The First Stable Diazonium Ion on Solid Support—Investigations on Stability and Usage as Linker and Scavenger in Solid-Phase Organic Synthesis**

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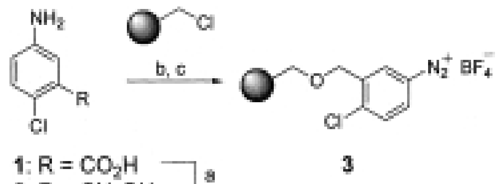
Diazonium ions represent one of the most versatile functional groups in organic chemistry.[1, 2] The most important reactions of aromatic diazonium ions are the Sandmeyer, Schiemann, Meerwein, Pschorr, and Gomberg-Bachmann reactions, but also the Heck reaction[3] and the formation of triazenes[4] and azo compounds[5] represent important processes. Diazonium ions are also of interest in theoretical chemistry. In more recent theoretical works they are considered as electron donor/acceptor complexes between a phenyl cation and a dinitrogen molecule.[6, 7]

The property that limits the application of diazonium ions most is their lability. Aromatic diazonium ions undergo fragmentation to nitrogen and reactive phenyl intermediates. Ionic and radical pathways, initiated by single-electron transfer reactions, are known. Also our linker for secondary amines (T2)[8] was only synthesized as an intermediate and had to be stored and handled below 0° C to avoid decomposition. Thus, one of our aims was to develop a stable diazonium ion on solid support, to combine the broad chemical usage of diazo chemisty with the simple handling of solid-phase organic chemistry.

Most important for the stability of aromatic diazonium ions is, besides the choice of the counterion,[9] the substitution pattern of the arene. Furthermore, the chosen arene had to be highly tolerant towards as many chemical reactions as possible. In the already mentioned theoretical studies of Glaser,[10] and from experimental data[11] it was shown that *p*-chloro-substituted diazonium ions are very stable. For that reason we chose 2-chloro-5-aminobenzyl alcohol (**2**) as starting material for the formation of a stable diazonium ion on solid support (Scheme 1).

The aminobenzyl alcohol **2** was synthesized in two steps from commercially available 2-chloro-5-aminobenzoic acid (**1**). Esterification with trimethylchlorosilane in methanol gave the methyl ester, which was reduced with lithium aluminum hydride ($LiAlH_4$) in THF to the corresponding benzyl alcohol **2**. Coupling to Merrifield resin and subsequent diazotation led to the polymer-bound diazonium ion **3**.



Scheme 1. Synthesis of the T2* linker **3**: a) 1. TMSCl in MeOH; 2. $LiAlH_4$, THF, 0 °C → reflux, 2 h; b) sodium hydride in DMF, 40 °C, 4 h; c) *t*BuONO, $BF_3 \cdot OEt_2$ in THF, 0 °C.

The stability of diazonium ions can be increased by complexation with crown ethers;[12] complexes with [21]crown-7 show the highest thermal stability. Therefore the polymer-bound diazonium ion **3** was treated with [18]crown-6 as well as [21]crown-7 and the resulting resins (**3** · [18]c-6 and **3** · [21]c-7, respectively) were examined by IR spectroscopy (Figure 1). The complexation by [18]crown-6 shifts the N≡N stretching vibration clearly to higher frequencies (shifts of 20–29 cm^{-1} are mentioned in literature[12]), whereas for complexes from [21]crown-7 only small shifts are observed (about $+5\ cm^{-1}$ compared to the uncomplexed diazonium ion).

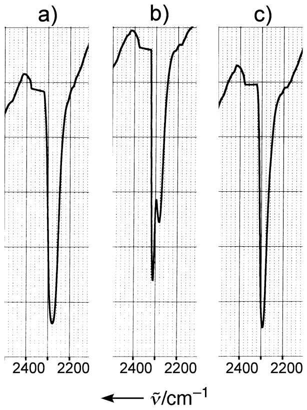


Figure 1. Part of the IR spectra of polymer-bound diazonium ions; the ν(N≡N) bands of the uncomplexed diazonium ion (a), as well as that of partly [18]crown-6 complexed (b), and that in the [21]crown-7 complex (c) are displayed.

The stability of these resins (**3** · [18]c-6, **3** · [21]c-7) was investigated by differential scanning calorimetry (DSC) measurements (Figure 2). The corresponding diazonium ions show a high thermal stability. The rate of decomposition is only significant at temperatures higher than 90 °C. Analysis of the DSC data gave a reaction enthalpy of $\Delta_R H = -120\ kJ\,mol^{-1}$ for the fragmentation reaction, which is independent of complexation. Kinetic analysis based on DSC measurements at different heating rates gave an activation energy for the thermal decomposition of **3** of $E_a = 114\ kJ\,mol^{-1}$. The decomposition rates are consistent with a first-order reaction, which was expected by comparison with the literature.[13]

To gain insights into the shelf life of resin **3** during normal laboratory use, decomposition studies were carried out at 60 °C, and the conversion was examined by elemental analysis

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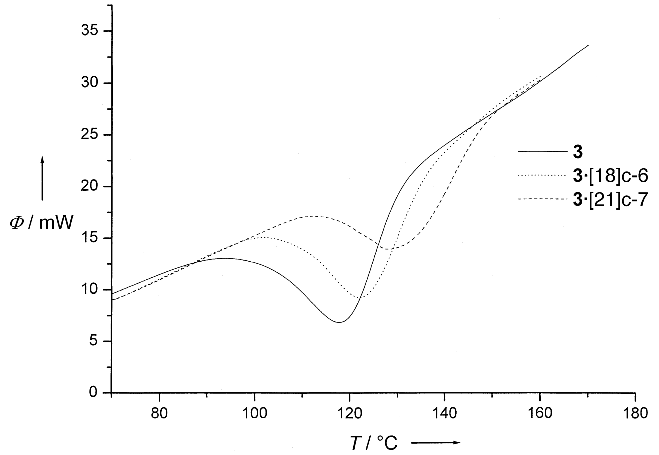
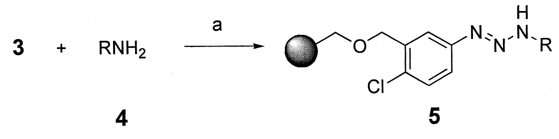


Figure 2. DSC measurements on the polymer-bound diazonium ions **3**, **3**·[18]c-6, and **3**·[21]c-7; measurements were performed with 8–12 mg resin and heating rates of 10.0 K min^{-1}.

(C,H,N).[14] The experimentally determined half-life of resin **3** was eleven hours at 60 °C, which leads to a calculated half-life of 130 days at room temperature (20 °C) or 10 years for storage at 0 °C. Thus resin **3** is, to the best of our knowledge, the first, storable polymer-bound diazonium ion.

This so-called T2* linker represents an improvement of the T2 linker and can be used to immobilize and modify secondary amines on solid support.[8] In addition it is possible to couple primary amines **4** with the diazonium resin **3** to give the corresponding polymer-bound triazenes, which can be used in further transformations (Scheme 2). In this case the use of a polymer-bound system enables the clean synthesis of 1,3-disubstituted triazenes **5**, while suppressing the formation of pentazenes, which is a competing reaction in the analogous liquid-phase synthesis.[1]

The synthesized 1,3-disubstituted triazenes **5** have successfully been applied in various reactions. Alkylation with alkyl bromides or acylation of the triazenes **5a–d** with carboxylic acid chlorides, isocyanates, and isothiocyanates were successfully carried out under mild conditions, and gave rise to the trisubstituted triazenes **6** in quantitative yields. The reaction is regioselective at the N3-nitrogen atom of the triazene group. The alkylation of the polymer-bound thiourea **6e** was performed, without affecting the triazene group. Cleavage of the products was conducted by using a solution of trifluoroacetic acid (TFA; 5%) in dichloromethane. In Scheme 3 some of the possible functionalizations of the T2* linker are summarized. With the possibility of attachment and subsequent acylation of primary amines, this linker represents a new BAL concept (backbone amide linker).[15]

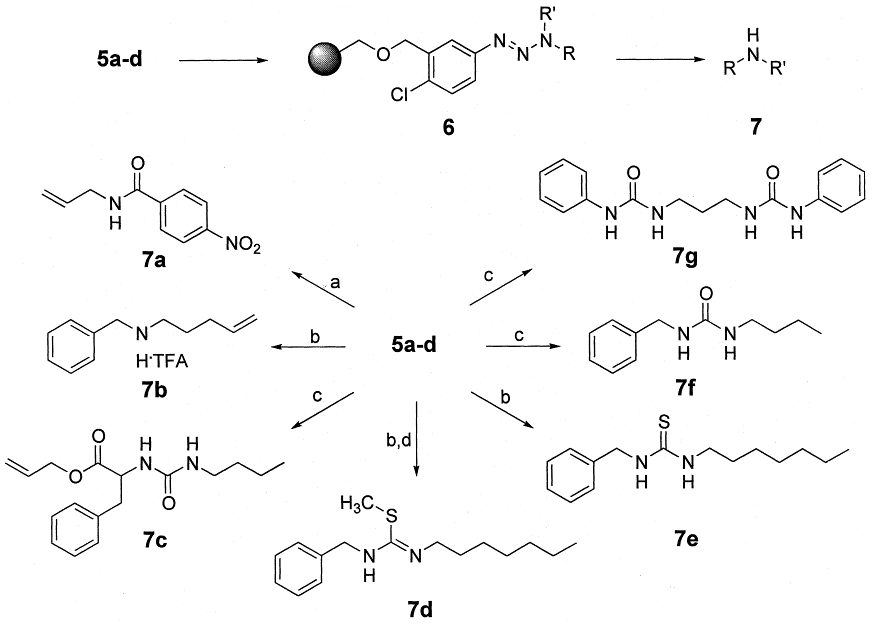


4,5	R
a	Benzyl
b	Allyl
c	$CH(CH_2C_6H_5)CO_2CH_2CHCH_2$
d	$(CH_2)_3NH_2$

Scheme 2. Attachment of amines to the T2* linker. a) Amine **4** (2–5 equiv) in THF, 30 min, 0 °C.

Owing to the constantly increasing application of combinatorial chemistry in liquid phase, the use of scavenger resins has become more and more important.[16, 17] In many cases the application of scavenger resins avoids complicated workup procedures to remove by-products or excess reagents and makes an efficient high-throughput synthesis possible. The temperature stability of the T2* linker should enable its application as a scavenger for the removal of amines, anilines, and phenols under formation of triazenes or azo compounds.

The ionic nature of diazonium ions requires the addition of bases to remove tetrafluoroboronic acid from the reaction equilibrium, which is generated by reaction with nucleophiles. Tertiary amines are not suitable, because they may cause a spontaneous decomposition of diazonium ions. On the other



Scheme 3. The T2* resin as a linker in the synthesis of amine derivatives. a) Carboxylic acid chloride (1.5–2 equiv), pyridine, DMF, room temperature, 2 h; b) sodium hydride, DMF, electrophile (2–5 equiv), room temperature, 2 h; c) isocyanate (1.5–2 equiv), DMF, room temperature, 2 h; d) MeI, THF, room temperature, 30 min. Cleavage was conducted with 5% TFA in dichloromethane, room temperature, 5 min. The overall yield for attachment, modification, and cleavage of the amines was between 20 and 100%, generally greater than 80%, where the yields refer to the theoretically possible loading of the resin given by the starting material. Attachment of the linker and diazotation are considered as quantitative reactions, which was also confirmed by elemental analysis. After cleavage all products were obtained in >95% purity, as determined by integration of the ^{1}H NMR signals and by HPLC analysis.

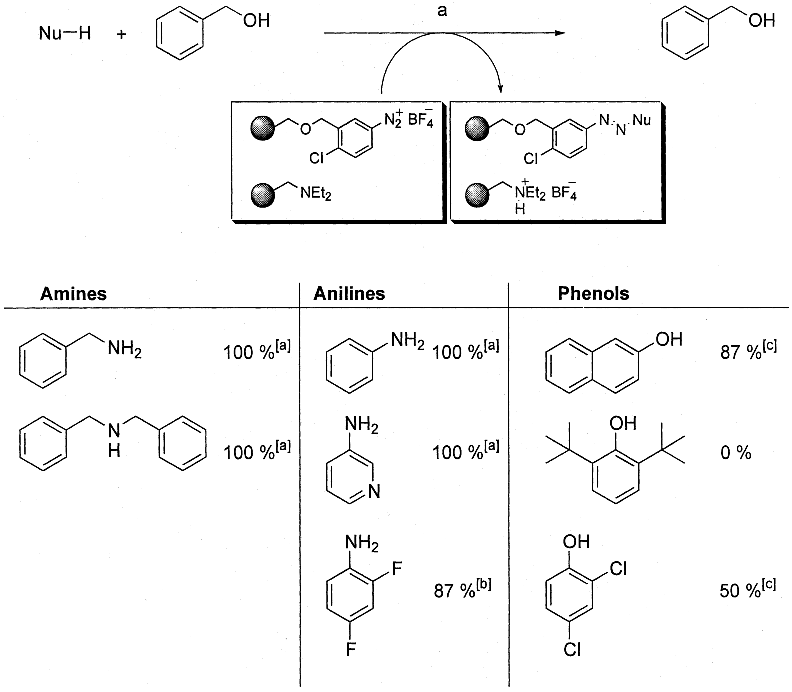
hand addition of insoluble bases (e.g. K_2CO_3 or KOH) or polymer-bound tertiary amines appears appropriate as these reagents undergo no side reactions with diazonium ions and are easily separated from the reaction mixture by filtration.

Scheme 4 shows that primary and secondary amines can be removed quantitatively from solution. Anilines and phenols are removed in high yields, as long as they are not too electron poor and therefore are not sufficiently nucleophilic. Nevertheless nearly all phenols could be removed by using the T2* resin upon deprotonation of the phenol, but this procedure requires strong bases like KOH or NaH, and therefore makes aqueous workup necessary. However phenols, which react only with very electrophilic diazonium ions (e.g. 2,6-di-*tert*-butylphenol) could not be removed.

In summary, immobilized diazonium ions can have a high stability, which enables their application as linkers and scavengers in solid-phase organic chemistry. They could, for example, be used as backbone amide linkers in peptide chemistry, or for the immobilization of carbon nucleophiles such as malonic acid esters or silylenol ethers. Furthermore they are easy to handle, both in terms of stability and toxicity of the compounds. Thus triazenes, which are formed upon reaction with amines and which are considered as carcinogens, can be easily and safely handled.

Experimental Section

All resins were characterized by IR spectroscopy, and loadings and conversions were evaluated by elemental analysis (C,H,N). Typical loadings of the used chloromethylpolystyrene were between 0.6 and 1.4 mmol g^{-1}. Chloromethylpolystyrene (Merrifield resin) was obtained from Calbiochem-Novabiochem or Polymer Laboratories. The T2* resin is available from Calbiochem-Novabiochem. All new compounds were fully characterized or compared to known substances.



Scheme 4. The T2* resin as a scavenger for amines, anilines, and phenols. The percentage of removed nucleophile is given. Benzyl alcohol was used as an internal standard. a) Resin **3** (2 equiv), base in THF, 1 h. Filtration of the resin and analysis of the filtrate by gas chromatography. [a] Base: diethylaminomethylpolystyrene (2 equiv, loading 2.33 mmol g^{-1}). [b] Base: a basic ion-exchange resin (Merck Lewatit MP 5080). [c] Base: finely powdered potassium hydroxide (4–5 equiv).

The DSC measurements were carried out on a Perkin Elmer DSC 7 with a polymer-bound diazonium ion with a loading of 1.0 mmol g^{-1}. The DSC analysis of the used chloromethylpolystyrene starting material resulted in an endothermic melting enthalpy of 2.6 J per gram resin at the melting point of 118 °C. The melting point lies in the region of the exothermal decomposition of the diazonium ions, but the melting enthalpy is about 50 times smaller. As the tolerance of the method is about 10 %, the melting enthalpy was not taken into account for the examination of the reaction enthalpy.

Typical procedure for the attachment of amines to the T2* resin: Resin **3** (5.0 g, 5.5 mmol, loading 1.1 mmol g^{-1}) was suspended in THF (50 mL) and cooled to 0 °C. Benzylamine (3.0 mL, 5 equiv, 27.5 mmol) was added slowly under careful stirring. After 1 h, the resin was filtered, washed alternately with THF and MeOH, and dried in high vacuum.

Typical procedure to remove nucleophiles with the T2* resin and diethylaminomethylpolystyrene: Resin **3** (100 mg, 0.11 mmol, loading 1.1 mmol g^{-1}) and diethylaminomethylpolystyrene (50 mg, 0.116 mmol, loading 2.33 mmol g^{-1}) were weighed into a reaction vessel. Then, 2 mL of an equimolar solution of nucleophile (0.05 mmol) and benzyl alcohol (0.05 mmol) as an internal reference in THF were added, the reaction vessel was closed and agitated for 1 h using a shaker. The resin was filtered off and the eluate was analyzed by gas chromatography.

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