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# Lewis acid–nitromethane complex-promoted Friedel–Crafts reactions of PS-DVB-resins

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**Abstract**—Aminomethyl-polystyrene resins were prepared using $FeCl_3$–nitromethane and $FeCl_3$–benzophenone complexes as Friedel–Crafts catalysts. All the resins were highly loaded and functionalized with Rink amide linker. A comparative synthesis of the classic difficult sequence ACP (65–74) on the prepared resins by Fmoc/*t*-Bu chemistry is presented. The target peptide of highest purity (91%) was that prepared using $FeCl_3$–nitromethane.


The Friedel–Crafts (F–C) reaction is one of the most fundamental C–C bond-forming reactions in organic synthesis.[1] The standard F–C alkylation of aromatic compounds involves a Brönsted or Lewis acid catalyzed reaction of an aromatic substrate with alkyl halides, alkyl esters of strong acids, alcohols or unsaturated compounds and its mechanism remains the subject of an interesting debate.[2] However, there are several problems associated with the standard F–C approach. These include uncertainty on the identity of the active electrophile, variable product distributions, acid-catalyzed isomerizations and disproportionations, over-alkylation, extreme sensitivity to traces of water, a rate-of-mixing effect, insolubility of the catalyst in the solvent used, etc.[3] Which problem will occur and to what extent depends on the nature of the reactants, the catalyst, the solvent and the remaining reaction conditions. Regarding the catalyst, a great number of Lewis acids has been evaluated and classified as F–C alkylation–acylation catalysts, according to their activity, as very active, moderately active or weak Lewis acid catalysts.[4] The choice of solvent for F–C reactions is also very important. Carbon disulfide, dichloromethane and 1,2-dichloroethane are the common solvents used. Basic solvents, such as nitromethane, neat or as co-solvent, are also well suited for F–C alkylation–acylation. These also form additional complexes with Lewis acids, which suppress isomerization and disproportionation[5] side reactions as well as maintain the solution homogeneity until completion of reaction.

In solid-phase organic synthesis, F–C alkylation–acylation reactions are widely applied methods for the functionalization of polystyrene supports (i.e., for the preparation of chloromethyl,[6] aminomethyl[7] and polyethylene glycol-grafted[8] polystyrene resins) as well as for the transformation of the pendant molecule.[9] However, it is well known that drastic processing conditions during resin modification and incompleteness in the multistep transformations involved can cause cross-linking modifications and other undesired side reactions.[10] For example, a standard procedure for the production of aminomethyl-polystyrenes,[7b] utilizes (hydroxymethyl)- or (chloromethyl)phthalimide in TFA–$CH_2Cl_2$ mixtures with TfOH as the strong acid catalyst, at elevated temperatures. These conditions invariably result in relatively inefficient incorporations and poorly swelling materials.[11] Since it is not possible to separate the side products from the desired products in these systems, any method for polymer modification should be carefully optimized.

In our earlier work,[7d] and in order to avoid some of these problems concerning aminomethylation of polystyrene, the reaction procedure was modified by

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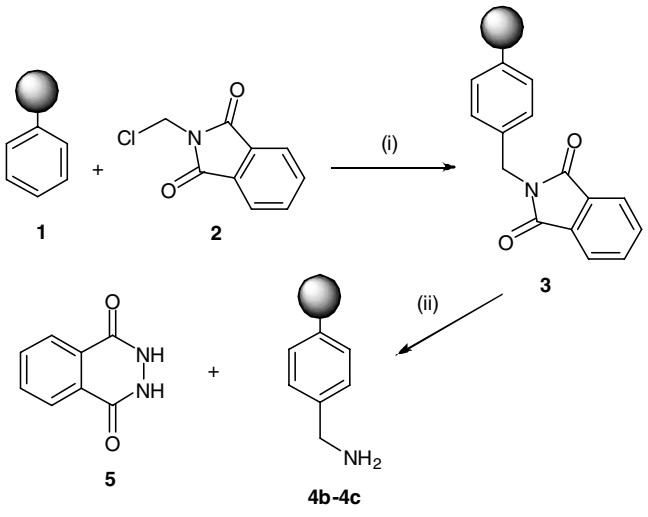
introducing ferric chloride as catalyst for the F–C alkylation. In this way, aminomethyl-polystyrene resins were synthesized with better swelling properties and uniquely high capacities, up to 7.3 mmol/g.

We later observed, however, that the ferric chloride method had several drawbacks, namely: (a) various contaminants 'dark specks' of commercial ferric chloride, which remained insoluble in the reaction mixture and could not be removed from the polystyrene resin, either by extensive washing or by repetitive sedimentations and decantations using various solvents, such as $CH_3OH$, $CH_2Cl_2$, etc., in attempts to physically separate the contaminants from the resin; (b) the polymer became gradually brownish during the reaction, due to the absorption of a portion of the existing ferric chloride in the reaction solution, leading to a lack of homogeneity as the reaction progressed; (c) the reagent and the catalyst were needed in large excess, especially in the case of high capacity resins. The removal of the by-product, 2,3-dihydrophthalazine-1,4-dione, after the dephthaloylation reaction was also problematic.

Any improvement of the quality of the polymer is very important, since the success of solid-phase organic chemistry depends crucially on the properties of the solid support.[12] To this end, and in an attempt to better solubilize the $FeCl_3$ catalyst, several aminomethyl-resins were prepared[13] using $FeCl_3$–nitromethane and $FeCl_3$–benzophenone complexes as F–C catalysts (Scheme 1).

To evaluate the new method of synthesis of aminomethyl-resins, we chose the following four polymeric supports: commercial AMPS **4a** (NOVAbiochemicals, 0.92 mmol N/g); AMPS resin **4b** (1.0 mmol N/g) prepared using $FeCl_3$; AMPS resin **4c** (0.95 mmol N/g) prepared using $FeCl_3$-nitromethane and AMPS resin **4d** (0.93 mmol/g) prepared by using $FeCl_3$–benzophenone complex. The following properties were monitored: (a) the swelling behaviour in solvents commonly used; (b) possible spatial alterations and, (c) the behaviour during the synthesis of difficult peptide sequences.




**Scheme 1.** General synthetic scheme for the functionalization of polystyrene resins; (i) Lewis acid, $CH_2Cl_2$, 45 °C; (ii) $NH_2NH_2$, EtOH, reflux.

Swelling studies were performed by studying the solvent uptake of the resin using the centrifuge method.[14] The swelling ratio was determined by the increase in net weight gain after swelling and was converted into the volume of solvent incorporated per weight of dry resin (swelling ratio, mL/g). Spatial alterations were detected following Rademann's protocol with a minor modification.[15,16] The swelling properties of resins **4a**–**d** and images of the sliced beads are summarized in Table 1 and Figure 1, respectively.

Of the synthetic resins, the one prepared using $FeCl_3$/benzophenone had considerably higher swelling ratios than the corresponding resin synthesized with $FeCl_3$/nitromethane. The corresponding values for resin **4c** were between the values for resins **4b** and **4d**. Although the swelling ratios are not correlated to the synthetic efficiency of the polymeric support,[17] the values in Table 1 strongly indicate that resins **4a**–**d** are structurally different. Since the starting materials and loadings of the resins are the same in all experiments the most probable explanation of the above trends might be associated with the position of the amino groups within the polymeric matrix.

The inspection of the sliced bead images in Figure 1 reveals small differences corroborating that the aminomethyl-resins are not identical. Specifically, resin **4a** contains slices that vary from homogeneously dark or bright fluorescent discs to heterogeneously distributed fluorescence on the perimeter of the disk. Comparing the sliced bead images of the three synthetic resins, a progressively more homogeneous distribution of the fluorescence on going from resin **4b** to resin **4d** is revealed.

Resins **4a**–**d** were further functionalized by incorporating [4-[(*R*,*S*)-α-[1-(9*H*-fluoren-9-yl)methoxycarbonyl amino]-2,4-dimethoxybenzyl]phenoxyacetic acid[18] (Rink amide linker). The loading capacities of the resulting resins, were 0.64, 0.62, 0.60 and 0.58 mmol N/g, respectively, as confirmed by quantification of the Fmoc group.[19]

**Table 1.** Swelling ratios in mL/g

| Solvent | Resin | | | |
|---|---|---|---|---|
| | **4a** | **4b** | **4c** | **4d** |
| PhMe | 3.3 | 3.9 | 3.6 | 4.0 |
| THF | 3.7 | 4.2 | 4.0 | 4.4 |
| DCM | 6.2 | 7.2 | 6.9 | 7.6 |
| DMF | 2.4 | 2.8 | 2.7 | 2.9 |
| NMP | 3.5 | 4.0 | 3.9 | 4.2 |
| *i*PrOH | 0.6 | 0.5 | 0.4 | 0.5 |

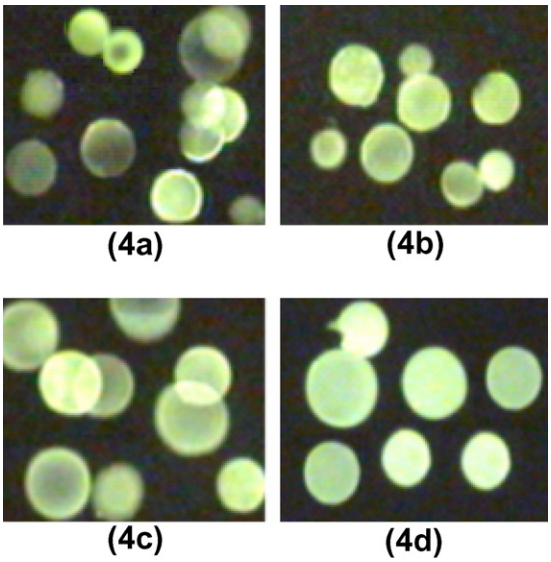



**Figure 1.** Sliced bead images of the four FITC-functionalized resins studied.

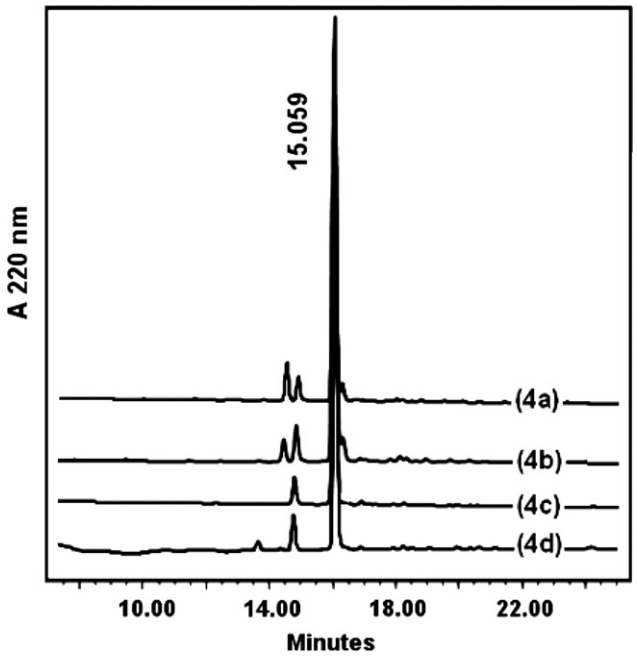



**Figure 2.** Analytical RP-HPLC of the crude peptides isolated from resins **4a**–**d**. For HPLC analysis, the elution of injected material was carried out using a gradient of 10–40% B over 20 min (solvent A, 0.05% TFA in 0.1 M $NaCl_{(aq)}$; solvent B, 0.05% TFA in 90% acetonitrile/10% water).

The well-known difficult sequence from the acyl carrier protein (ACP), residues 65–74 (**6**) was chosen in order to examine the synthetic efficacy of supports **4a**–**d**. ACP (65–74) is known to aggregate significantly on deprotection of the penultimate glutamine residue. Incorporation of the final valine residue is often incomplete via traditional solid phase procedures.[20]

H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-$NH_2$**6**

The peptides were synthesized in parallel using manual batch-wise protocols for Fmoc/*t*-Bu chemistry. The mild activating DIC/HOBt procedure was chosen in order to expose the synthetic difficulties. All syntheses employed the same batches of amino acids, resins, and other reagents and all procedures, from the initial linker loading step until the final cleavage work-up, were performed identically. The protected peptides were cleaved from the resin by treatment with TFA/$H_2O$/TIPS/$CH_2Cl_2$ (170:5:5:20), at room temperature, for 2 h. After filtration of the exhausted resins, ether was added to the filtrates and the residues were removed by centrifugation. The purities of the obtained crude peptides from resins **4a**, **4b**, **4c** and **4d** were 82%, 83%, 91% and 89%, respectively, as estimated by analytical RP-HPLC chromatography (Fig. 2). After purification by semi-preparative RP-HPLC, the overall yields of the peptides synthesized on resins **4a**, **4b**, **4c** and **4d** were 60%, 59%, 74% and 73%, respectively.

Since the results, as far as the synthetic efficiency of difficult sequence peptides is concerned, were optimal using resins **4c** and **4d**, and slightly better using resin **4c** a series of aminomethyl-resins with various capacities were synthesized using $FeCl_3$–nitromethane as the catalyst. The capacities, reaction conditions and swelling properties of the various aminomethyl-resins[12] prepared, are given in Table 2.

From the results of the experiments shown in Table 2, it is apparent that the aminomethylation was quantitative up to substitution of 7.15 mmol N/g and neither an excess of reactants nor longer reaction times were needed. The swelling ratios of the resins in the aprotic solvents used decrease as the capacity increases, while in protic methanol the capacity increases.

**Table 2.** Aminomethylation of copoly-(styrene-l%-divinylbenzene) using $FeCl_3$–nitromethane as catalyst

| Run | **2** (mmol/g resin) | Catalyst[a] (ml) | Loading | Swelling ratio in mL/g | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | DCM | DMF | NMP | THF | MeOH |
| 1 | 1.1 | 0.5 | 1.05 | 6.81 | 2.51 | 3.96 | 3.80 | 0.36 |
| 2 | 2.2 | 1.0 | 1.98 | 7.31 | 2.88 | 4.00 | 3.71 | 0.59 |
| 3 | 3.3 | 1.5 | 3.05 | 7.46 | 2.96 | 4.00 | 3.31 | 0.98 |
| 4 | 4.4 | 2.0 | 3.96 | 7.06 | 2.96 | 3.89 | 3.02 | 1.54 |
| 5 | 5.5 | 2.5 | 5.10 | 6.36 | 2.97 | 4.60 | 2.69 | 1.98 |
| 6 | 6.6 | 3.0 | 6.02 | 5.42 | 2.38 | 3.22 | 1.92 | 2.50 |
| 7 | 7.7 | 3.5 | 7.15 | 5.67 | 2.47 | 3.35 | 1.48 | 3.60 |

The swelling ratio in mL/g.

[a] $FeCl_3$ 0.6 M in nitromethane/DCM (4:6 v/v).

In the high capacity resins, the insoluble in most organic solvents but highly soluble in water by-product, 2,3-dihydrophthalazine-1,4-dione, was easily and effectively removed by adding water during the washing steps. Finally, under the same conditions, the polystyrene resin reacts with benzoyl chloride and 2-chlorobenzoyl chloride to give benzophenone- and 2-chlorobenzophenone-resins, which are important key intermediates for the synthesis of trityl-type resins.

In conclusion, we have demonstrated that ferric chloride complexes with either nitromethane or benzophenone are effective catalysts for the Friedel–Crafts aminomethylation of polystyrene resins. Ferric chloride produces resins with different properties when used either alone or complexed and the nature of the ligand is also important. These differences were expressed in the swelling properties, images of the sliced beads, as well as in the synthesis of difficult sequence peptides. All the aminomethyl-resins prepared with the $FeCl_3$-complexes as catalysts afforded the difficult ACP peptide with a higher purity than the commercial resin and $FeCl_3$ alone, while the peptide with the greatest purity was obtained from those resins prepared with the $FeCl_3$–nitromethane complex. This phenomenon could be attributed to the different positions occupied by the amino groups within the polymeric matrix. Further studies directed towards elucidation of the factors governing the preparation and properties of the high quality resin **4c** are currently in progress.

## Acknowledgements

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13. General procedure for the synthesis of aminomethyl-resin **4a**. Underivatized cross-linked copoly-(styrene-l%-divinylbenzene) resin **1** (1 g) 100–200 mesh, *N*-(chloromethyl)phthalimide **2** (0.21 g, 1.1 mmol) and DCM (12 mL) were placed in a three-neck round-bottomed flask, equipped with an overhead stirrer. After 15 min stirring, a centrifuged solution (0.5 mL) of $FeCl_3$ 0.6 M in nitromethane: DCM (4:6 v/v) was added and the stirred mixture was heated at 45 °C for 2 h (as far as $FeCl_3$–benzophenone is concerned, a mixture of $FeCl_3$ and benzophenone 0.6 M in DCM was used). The resin was subsequently filtered, washed with DMF–$HCl_{(aq)}$ 0.1 M (3 × 10 mL), DMF (3 × 10 mL), DCM (5 × 10 mL), MeOH (2 × 10 mL) and dried under vacuum over $P_2O_5$. The IR-spectrum showed the characteristic bands of phthalated resin **3** at 1772 and 1712 $cm^{-1}$. Phthalimidomethyl-resin **3** (1.1 g) was refluxed with stirring for 4 h in ethanol (20 mL) containing 5% hydrazine. Water (10 mL) was added and the resin was filtered and washed with ethanol–water (1:1) (2 × 10), ethanol (4 × 10 mL) (for high capacity resins, the procedure was repeated until no insoluble 2,3-dihydrophthalazine-1,4-dione **5** by-product appeared), DMF (2 × 10 mL), DCM (4 × 10 mL), MeOH (3 × 10 mL). The colourless product was dried in vacuo over $P_2O_5$. Elemental analysis showed 1.47% N, corresponding to a loading of 1.05 mmol N/g. Titration[21] with HCl 0.01 M in THF gave 1.00 mmol/g (91% yield from chloromethyl phthalimide), and in the IR-spectrum the characteristic bands of the phthalylated intermediate at 1772 and 1712 $cm^{-1}$ had disappeared.
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16. A mixture of Fmoc–β-alanine (0.02 equiv) and benzoic acid (0.98 equiv) was activated by DIC/HOBt for 15 min and then added to each AMPS resin (50 mg, 1 mmol/g). After 20 h the resins were washed with DMF (4 × 1 mL), the Fmoc group was removed with piperidine/DMF (20%), then a pyridine solution of fluorescein isothiocyanate (4 equiv) was added and the reaction left overnight. Upon completion of the reaction, the resins were washed thoroughly with pyridine, DCM and ether and dried in vacuo. The beads were sliced (5 μm) using a Leica microtome. Fluorescence microscopy was conducted with a Nicon ECLIPSE E400 epifluorescence microscope. The excitation of the fluorescence was effected by a super high pressure mercury lamp. The images were recorded with a PCO Sensicam Super VGA camera. For all measurements a 10 × 0.25 objective lens was used.

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