



# Cleavage of immobilized disubstituted triazenes with electrophiles: solid-phase synthesis of alkyl halides and esters

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**Abstract**—An efficient, selective cleavage of polymer-bound disubstituted triazenes with trimethylsilyl halides produces alkyl chlorides, bromides and iodides in good to excellent purities and yields. Similarly, alkyl esters are formed upon cleavage with carboxylic acids. © 2001 Elsevier Science Ltd. All rights reserved.

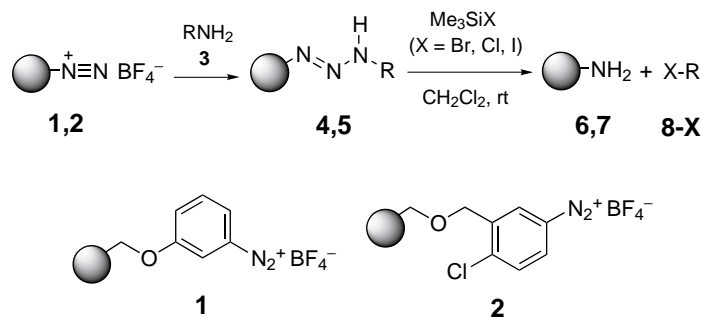
The reaction of diazoalkanes<sup>1</sup> with nucleophiles is a frequently used process to synthesize carboxylic esters<sup>2</sup> and alkyl and aryl ethers.<sup>3</sup> However, the parent compound for this transformation, diazomethane, and its higher homologues are considered to be highly toxic and explosive.<sup>1</sup> Similarly, the well-known precursors for diazomethane (such as Diazald<sup>®</sup>) are also irritants.<sup>4</sup>

During the investigation of the synthesis of amides on solid support using the triazene T2 linker family,<sup>5</sup> we observed that in some cases the acyl coupling was not effective. When the subsequent cleavage was performed with trimethylsilyl chloride, alkyl chlorides were produced in good yields and excellent purities. These preliminary results<sup>6–8</sup> prompted us to investigate this reaction in more detail.

The transformation depicted in Scheme 1 can be used for the synthesis of alkyl halides. The synthesis starts

from the diazonium resin **1**<sup>9</sup> or, more conveniently, from the room temperature stable diazonium resin T2\* (**2**),<sup>10,11</sup> which are both available in two steps from Merrifield resin (1–2% cross-linked with DVB, 100–200 mesh, approx. 1 mmol/g loading). Coupling with various primary aliphatic amines **3** proceeds smoothly to give disubstituted triazenes **4** or **5**, respectively.<sup>12</sup>

Reaction of the triazene resins **4,5** with trimethylsilyl chloride (10% in dichloromethane) was found to proceed smoothly at room temperature within a few minutes. Filtration and evaporation of the solvent (ca. 1.0 mbar) afforded the alkyl chlorides **8-Cl** in 70–95% yield and over 90% purity without any further purification (NMR, GC, and GC–MS).<sup>13</sup> Similarly, trimethylsilyl bromide and trimethylsilyl iodide are suitable to result in the formation of alkyl bromides and iodides, respectively. Interestingly, the formation of alkenes, a general



**Scheme 1.** Synthesis of alkyl halides.

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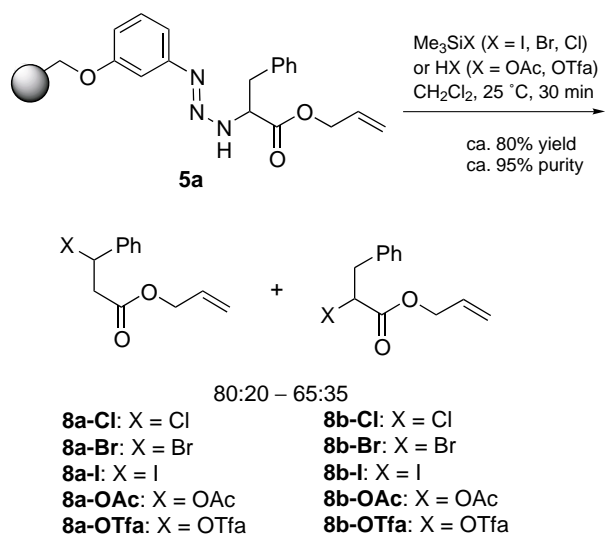
byproduct of the solvolysis of aliphatic diazonium salts due to elimination reactions,<sup>2</sup> has only been detected in traces (Scheme 2).

Mechanistically, this reaction proceeds via cleavage of the disubstituted triazene to the corresponding aniline resin **6,7**<sup>8</sup> and an aliphatic diazonium ion, which decomposes in the presence of a nucleophile to give the alkyl halides. The reaction of alkyl diazonium salts with halides to give alkyl halides is a commonly used transformation. The general entry into this reaction is the use of azoalkanes, which are cleavable with HCl,<sup>14,15</sup> HBr<sup>16</sup> or HI to give the corresponding alkyl halides. To the best of our knowledge, the reaction of azoalkanes

with trimethylsilyl halides has not been studied before (Scheme 3).

The reaction mechanism also explains the rearrangement of homobenzyl residues **5e** to the corresponding phenylpentenyl residue **8f** (Scheme 4), which has also been observed earlier during the diazotation of  $\alpha$ -amino acids.<sup>17</sup> Complex triazenes such as the acetal **4d** or the ephedrine derivative **5c** undergo elimination reactions to produce ketones **14** or aldehydes **13**, respectively.

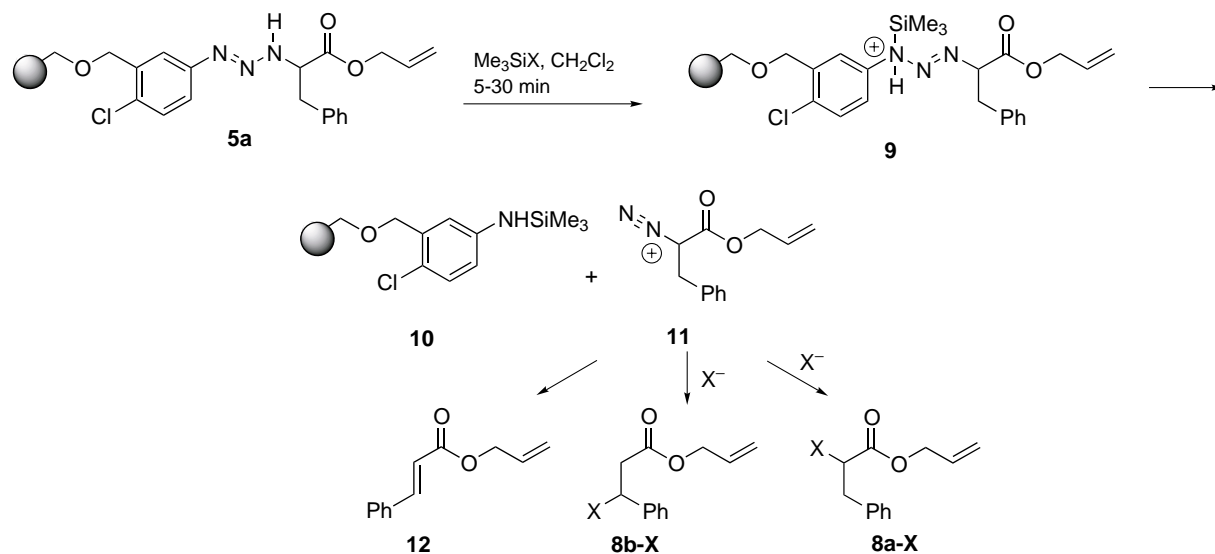
The cleavage with carboxylic acids was also examined in this context.<sup>18</sup> It is known that disubstituted triazenes can be used for the alkylation of sensitive acids.<sup>19</sup> Thus, treatment of the disubstituted triazene **5a**, as demonstrated above resulted in the formation of esters **8a-OAc,OTfa** and **8b-OAc,OTfa**, respectively, in good yields. Similarly, homobenzyl resins **5g,h** were cleaved to give the esters **8g,h-OAc,OTfa** without detectable amounts of styrenes caused by elimination. Interestingly, even the less nucleophilic trifluoroacetic acid can be used for this transformation (Scheme 4).



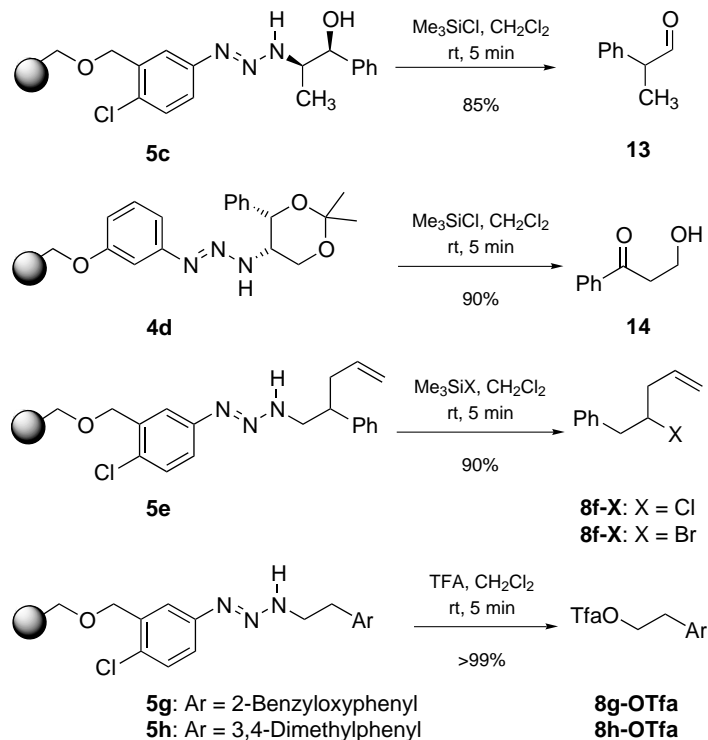
Scheme 2. Cleavage of phenylalanine esters.

*General procedure for the cleavage of the T2 linker:* A suspension of the resin (200 mg) in dichloromethane was treated with 4 equiv. of trimethylchlorosilane and the mixture was stirred at room temperature for 5 min. The mixture was filtered and the solvent was removed. This reaction can also be performed in a pipette or fritted syringe filled with the resins.

In conclusion, a novel technique<sup>20</sup> for the synthesis of alkyl halides using solid-phase methods<sup>21</sup> was developed, giving rise to products in high yield and purity. The method was also successfully applied to the synthesis of alkyl esters.<sup>22</sup>



Scheme 3. Mechanistic rationale for the cleavage of disubstituted triazenes.

Scheme 4. Cleavage of resins **4d**, **5c**, **e**, **g**, **h**.

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