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# Rapid microwave-assisted preparation of amino-functionalized polymers

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ABSTRACT

Two different methods for the rapid microwave-assisted amination of halide-functionalized polymers were investigated. Nucleophilic substitution by phthalimide, followed by ring opening with methylamine to liberate the free amine, afforded amino-substituted polymers with up to 76% conversion. The second method involves nucleophilic substitution with azide ions and subsequent treatment with triphenylphosphine. The latter method was found to be more efficient, with up to 99% conversion in favourable cases and with a reaction time of 2 × 30 min.

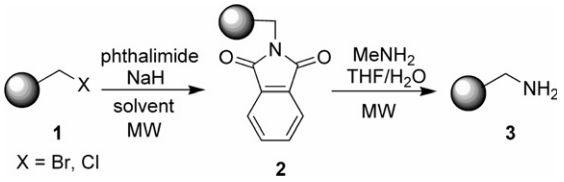


As part of a project concerning the immobilization of chiral ligands on solid supports, we were in need of an amino-functionalized polymer with a longer tether than the normal aminomethyl polystyrene type resin. Although aminoethyl-resins are commercially available in both polystyrene and Tentagel form, the corresponding aminobutyl polymer is not as easily accessible.[1] Some functionalized resins with longer aminoalkyl chains are commercially available (trityl, aminodendrimer), but these polymers contain functionalities that were not compatible with the applications we desired. We thus investigated the possibilities of converting bromobutyl polystyrene to the corresponding amine on solid support. Direct amination using an excess of ammonia can be used to convert a halide to an amino-group on solid phase,[2] but this reaction requires several days for completion with a potential risk of undesired cross-linking due to the nucleophilic nature of the aminoalkyl resin formed in the presence of unreacted halide sites.[3] We instead opted for introducing the amine functionality in the form of phthalimide. This method has been used in several instances on solid phase,[1,4] but involved the use of strongly basic conditions or toxic hydrazine for liberation of the amino group, and long reaction times.[5] We were thus interested in seeing if milder conditions for the cleavage step and microwave heating[6] could be applied to give a more efficient reaction protocol for this transformation. For comparison, we also employed an alternative method for converting the halide-functionality to an amine, involving displacement by azide ions, followed by reduction using triphenylphosphine and water. Although the latter method is efficient for this functional group conversion in solution,[7] to our knowledge, there are few reports of its application in the synthesis of primary amines on solid phase, and none involving the use microwave heating.[8] Despite the sensitive nature of azides, numerous examples of their application in other microwave-mediated reactions have appeared, that is, as components in [3+2] cycloadditions (click reactions),[9] as nucleophiles in the ring-opening of epoxides[10] and in the Tsuji-Trost reaction with allylic acetates using an ionic liquid and water solvent system.[11]

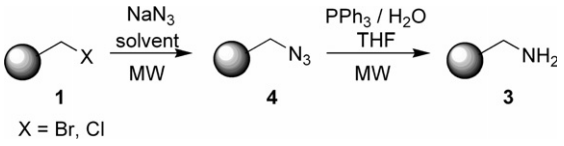
The first method to be studied (method I) involved the displacement of a polymer-bound halide (**1**) by the anion of phthalimide to form polymer-bound intermediate **2** (Scheme 1).

Methylamine has been used in some instances as an alternative to hydrazine or hydroxide ions, and the use of an aqueous or methanolic solution facilitates handling of the amine.[4f] We thus opted for these milder conditions for the liberation of the polymer-bound amine **3**.

In method II, the halide resin was heated together with sodium azide in the first step to form **4**, and after washing, the polymer was subsequently treated with triphenylphosphine followed by water to afford the free amine **3** (Scheme 2).




**Scheme 1.** Method I using phthalimide for introducing the amine functionality.




**Scheme 2.** Method II: Displacement by azide ions followed by reduction with triphenylphosphine.

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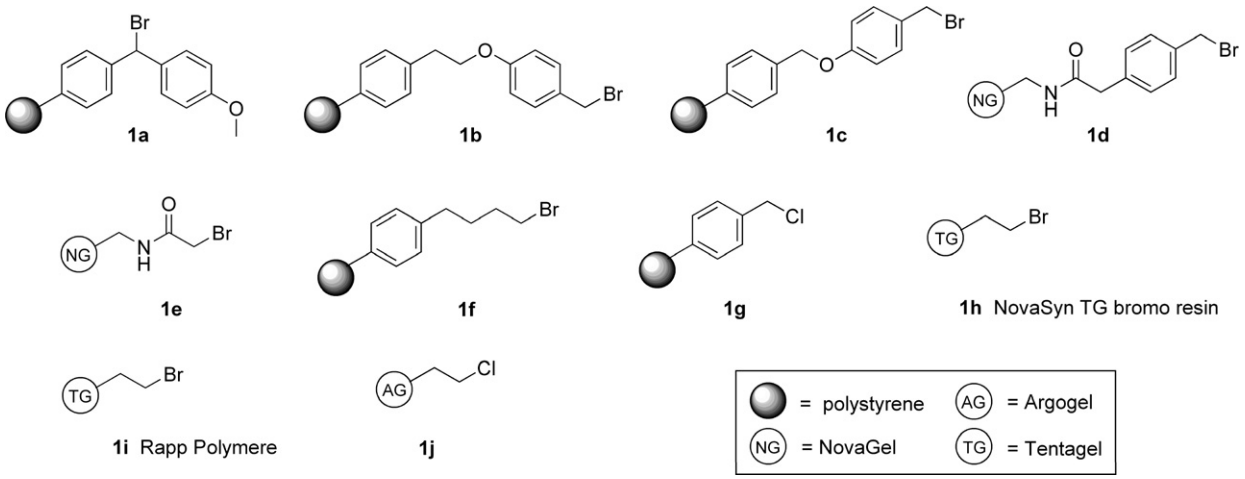


**Figure 1.** Polymers used in the microwave-assisted conversion of halides to amine.

Although we were primarily interested in longer chain polymer-bound alkyl amines, we also wanted to investigate the scope and applicability of the microwave-assisted methods on a wider group of polymer types and linkers. Ten different commercially available bromo- and chloro-substituted resins were thus selected for the study (Fig. 1). A preliminary screening involving polymer **1f** identified NMP and THF as suitable solvents for method I, and DMF followed by THF for method II. For the initial screening, a Fmoc test[12] was used for determining the loading, which involved attachment of Fmoc-alanine to the amine resin followed by Fmoc-cleavage with piperidine in DMF. However, even if some trends could be seen, this method consistently afforded low degrees of conversion and we suspected that this could be due to the fact that an extra step was added to the sequence, thus reducing the yield. We instead switched to measuring the loading via a picric acid test.[13] In each sequence, the reaction mixtures were heated at 100 °C for 30 min for each step to ensure complete conversion. The results are shown in Table 1.[14]

In general, method II gave a higher conversion than method I, reflecting the efficiency of azide ions as nucleophiles. Resin **1a** (entry 1), containing a secondary bromide functionality, not surprisingly performed rather poorly. The lower conversion attained for polymers **1c** and **1d** as compared to **1b**, using method II, could reflect the more stable two-carbon ether linkage in **1b**. The bromo-substituted mixed polystyrene-polyethylene glycol resins in general gave excellent results with method II (entries 5, 8 and 9), probably due to the flexible structure of this polymer. Chloro-substituted resins **1g** (polystyrene) and **1j** (Argogel) gave poorer results with method II, however, indicating that this method is more suited for bromo-substituted resins. Resin **1f** (entry 6) gave a low degree of conversion using both methods, despite the four-carbon tether used to link the bromo-functionality to the resin. This resin has an unusually high loading (2.7 mmol/g) compared to the other resins, and it may be that steric hindrance, especially in the second step of method II, could play a part here.

In summary, we have shown that the microwave-assisted conversion of polymer-bound halides by treatment with azide ions followed by triphenylphosphine/water, is a viable method for the formation of aminoalkyl resins.[15] The alternative substitution with phthalimide anions, followed by cleavage with methylamine, was found to be less useful under microwave conditions. Applications of the described methodology are in progress.

**Table 1**
Results from the microwave-mediated converson of halide polymers **1a–k** to amino polymers **3**

| Entry | Polymer | Conversion (%)[a] | |
|---|---|---|---|
| | | Method I[b] | Method II[c] |
| 1 | **1a** | 23 | 36 |
| 2 | **1b** | 32 | 96 |
| 3 | **1c** | 55 | 33 |
| 4 | **1d** | 28 | 45 |
| 5 | **1e** | 57 | 99 |
| 6 | **1f** | 22 | 21 |
| 7 | **1g** | 37 | 60 |
| 8 | **1h** | 34 | 96 |
| 9 | **1i** | 40 | 91 |
| 10 | **1j** | 76 | 30 |

[a] Conversion measured by picric acid test.
[b] Method I: (a) NaH, phthalimide, NMP, MW 100 °C, 30 min; (b) $MeNH_2$ in $H_2O$, 100 °C, 30 min.
[c] Method II: (a) $NaN_3$, DMF, MW 100 °C, 30 min; (b) $PPh_3$, THF, MW 100 °C, 15 min, then $H_2O$, THF, MW 100 °C, 15 min.

## Acknowledgements

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14. *General procedure for the conversion of immobilized halide to phthalimide* **2.** 0.1 mmol of polymer **1** was allowed to swell in 1 mL of NMP in a microwave vial for 15 min. 1 mmol of phtalimide was dissolved in the same solvent and 1 mmol of NaH was added. As soon as gas evolution ceased, the mixture was added to the polymer. The vial was sealed, flushed with nitrogen and heated under microwave irradiation at 100 °C for 30 min, using a Biotage Series 60 Initiator. The resulting polymer was washed with 3 × 2 mL of THF, MeOH, DCM and MeOH, and dried in vacuo and subjected to the next reaction step. IR 1772 $cm^{-1}$, 1709 $cm^{-1}$.
*General procedure for the conversion of immobilized phthalimide to amine* **3.** 0.1 mmol of **2** was allowed to swell in 1 mL of THF in a microwave vial for 15 min. 1 mmol of a 40% solution of $MeNH_2$ in $H_2O$ was added dropwise. The vial was sealed, flushed with nitrogen and heated under microwave irradiation at 100 °C for 30 min. The resulting polymer was washed with 3 × 2 mL of THF, MeOH, DCM and MeOH, and dried in vacuo. IR 3379 $cm^{-1}$, 1646 $cm^{-1}$.
*General procedure for the conversion of immobilized halide to azide* **4.** 0.1 mmol of polymer **1** was allowed to swell in 1 mL of DMF in a microwave vial for 15 min. 1 mmol of sodium azide was added, the vial was sealed, flushed with nitrogen and heated under microwave irradiation at 100 °C for 30 min. The resulting polymer was washed with 3 × 2 mL of THF, MeOH, DCM and MeOH, and dried in vacuo and subjected to the next reaction step. IR 2083 $cm^{-1}$, 1244 $cm^{-1}$.
*General procedure for the conversion of immobilized azide to amine* **3.** 0.1 mmol of **4** was allowed to swell in 1 mL of THF in a microwave vial for 15 min. 1 mmol of triphenylphosphine was added, the vial was sealed, flushed with nitrogen and heated under microwave irradiation at 100 °C for 15 min. 1 ml of $H_2O$ was added, and the reaction mixture was heated under microwave irradiation at 100 °C for another 15 min. The resulting polymer was washed with 3 × 2 mL of THF, MeOH, DCM and MeOH, and dried in vacuo IR 3371 $cm^{-1}$.
*General procedure for the picric acid test*.[13a] A weighed amount of resin (in the range of 10–20 mg) was washed with 2 × 1 mL $CH_2Cl_2$, 3 × 1 mL 5% DIPEA in $CH_2Cl_2$, and 2 × 1 mL $CH_2Cl_2$. The resin was then treated with 4 × 1 mL 0.05 M picric acid in $CH_2Cl_2$ (pre-dried with $MgSO_4$), and washed with 3 × 1 mL $CH_2Cl_2$, 2 × 1 ml 10% EtOH in $CH_2Cl_2$ and 1 × 1 mL $CH_2Cl_2$. Cleavage was effected with 4 mL of 5% DIPEA. The solutions were diluted with an exact amount of $CH_2Cl_2$ (in the range of 250–500 mL). Absorbance was measured at 362 nm. The picrate concentration was calculated using Beer's law ($\varepsilon$ = 15100 $M^{-1}$ $cm^{-1}$) and compared to the initial loading of the resin.
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