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A straightforward preparation of amino–polystyrene resin from Merrifield resin

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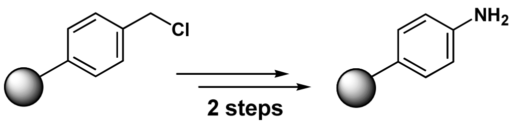
Abstract—Azidomethyl–polystyrene, obtained by nucleophilic substitution of chloromethyl–polystyrene, undergoes a Schmidt rearrangement when treated with trifluoromethanesulfonic acid, affording amino–polystyrene. To assess its loading and reactivity the resin is used as a support for the preparation of triazene-linked amine. © 2002 Elsevier Science Ltd. All rights reserved.

Due to the establishment of high-throughput-screening[1,2] (HTS) processes over the last few years, there has been tremendous work devoted to developing suitable resins, linkers and supported reagents.[3] Most of these novel resins were prepared by grafting functional molecules onto readily available chloromethyl–polystyrene. This strategy results in a relative fragility of the functionalized resins because of the labile polymer-linker benzylic bond.

Polymer-bound aniline, used in SPS as a precursor of the versatile triazene-linkers[4] is generally prepared by grafting hydroxyaniline, or analogs, to Merrifield resin. Herein, we report the preparation of a novel resin in which the aniline structure is part of the polymeric skeleton (Scheme 1).

To our knowledge such an equivalent of styrene/vinyl aniline copolymer has never been reported and could find interesting applications in parallel synthesis as a scavenger, for the development of supported triflating agents[5] or, as it will be shown, as precursor for the preparation of triazene linkers.



Scheme 1. Straightforward preparation of amino–polystyrene resin from Merrifield resin.

Amino polystyrene is obtained in a two-step process. First azidomethyl–polystyrene (**2**) is prepared by heating Merrifield resin and sodium azide in DMF. Then a one-carbon degradation reaction is performed by treating **2** with trifluoromethanesulfonic acid. This reaction, known as a Schmidt rearrangement, proceeds via the formation of a reactive methyleneiminium intermediate (**4**) that is quenched by addition of methanol and water (Scheme 2).

Interestingly, since Merrifield resin is available with a wide range of loading and properties, using it as starting material enables easy tuning of the aniline-resin characteristics, i.e. particle size, reticulation, polymer morphology.

Each step was monitored using on-bead IR spectroscopy (recorded with a Perkin–Elmer 2000 FT-IR coupled to an Autoimage microscope). The azidomethyl-resin **2** showed a characteristic signal $\nu_{N=N=N} = 2095\ cm^{-1}$. The efficiency of the transformation according to nitrogen elemental analysis proved to be over 95% (loading = 1.48 mmol/g).

The resin **2** was subjected to an acid-promoted Schmidt rearrangement under conditions adapted from Aube[6] and Pearson.[7] Treatment of a suspension of **2** (1 g) in CH_2Cl_2 (10 mL) with triflic acid (1.4 mL) at 0°C for 1 h promoted the 1,2-polymer migration with concomitant release of molecular nitrogen, leading to the

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Keywords: solid phase synthesis; amino–polystyrene; Schmidt rearrangement; triazene linker.

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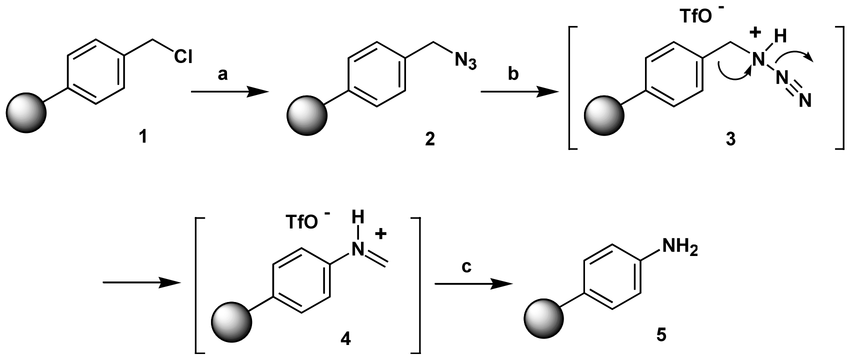
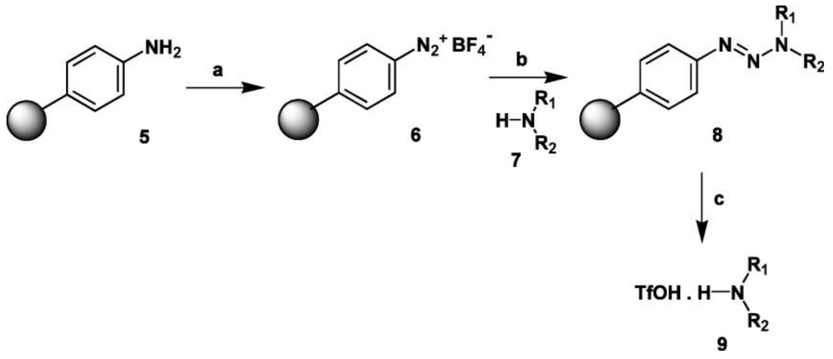


Scheme 2. *Reagents and conditions*: (a) 4 equiv. NaN_3, DMF, 90°C; (b) 4 equiv. TfOH, CH_2Cl_2, 0°C to rt; (c) $MeOH/H_2O$, rt.



Scheme 3. *Reagents and conditions*: (a) 9 equiv. $BF_3{\cdot}OEt_2$, 8 equiv. *t*BuONO, CH_2Cl_2, −20°C; (b) 4 equiv. HNR_1R_2 (**7**), CH_2Cl_2, −20°C to rt; (c) 10% TFA in CH_2Cl_2, rt.

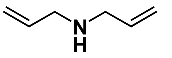
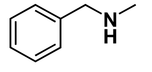
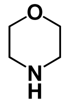
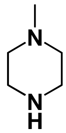
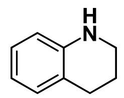
methyleneiminium intermediate **4**. Methanol (10 mL) was added and the slurry stirred at room temperature for another hour. The resin was then filtered and washed subsequently with $MeOH/H_2O$, $MeOH/NEt_3$ and CH_2Cl_2. The resin was dried under vacuum. The efficiency of the sequence was determined to be over 95% by fluorine elemental analysis of the corresponding 4-fluorobenzoylated resin.

In order to investigate the reactivity and assess the loading of our 'aniline-resin', we used it as a precursor of the versatile triazene linker developed by Bräse and co-workers (Scheme 3).[4]

Treatment of **5** with *t*BuONO and tetrafluoroboric acid diethylether complex in CH_2Cl_2 at −20°C for 1 h resulted in the formation of the corresponding resin-linked aryl–diazonium salt **6**. The latter was converted into the corresponding triazene **8** by reacting it with different amines in CH_2Cl_2 at −20°C up to room temperature. The reaction was monitored using IR spectroscopy by observing the disappearance of the diazonium signal at 2271 cm^{-1}. Cleavage was then performed by treatment with 10% trifluoroacetic acid in CH_2Cl_2 at room temperature. In all cases, ammoniums were recovered in good purity (over 95%) and high yield based on the theoretical loading of **5** (1.66 mmol/g) (Table 1).

The high yield of the overall process shows that the resin preparation is very efficient. The experimental loading is found to be close from that of the original Merrifield resin (1.6 mmol/g in the present case). In addition we also have shown that our amino–polystyrene resin is stable at room temperature over several weeks as its efficiency as a triazene precursor remained unchanged.

Table 1. Amines tested in the bound and release process

Amines **9**	Yield (%)
	81
	85
	82
	84
	79

In conclusion, we reported a straightforward preparation of a novel resin-grafted aniline from the readily available Merrifield resin. This resin proved to be an efficient precursor of the useful triazene linker and should find other important applications for the preparation of many supported reagent catalysts or scavengers.

Acknowledgements

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