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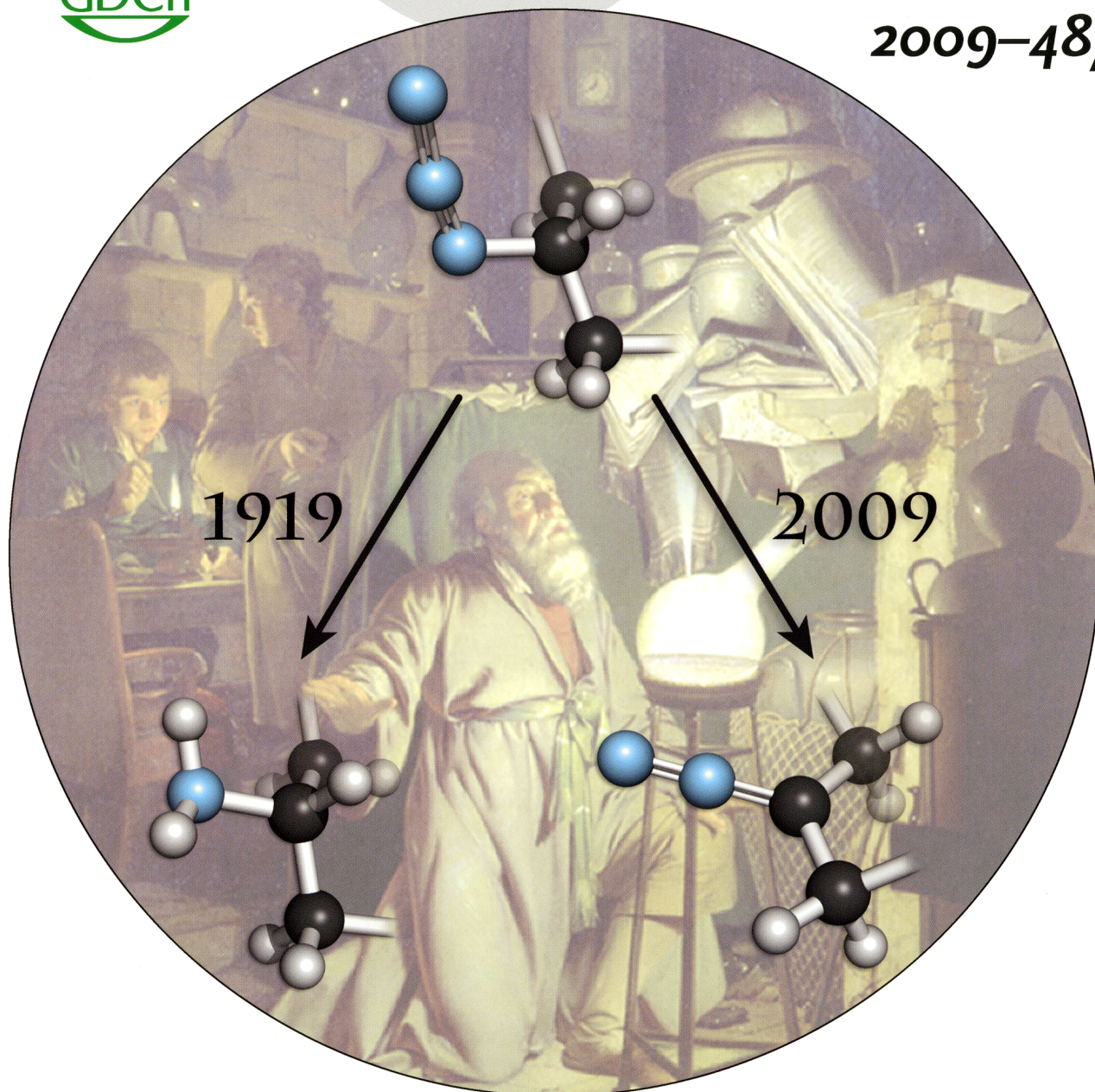
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In 1919 ...

... H. Staudinger and J. Meyer reported the reductive fragmentation of an azide to an amine. In their Communication on page 2359 ff., E. L. Myers and R. T. Raines report the complementary reaction—cleavage of the other N–N bond in an azide to yield a diazo compound. Both transformations rely on a reagent that contains P^{III} . The painting, *The Alchemist, in Search of the Philosopher's Stone, Discovers Phosphorus*, by J. Wright (1771), depicts the discovery of phosphorus by H. Brandt in 1669 (cover art by H. A. Steinberg).

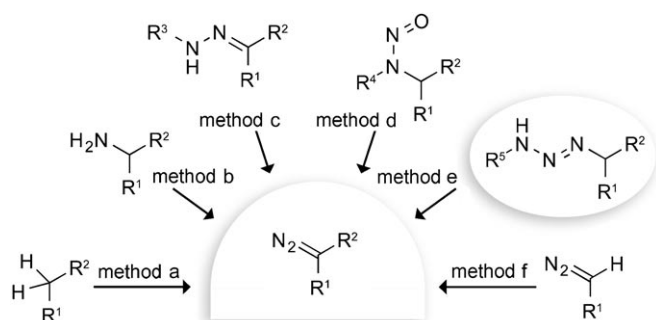
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Diazo Compounds

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

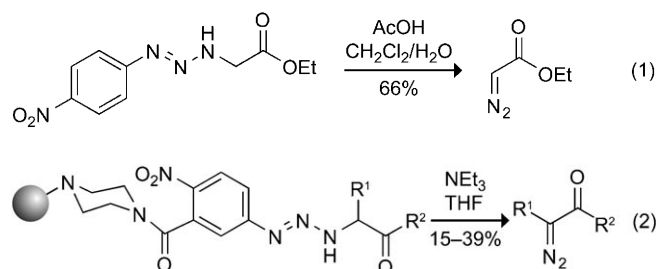
Eddie L. Myers and Ronald T. Raines*

Diazo compounds are remarkably versatile intermediates in organic synthesis that participate in a variety of thermal, photochemical, and metal-catalyzed rearrangement, addition, typically cycloaddition, and insertion reactions with concomitant expulsion of N₂.^[1] Diazo compounds are found in nature, examples of which include azaserine^[2] and members of the kinamycin^[3] and lomaivictin^[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]



Scheme 1. Methods for preparing diazo compounds.

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 [Eq. (1)].^[10a] More recent work by Schroen and Bräse demonstrated that similar solid-supported triazenes, specifically those substituted with electron-deficient aryl groups, also undergo fragmentation under basic conditions [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 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 reasoned that triazenes (and thus diazo compounds) might be accessible from the phosphazides produced by the highly chemoselective reaction of a phosphine and an azide. Much of the chemistry associated with this partnership emanates from an iminophosphorane, a species generated by the rapid extrusion of N₂ from the phosphazide.^[13] A requirement for accessing triazenes would be the avoidance of N₂ 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 by an intramolecular acylation event reminiscent of the Staudinger ligation (Scheme 2).^[15]

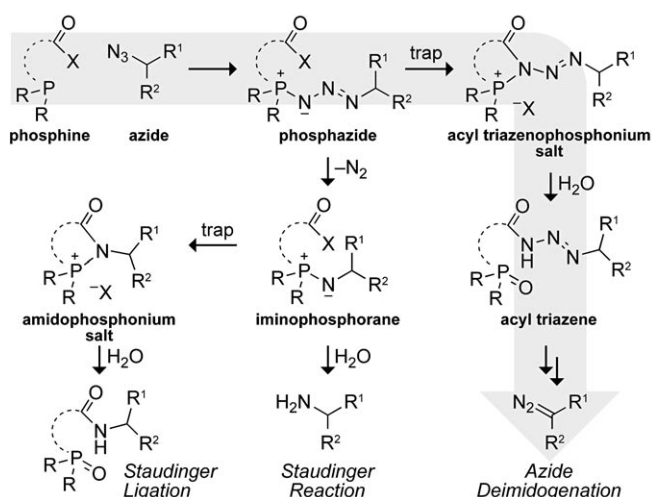
Phosphines employed in the non-traceless Staudinger ligation possess an *O*-ester proximal to the phosphorus atom. This ester is reactive enough to trap the iminophosphorane but not the foregone phosphazide because the extrusion of N₂ is the faster process (Scheme 2).^[16] We anticipated that the

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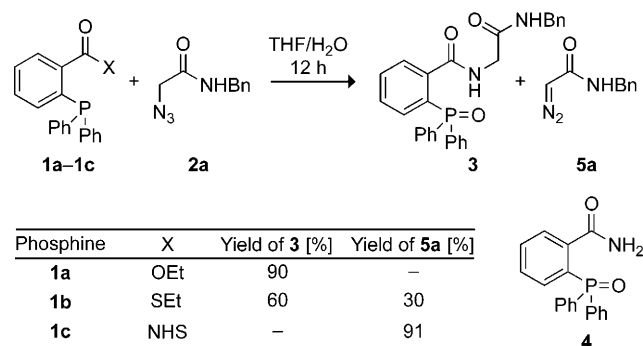
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200804689>.



Scheme 2. Reactions of phosphines and azides.

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; Azide deimidogenation pathway). The electron distribution in acyl triazenes is similar to that in the triazenes employed by Baumgarten, and Schroen and Bräse [Eqs. (1) and (2)]^[10], and we suspected that such triazenes would be competent precursors of diazo compounds.

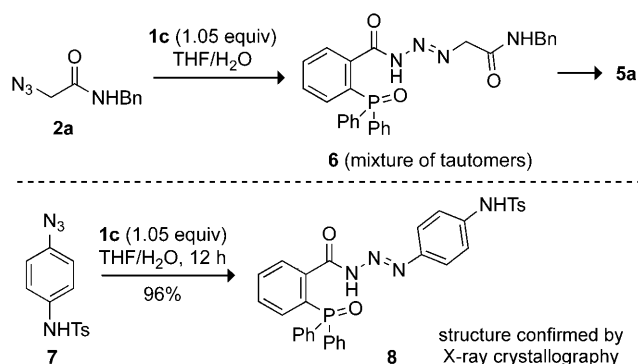
We began our study by investigating the reaction of azido glycine derivative **2a** with a series of phosphines that contained ester substituents of increasing leaving-group ability (Scheme 3). As expected, the reaction of azide **2a** and phosphinoester **1a**, the latter being of the type used in a Staudinger ligation, provided amide **3** as the predominant product (ca. 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 that was indicative of the presence of a diazo compound. Purification by using column chromatography, and subsequent analysis of the product confirmed the presence of diazo compound **5a** (30% yield) along with primary amide **4** (33%



Scheme 3. Distribution of products for the reaction of phosphines with azide **2a**. For the reactions: THF/H₂O = 20:3. Bn = benzyl, NHS = *N*-hydroxy succinimyl

yield) and Staudinger ligation product **3** (60% yield). Ultimately, conditions were developed by which phosphine-*N*-hydroxysuccinimyl ester **1c** mediated the transformation of azide **2a** into diazo compound **5a** in excellent yield. For this particular substrate combination, a white precipitate formed after a few hours in 1,4-dioxane/H₂O (20:3) or THF/H₂O (20:3) 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 saturated aqueous 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 peaks in the ¹H NMR

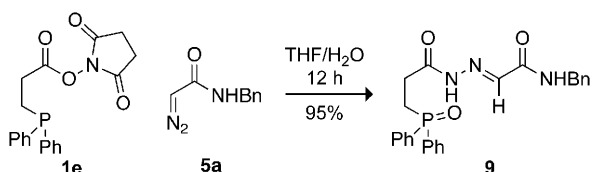


Scheme 4. Synthesis of acyl triazene **8**. For the reactions: THF/H₂O = 20:3. Ts = 4-toluenesulfonyl.

spectrum of the intermediate, acquired in CDCl₃ at 25 °C, were broad and exhibited a conspicuous downfield signal at approximately $\delta = 13.4$ ppm. Lowering the temperature to -6 °C led to decoalescence and sharpening of the peaks in the spectrum to reveal a pair of isomers in a ratio of 3:1, exhibiting downfield signals at approximately $\delta = 13.5$ ppm and $\delta = 12.8$ ppm, which disappear after 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 reacted with phosphine **1c**, acyl triazene **8** was isolated in excellent yield after 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 approximately $\delta = 12.9$ ppm, providing strong evidence that the 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 the reaction was unacceptably low. By monitoring the progress of the reaction of **1c** and **2a** by ³¹P NMR spectroscopy, we observed that only 50% conversion into acyl triazene **6** was achieved after 100 minutes. We attributed this low reaction rate to delocal-

ization 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

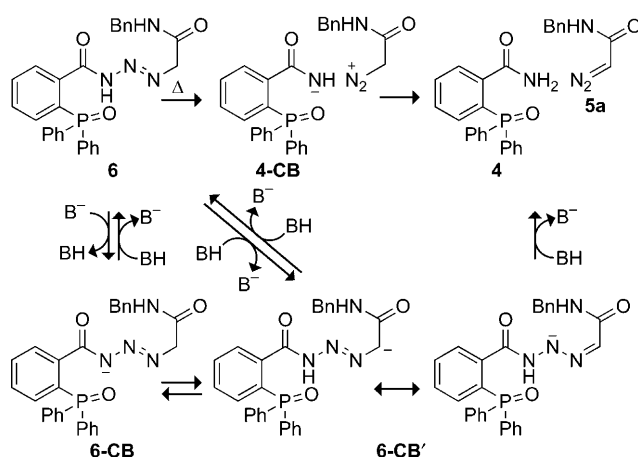


Scheme 5. Further reaction of diazo compound **5a**. For the reactions: THF/H₂O = 20:3.

in excellent yield by 1,4-addition of diphenylphosphine to methyl acrylate and subsequent saponification and carbodiimide-mediated esterification, reached 50 % conversion upon reaction with **2a** after just 20 minutes. Hence, phosphine **1e** is a preferred reagent for mediating the conversion of an azide into 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 into the 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 by fragmentation of the putative acyl triazenophosphonium salt (Scheme 2). Although the phosphine was consumed completely, the yield of diazo compound **5a** was moderate (ca. 50 %), and a substantial amount of the azide starting material was reisolated (ca. 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 a basic workup, the thermal decomposition of acyl triazene **6** (the hydrolysis product of the acyl triazenophosphonium salt) is slow, allowing near complete consumption of the azide and phosphine before accumulation of appreciable concentrations of the diazo compound.

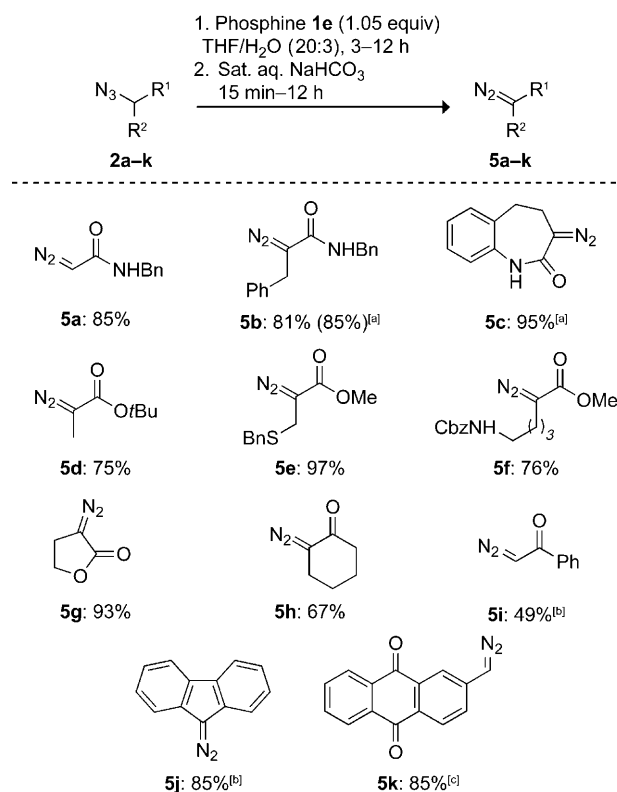
The mechanism of fragmentation of acyl triazene **6** under thermal conditions presumably involves scission of the pertinent N–N bond to give the diazonium salt and the conjugate base of primary amide **4** (**4-CB**) and subsequent proton transfer to give diazo-compound **5a** and **4** (Scheme 6). As acyl triazene **6** is likely to be relatively acidic, the fragmentation might be acid-catalyzed and thus autocatalytic.^[19] In a basic environment, 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**



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

through an intramolecular proton transfer. For certain substrates the latter might be a plausible reaction pathway prior to basic workup.

The scope of the reductive fragmentation reaction was found to be general. By using phosphine **1e**, α -azido esters and lactones (**2d–g**; Scheme 7) were converted into their diazo compound derivatives (**5d–g**) in excellent yield. As complete consumption of the azide was achieved within a few

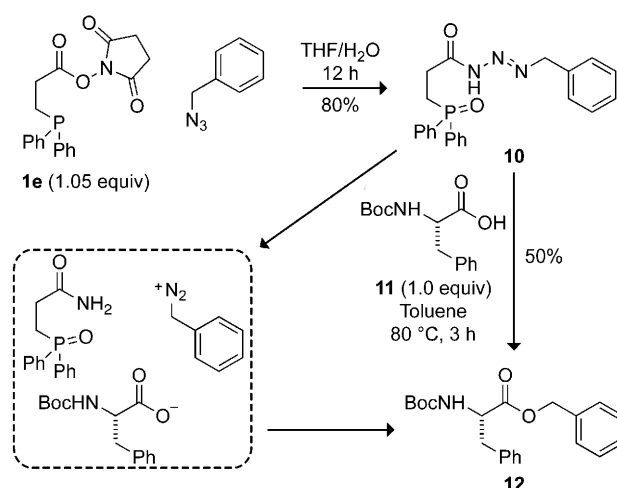


Scheme 7. Scope of the diazo compound formation mediated by phosphine **1e**. a) Workup: DBU (1.2 equiv), CH₂Cl₂, 20 min; b) Conditions: **1e** (1.05 equiv), toluene, 0°C → RT; c) **1e** (1.1 equiv). Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

hours and the side products (primary amide, hydrolyzed phosphine reagent, or trace amounts of hydrazone) were relatively polar, a short-path column chromatography procedure was sufficient to provide the diazo compound in excellent purity. α -Azido ketones proved to be problematic because of the difficulty of avoiding pre-workup fragmentation to a diazo compound and the subsequent reaction to form an acyl hydrazone (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 and subsequent column chromatography proved to be slightly superior with respect to the 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 into diazo compound **5b** in 81 % yield. A prolonged basic workup (sat. aq. NaHCO_3 , overnight) was required for fragmentation of the putative triazene, presumably because of 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 CH_2Cl_2 furnished **5b** within a few minutes and in 85 % yield; NEt_3 was ineffective in this instance. Similarly, azido lactam **2c** (with DBU workup) gave diazo compound **5c** in 95 % yield.

To probe the scope of the reaction 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), and then loading the red solution directly onto basic alumina (Grade 5) and eluting with 10 % CH_2Cl_2 /hexanes, 9-diazo-fluorene **5j** was isolated in 85 % yield and excellent purity (96 % determined by NMR methods). Apparently, thermal fragmentation of the putative triazenophosphonium salt, which more than likely exists in its neutral λ^5 -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/ H_2O (20:3)), 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 determined by NMR methods) was prepared in good yield from anthraquinone-based azide **2k** by using the standard conditions.

Benzyl azide, whose pertinent hydrogen atoms are relatively nonacidic, was converted in good yield into acyl triazene **10** and, unsurprisingly, failed to undergo smooth conversion into the diazo compound under the standard conditions (Scheme 8). Yet, when a toluene solution of **10** was heated at 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 the alkylation of triazene, homolytic



Scheme 8. Acyl triazenes as precursors to alkyl diazonium salts. For the reaction: THF/ H_2O = 20:3. Boc = *tert*-butoxycarbonyl.

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 into ester **12**.

To conclude, we have developed a mild method for the conversion of azides into their diazo compound derivatives using a phosphine reagent. This “deimidogenation” reaction is highly selective in most chemical environments and allows the synthesis of diazo compounds in the presence of delicate functional groups, which is a challenge given the 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 placement of the target azide moiety onto biomolecules.^[22]

Experimental Section

Experimental details can be found in the Supporting Information.

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