Published in final edited form as:

Angew Chem Int Ed Engl. 2009 ; 48(13): 2359–2363. doi:10.1002/anie.200804689.

A Phosphine-Mediated Conversion of Azides to Diazo-Compounds**

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Keywords

Acyl triazene; Azide; Diazo-compound; Phosphine; Staudinger ligation; Staudinger reaction

Diazo-compounds are remarkably versatile intermediates in organic synthesis, participating in a variety of thermal, photochemical and metal-catalyzed rearrangement, addition, cycloaddition and insertion reactions, typically with concomitant expulsion of N₂.^[1] They have been found in nature, examples of which include azaserine^[2] and members of the kinamycin^[3] and lomaiviticin^[4] families of marine natural products. Depending upon their stability and coexisting functional groups, diazo-compounds can present a challenge with respect to their preparation and isolation. Current methods include (a) diazo-transfer,^[5] (b) diazotization,^[6] (c) decomposition^[7] or oxidation^[8] of hydrazones, (d) rearrangement of *N*-alkyl *N*-nitroso-compounds,^[9] (e) fragmentation of 1,3-disubstituted alkyl aryl-triazenes,^[10] and (f) elaboration of more readily available diazo-compounds (Scheme 1).^[11]

The preparation of diazo-compounds via the fragmentation of triazenes is uncommon. This route was described originally by Baumgarten, who isolated ethyl diazoacetate by the acid-catalyzed fragmentation of an aryl-triazene derivative (Scheme 1, Eq. 1).^[10a] More recent work by Bräse demonstrated that similar solid-supported triazenes, specifically those substituted with electron-deficient aryl groups, also undergo fragmentation under basic conditions (Scheme 1, Eq. 2).^[10b] The triazene precursors can be prepared by the addition of nitrogen-based nucleophiles to aryl diazonium salts or by the addition of organometallic species to azides with subsequent trapping of the resulting triazenyl anion with electrophiles, the former being the more popular approach.^[12] These methods have limited synthetic utility. Herein we report a convenient synthetic route to 1,3-alkyl-acyl triazenes that uses azides as substrates and employs mild conditions; furthermore, we disclose that these acyl triazenes undergo thermal or base-catalyzed fragmentation *in situ* to form diazo-compounds in high yield.

**We thank Dr. Ilia A. Guzei and Amit Choudhary for X-ray data pertaining to triazene 8 and Dr. Annie Tam for preparing azide 2d. We acknowledge use of the National Magnetic Resonance Facility (NMRFAM) and services of the Mass Spectrometry Facility in the Department of Chemistry. This work was supported by NIH grant GM044783; NMRFAM was supported by NIH grant P41RR02301.

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We reasoned that triazenes (and thus diazo-compounds) might be accessible from the phosphazides produced by the highly chemoselective reaction of a phosphine and azide. Much of the chemistry associated with this partnership emanates from an iminophosphorane, a species generated by the rapid extrusion of N₂(g) from the phosphazide.^[13] An obvious requirement for accessing triazenes would be the avoidance of N₂(g)-extrusion. Although we were encouraged by numerous reports in the literature on the isolation and trapping of phosphazides, typically achieved through careful choice of both the phosphine and the azide components,^[14] we were intrigued by doing so via an intramolecular acylation event reminiscent of the Staudinger ligation (Scheme 2).^[15]

Phosphines employed in the Staudinger ligation possess an *O*- or *S*-ester proximal to the phosphorus. This ester is reactive enough to trap the iminophosphorane but not the foregone phosphazide, whence extrusion of N₂ is the faster process (Scheme 2).^[16] We anticipated that the presence of a more potent acylating moiety could entice the phosphazide to form a triazenophosphonium species, which upon hydrolysis would provide an acyl triazene (Scheme 2). The electron distribution in acyl triazenes is similar to that in the triazenes employed by Baumgarten and Bräse (Scheme 1^[10]), and we suspected that they too would be competent precursors of diazo-compounds.

We began our study by investigating the reaction of azido glycine derivative **2a** with a series of phosphines that contained ester substituents of increasing leaving-group ability (Scheme 3). As expected, the reaction of azide **2a** and phosphinoester **1a**, the latter being of the type used in a Staudinger ligation, provided the amide **3** as the predominant product (~90% yield). Early success was achieved with phosphinothioester **1b**: upon allowing the reaction mixture to stir beyond the time necessary for complete consumption of the phosphine, the solution gradually turned a yellow color, indicative of the presence of diazo-compound. Chromatography and subsequent analysis confirmed the presence of diazo-compound **5a** (30% yield) along with primary amide **4** (33% yield) and Staudinger ligation product **3** (60% yield). Ultimately, using phosphine-*N*-hydroxysuccinimyl ester **1c**, conditions were developed that provided diazo-compound **5a** in excellent yield. For this particular combination, a white precipitate formed after a few hours in 1,4-dioxane/H₂O or THF/H₂O solvent mixtures. Upon allowing the mixture to stir for a few days, the suspension eventually gave way to a clear yellow solution. After some experimentation, we found that treating the suspension with sat. aq. NaHCO₃ or NEt₃ (2 equiv), facilitated the formation of the diazo-compound within minutes.

The aforementioned white precipitate and presumed precursor to the diazo-compound was tentatively characterized as acyl triazene **6** (Scheme 4). The ¹H NMR spectrum of the intermediate, acquired in CDCl₃ at 25 °C, was broad and exhibited a conspicuous downfield signal at ~13.4 ppm. Lowering the temperature to -6 °C led to decoalescence and sharpening of the spectrum to reveal a pair of isomers, in a ratio of 3:1, exhibiting downfield signals at ~13.5 ppm and ~12.8 ppm, respectively, that disappear following a "D₂O shake". Acyl alkyl-triazenes and alkyl aryl-triazenes are known to exist in solution as a mixture of tautomers, wherein the acidic proton resides on either terminus of the triazene moiety.^[14f,17] Unfortunately, we failed in our attempts to obtain crystals of the intermediate that were suitable for X-ray crystallography, due in part to its thermal instability. When, however, aryl azide **7** was allowed to react with phosphine **1c**, acyl triazene **8** was isolated in excellent yield by column chromatography, and its structure was confirmed by X-ray crystallography (Scheme 4). The ¹H NMR spectrum of acyl triazene **8** exhibited a downfield signal at ~12.9 ppm, providing strong evidence that the asserted precursor to diazo-compound **5a** is indeed acyl triazene **6**.

Although the yield of diazo-compound **5a** from azide **2a** was satisfactory, the rate of reaction was unacceptably low. By following the progress of the reaction of **1c** and **2a** by ^{31}P NMR spectroscopy, we observed that only 50% conversion to acyl triazene **6** was achieved after 100 min. We attributed this low reaction rate to delocalization of electron density from the phosphorous atom into the electron-deficient aromatic ring, thereby slowing down its addition to the azide. Accordingly, we designed an alternative reagent in which the phosphine and activated-ester moieties were not in conjugation. Phosphine **1e** (Scheme 5), prepared in excellent yield by 1,4-addition of diphenylphosphine to methyl acrylate followed by saponification and carbodiimide-mediated esterification, reached 50% conversion in its reaction with **2a** after just 20 min. Hence, phosphine **1e** is a preferred reagent for mediating the conversion of an azide to a diazo-compound.

Conducting the reaction in a wet solvent (THF/H₂O) and using near equimolar amounts of phosphine (1.05 equiv) were found to be crucial for effectuating good conversion to diazo-compound. When the reaction of azide **2a** was conducted under anhydrous conditions (*e.g.*, in CH₂Cl₂), diazo-compound **5a** was formed quickly in situ, presumably via fragmentation of the putative acyl triazenophosphonium salt (Scheme 2). Unfortunately, although the phosphine was consumed completely, the yield of diazo-compound **5a** was moderate (~50%) and a substantial amount of the azide starting material was reisolated (~10–15%). Subsequent investigation revealed the origin of the diminished conversion: phosphine **1e** (and **1c**) reacted with diazo-compound **5a** at a rate that was comparable to that of its reaction with azide **2a** to give a compound whose spectroscopic data were consistent with acyl hydrazone **9** (Scheme 5).^[14a,18] Under wet conditions and preceding basic workup, the thermal decomposition of acyl triazene **6** (the hydrolysis product of the acyl triazenophosphonium salt) is slow, allowing near complete consumption of azide and phosphine before accumulation of appreciable concentrations of the diazo-compound.

The mechanism of fragmentation of acyl triazene **6** under thermal conditions presumably involves scission of the pertinent N–N bond to give the diazonium salt and the conjugate base of primary amide **4** (**4-CB**) followed by proton transfer to give diazo-compound **5a** and **4** (Scheme 6). As acyl triazene **6** is likely to be relatively acidic, the fragmentation might be acid-catalyzed and thus autocatalytic.^[19] In a basic environment, the acyl triazene **6** would exist primarily as its conjugate base (**6-CB**), albeit in equilibrium with **6**. Deprotonation of **6** at the α -carbon would give the alternative conjugate base **6-CB'**. In a manner reminiscent of the Bamford–Stevens reaction—the base catalyzed fragmentation of *p*-toluenesulfonylhydrazones^[7a]—such a species could undergo N–N scission to give diazo-compound **5a**. Alternatively, unstable **6-CB'** could arise directly from **6-CB** via an intramolecular proton transfer. For certain substrates the latter might be a contributory pathway under the conditions prior to basic workup (*vide infra*).

The scope of the reductive fragmentation reaction was found to be quite general. Using phosphine **1e**, α -azido esters and lactones (**5d–g**, Scheme 7) were converted to their diazo-compound derivatives in excellent yield. As complete consumption of the azide was achieved within a few hours and the side products were relatively polar (primary amide, hydrolyzed phosphine reagent, and/or trace amounts of hydrazone), short-path column chromatography was sufficient in providing diazo-compound in excellent purity. α -Azido ketones proved to be problematic due to the difficulty of avoiding pre-workup fragmentation to a diazo-compound and subsequent reaction to form an acyl hydrazone, as in Scheme 5. Nevertheless, α -diazo cyclohexanone **5h** and α -diazo acetophenone **5i** were obtained in yields of 67% and 49% respectively. For the latter, conducting the reaction in anhydrous toluene followed by column chromatography proved to be slightly superior with respect to yield. In addition to the glycine derivative **2a**, other azido-amides were found to be excellent substrates. For example, the azido-amide derivative of phenylalanine **2b** was transformed to

diazo-compound **5b** in 81% yield. It was observed that a prolonged basic workup (sat. aq. NaHCO₃, overnight) was required for fragmentation of the putative triazene, presumably due to steric hindrance at the pertinent site of deprotonation. In contrast, an alternative workup involving isolation of the crude triazene and its treatment with the much stronger base DBU (1.2 equiv) in CH₂Cl₂ furnished **5b** within a few minutes and in 85% yield; NEt₃ was ineffectual in this instance. Similarly, azido lactam **2c** (with DBU workup) gave the diazo-compound **5c** in 95% yield.

To probe the scope of the reaction even further, we investigated the synthesis of semi-stabilized diazo-compounds. Treatment of 9-azido-fluorene **2j** with phosphine **1e** under anhydrous conditions at low temperature (toluene, 0 °C), followed by loading the red solution directly on basic alumina (Grade 5) and eluting with 10% CH₂Cl₂/hexanes, 9-diazo-fluorene **5j** was isolated in 85% yield and excellent purity (96%). Apparently, thermal fragmentation of the putative triazenophosphonium salt, which more than likely exists in its neutral λ⁵-phosphorane form,^[16] is suppressed sufficiently for this substrate under the reaction conditions. The low temperature and low polarity of the solvent probably contribute to that greater stability. Under the standard conditions (THF/H₂O), incomplete conversion of the azide **2j** and contamination of the diazo-compound **5j** with substantial amounts of other products, probably arising from alternative triazene decomposition and dimerization of the diazo-compound, were apparent. Finally, a vinylogous diazo-carbonyl compound **5k** (96% purity) was prepared in good yield from anthraquinone-based azide **2k** using the standard conditions.

Benzyl azide, whose pertinent hydrogens are relatively non-acidic, was converted in good yield to acyl triazene **10** and, unsurprisingly, failed to undergo smooth conversion to the diazo-compound under the standard conditions (Scheme 8). Yet, when a solution of **10** in toluene was heated to 80 °C in the presence of phenylalanine carboxylic acid derivative **11**, the benzyl ester **12** was isolated in 50% yield. Presumably, under the latter conditions the acyl triazene undergoes protic acid-induced fragmentation to the benzyl diazonium salt and primary amide followed by rapid alkylation of carboxylate.^[19] These conditions might also be conducive towards alkylation of triazene, homolytic fragmentation of triazene (to give amidyl and alkyl radicals),^[20] and 1,3-acyl migration processes,^[20a] some of which might contribute to the moderate conversion to ester **12**.

To conclude, we have developed a mild method for the conversion of azides to their diazo-compound derivatives using a phosphine reagent. This “deimidogenation” reaction is highly selective in most chemical environments and thus allows for the synthesis of diazo-compounds in the presence of delicate functionality, which is a challenge given current methodology. Along those lines, we are in the process of preparing water-soluble phosphine reagents for applications in chemical biology,^[21] a field already adept at the emplacement of the target azide moiety on biomolecules.^[22]

Experimental Section

Experimental details can be found in Supporting Information

Supplementary Material

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Scheme 1.
Methods for preparing diazo-compounds.

Scheme 2.
Reactions of phosphines and azides.

Scheme 3.

Distribution of products for the reaction of phosphines with azide **2a** (NHS = *N*-hydroxy succinimyl).

Scheme 4.
Synthesis of aryl acyl triazene **8**.

Scheme 5.
Further reaction of diazo-compound **5a**.

Scheme 6.

Putative mechanistic scheme for the thermal or base-catalyzed fragmentation of acyl triazene **6**.

Scope of diazo-compound formation mediated by phosphine **1e**. Footnotes: a) Workup: DBU (1.2 equiv), CH_2Cl_2 , 20 min; b) Conditions: **1e** (1.05 equiv), toluene, 0 °C to rt; c) **1e** (1.1 equiv).

Scheme 8.

Acyl triazenes as precursors to alkyl diazonium salts.