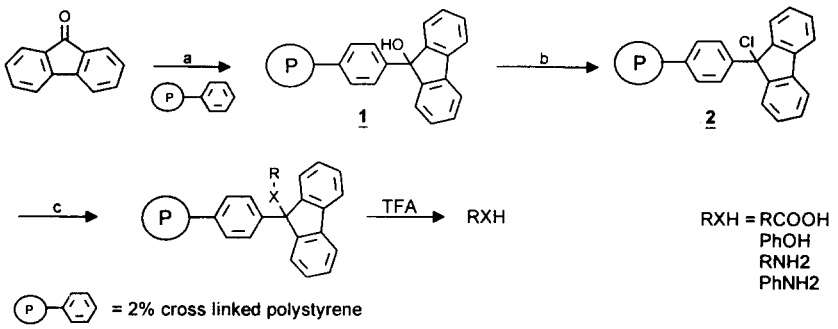
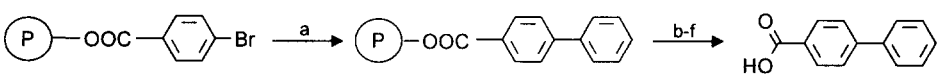


Scheme 1: *Preparation, activation and immobilization of nucleophiles onto PhFl polystyrene resin. The compounds are cleaved under TFA treatment. a) n-Butyl lithium b) 20% Acetyl chloride c) Nucleophile*

To investigate the improved acid stability compared to the trityl resins, 4-bromobenzoic acid was loaded onto the activated PhFl resin **2**.[9] The immobilized compound was derivatized by Suzuki coupling leading to the corresponding biphenyl product.[10] Five 40 mg portions of this resin were then treated under five different acidic conditions for 30 min as shown in Scheme 2. The cleavage solutions were filtered, evaporated and the resulting material weighed and analyzed by HPLC. While carboxylic acids are cleaved quantitatively from trityl resins under very mild conditions (dilute acetic acid or hexafluoroisopropanol)[2] less than 5% cleavage was observed from the PhFl resin after treatment with up to 5% TFA for 30 min.



a) $PhB(OH)_2$, $Pd(PPh_3)_4$, b-f) Acidic treatment (see below)

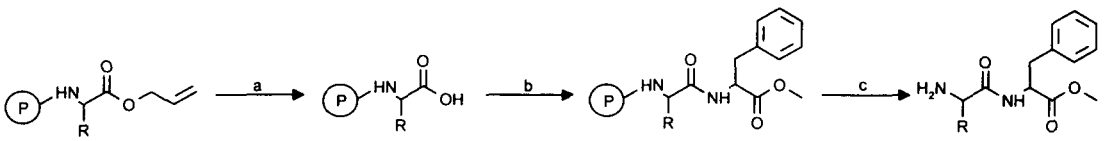
P = PhFl polystyrene

Acidic Conditions	50%Acetic Acid/CH_2Cl_2	2%TFA CH_2Cl_2/MeOH	5%TFA CH_2Cl_2/MeOH	20%TFA CH_2Cl_2/MeOH
Yield (crude)	-	-	0.5mg (4%)	7.3mg (68%)

Scheme 2: *Crude yield of 4-phenyl benzoic acid after acid treatment for 30 min. For TFA cleavage a solvent mixture of methylene chloride and methanol (9:1) was used.*

Quantitative cleavage was obtained with 20% TFA in CH_2Cl_2/MeOH (9:1) in 2h with a crude product purity of > 95% as determined by HPLC and MS. The compound was also co-injected with commercially available material for further structure confirmation. For yield determination 250 mg of resin was treated with 20% TFA for 2h. The resulting material (white crystalline product, HPLC purity > 95%) was further purified by Kieselgel chromatography with a final yield of 88% of theory (based on a loading of 1.6 meq/g). As a second oxygen nucleophile, 4-bromophenol was immobilized[9] and Suzuki coupling and cleavage (20% TFA in CH_2Cl_2/MeOH(9:1)/2h) gave a white crystalline product in excellent purity (> 95% HPLC). After additional Kieselgel chromatography 32% of 4-phenyl phenol was recovered. The compound was again identified by MS and HPLC co-injection with commercially available material. A parallel experiment using 2-chlorotrityl resin gave the same modest yield but the PhFl resin may offer the advantage of higher acid stability in some situations.

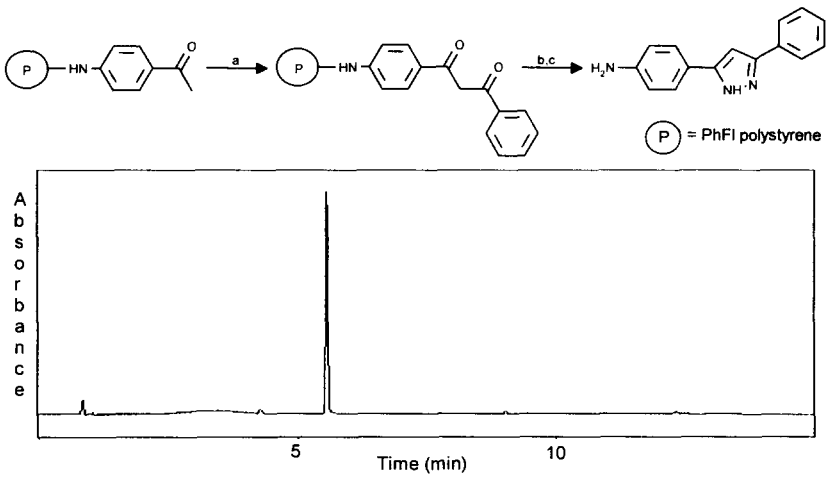
To demonstrate the utility of the PhFl resin for immobilizing N-nucleophiles an inverse peptide ester synthesis was performed by loading amino acid allyl esters via their N-terminus onto PhFl polystyrene. Four different amino acid allyl esters (Val, Ile, Leu and Phe) were loaded by adding the appropriate toluenesulfonate salts in DMF/NMM.[11] Allyl ester cleavage and 'inverse' coupling of phenyl alanine methyl ester gave the corresponding dipeptide esters.[12] The compounds were cleaved by 95% TFA/water overnight. Scheme 3 shows the HPLC purities and crude product yields of the dipeptide esters.



Dipeptide Ester	Crude Yield	HPLC Purity (Crude)	MS (Electrospray)
Val-PheOMe	95%	> 95%	279 (MH+)
Ile-PheOMe	77%	> 95%	293 (MH+)
Leu-PheOMe	82%	> 95%	293 (MH+)
Phe-PheOMe	90%	> 95%	326 (MH+)

Scheme 3: *'Inverse' peptide ester synthesis on PhFl polystyrene.*

As an example for the immobilization of anilines, 4-aminoacetophenone was loaded onto the PhFl polystyrene.[13] To achieve a lower loading only 0.7 eq of nucleophile was added to the activated resin to yield a theoretical loading of 1.0 meq/g. Unreacted PhFl chloride was quenched with methanol. Claisen condensation and cyclization with hydrazine as described by Marzinzik and Felder[14] gave the corresponding pyrazole derivative in an HPLC crude product purity of > 95%. Scheme 4 shows the HPLC chromatogram of the crude product. The sample was purified by Kieselgel chromatography with a final yield of 78% based on an estimated loading of 1.0 meq/g. Identification of the product was obtained by MS and ^{1}H-NMR.



Scheme 4: *HPLC chromatogram of crude product pyrazole synthesized via immobilized anilines on PhFl resin. a) Methyl benzoate/sodium hydride, b) Hydrazine c) 20% TFA/CH_2Cl_2/MeOH(9:1) for 2h.*

For more basic amines only about 5-10% of product is recovered after treating the PhFl resin with TFA. Improved cleavage conditions and immobilization of additional nucleophiles are under investigation. The corresponding linker system has been synthesized and is described in the following paper in this issue.

In summary, the preparation and application of a PhFl modified polystyrene resin for SPOS is shown. The higher acid stability in comparison to 2-chlorotrityl resin is demonstrated for immobilized carboxylic acids. Phenols, amino acid esters and anilines are immobilized, modified, and the products cleaved by TFA treatment in high purity and moderate to high yield.

Acknowledgment

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References and Notes

(All wash steps use the appropriate volume of the indicated solvent to create a resin slurry)

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8. 25g of 2% cross-linked polystyrene resin (200-400 mesh) were extensively washed and dried as described in ref. 7. The dry resin was suspended in 200 ml dry cyclohexane. 40 ml of TMEDA and 100 ml 2.0M butyl lithium/cyclohexane were added. The suspension was stirred under nitrogen atmosphere for 4 1/2h at 65°C. Excess of reagent was removed and the resin was washed with dry cyclohexane (x 4). 37g 9-fluorenone were dissolved in 150 ml dry benzene and added to the resin. A slight exothermic reaction was observed. After stirring for 2h the resin was washed as described and dried under vacuum. For activation the resin was treated with 20% acetyl chloride/CH_2Cl_2 for 6h. The resin was washed twice with CH_2Cl_2 and dried under vacuum overnight.
9. *Loading of oxygen nucleophiles:* 10 eq of nucleophile (4-bromobenzoic acid 4-bromophenol) were dissolved in DMF. 10 eq of N-Methylmorpholine (NMM) were added and the mixture added to the activated resin. After stirring for 4d at 80°C the reaction was quenched with methanol and the resin washed with DMF, MeOH and CH_2Cl_2 (3 x each).
10. *Suzuki cross-coupling:* 2 eq of phenyl boronic acid, 2.5 eq of Na_2CO_3 (2M aq. solution) and 0.05 eq tetrakis(triphenylphosphine) palladium were added in DME for 16h at 80°C. The resin was rinsed with DME/ water, sodium diethyldithiocarbamate/DIPEA (1:1) in DMF (20 mmol), DMF, MeOH and CH_2Cl_2 (3 x each). For Suzuki coupling on solid support also see: Frenette, R.; Friesen, R.W. *Tetrahedron Lett.*, **1994**, *35*, 9177
11. *Loading of amino acid allyl ester:* 3 eq of the corresponding amino acid allyl ester toluenesulonate salts were dissolved in DMF by adding 5 eq of NMM. This solution was added to the activated resin and stirred for 20h at 80°C. The reaction was quenched with methanol and the resin washed with DMF, MeOH and CH_2Cl_2 (3 x each).
12. *Allyl ester cleavage:* 0.2 eq $Pd(PPh_3)_4$ and 10 eq morpholine were dissolved in CH_2Cl_2 and added to the resin for 2h. The resin was rinsed with CH_2Cl_2, a solution of sodium diethyldithiocarbamate/DIPEA (1:1) in DMF (20 mmol), DMF, MeOH and CH_2Cl_2. *Activation and coupling:* 5 eq TBTU and 5 eq NMM in DMF were added to the resin for 30 min. The resin was drained and 5 eq of the amino acid ester in DMF was added. Quantitative coupling was achieved within 4h. The resins were washed with DMF, MeOH and CH_2Cl_2.
13. *Loading of 4-aminoacetophenone*: 0.7 eq of 4-aminoacetophenone were dissolved in DMF and 2 eq of NMM were added. This solution was added to the activated resin and stirred for 20h at 80°C. The reaction was quenched with methanol and the resin washed with DMF, MeOH and CH_2Cl_2 (3 x each).
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