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Selective Protection of Secondary Amines as the *N*-Phenyltriazenes. Application to Aminoglycoside Antibiotics

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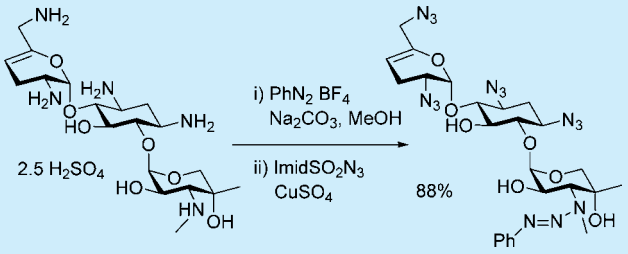
Supporting Information

ABSTRACT: Selective protection of secondary amines as triazenes in the presence of multiple primary amines is demonstrated, with subsequent protection of the primary amines as either azides or carbamates in the same pot. Aminoglycoside antibiotic examples reveal broad functional group compatibility. The triazene group is removed with trifluoroacetic acid and, because of the low barrier to rotation, affords sharp ^{1}H NMR spectra at room temperature.



Ongoing studies in our laboratories in the aminoglycoside field highlighted the challenges of working with highly basic polyamines and the need for selective protection methods.[1] In particular, we were struck by the need for selective protection of dissymmetric secondary amines[2] without complications of the NMR spectra by the presence of slowly interconverting conformers. The use of carbamates and amides affords rotamers and thus hinders routine spectral interpretation,[3] while sulfonamides require less than ideal conditions for eventual deprotection.[4] To solve this problem, we explored the use of a number of alternative protecting groups, required to be rotamer-free and cleavable under mild conditions, before selecting the phenyl triazenes.[5]

The trisubstituted triazene function has been widely employed in recent years for the protection and/or derivatization of aryl amines, when it is typically introduced by reaction of an arene diazonium salt with either a free or polymer-bound secondary amine.[6] Alternatively, the same trisubstituted triazenes can be employed to protect secondary amines where they display a useful tolerance of a range of oxidizing and reducing conditions yet are readily cleaved on exposure to trifluoroacetic acid.[7] A recent report on the palladium-catalyzed carbonylative removal of nitrogen from 1,1-dialkyl-3-aryltriazenes (R_2N-N_2Ar) affording amides (R_2NCOAr) offers the additional possibility of protecting group interconversion in a single step.[8]

1,3-Disubstituted triazenes, on the other hand, while accessible by the reaction of primary amines with diazonium salts, are much less stable.[7c,9] Accordingly, such 1,3-disubstituted triazenes are more commonly exploited as nucleophiles in the capture of a range of electrophiles, either inter- or intramolecularly.[9a,10]

In view of the relative instability of the disubstituted triazenes with respect to their trisubstituted congeners, and the anticipated sharp NMR spectra, we considered the possibility of employing the triazene function for the selective protection of secondary amino groups in the presence of primary amino groups. We describe here the reduction of this concept to practice and its application to the selective protection of aminoglycoside antibiotics.

Barriers to rotation about the RR′N−N_2Ph bond in 1,1-dialkyl-3-phenyltriazenes have been determined by VT-NMR methods to be in the range 13.8−14.7 kcal mol^{-1} depending on the substituent pattern.[11] The barrier increases significantly when the phenyl group is replaced by an electron-deficient arene[11b,c] or other electron-withdrawing group,[12] but is reported to be 1 kcal mol^{-1} lower in $CDCl_3$ than in CS_2.[11c] Notably steric bulk in the alkyl groups is reported to have little influence on the barrier to rotation about the N−N single bond, but in the extreme case of 2,2-dimethyl- and 2,2,6,6-tetramethylpiperidine-based triazenes the barrier is reduced to ∼11 kcal mol^{-1} in CS_2. Overall, ^{1}H NMR spectra recorded in $CDCl_3$ at room temperature for the 1,1-dialkyl-3-phenyltriazenes are expected to be above the coalescence temperature and to be correspondingly sharp.

A series of primary and secondary diamines were treated with 1.1 equiv of benzenediazonium tetrafluoroborate in Methanol/water in the presence of powdered potassium or sodium carbonate followed by addition of an excess of imidazolesulfonyl azide and catalytic copper sulfate.[13] Workup and silica gel chromatography then gave the azido triazenes in moderate to good yield as reported in Table 1. Yields are not improved by the use of excess benzenediazonium tetrafluoroborate as this leads to complications in isolation arising from decomposition of the reagent.

The examples presented in Table 1 (entries 1−5) demonstrate the viability of this two step-one pot protocol: secondary amino groups of varying steric environments can be selectively protected in the presence of one or more primary aliphatic or aromatic amino groups, which can then be converted to the corresponding azides. Entry 6 of Table 1

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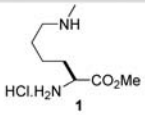
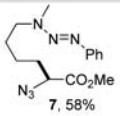
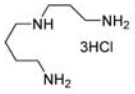
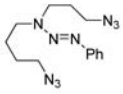
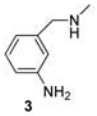
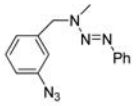
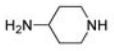
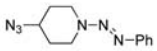
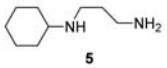
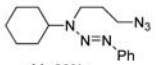
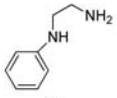
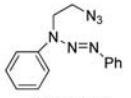
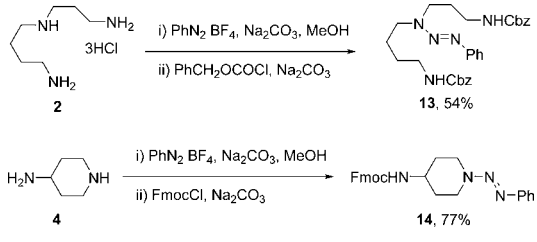
Table 1. Selective Protection of Diamines as Azido Triazenes

entry	substrate	product, % yield
1	 1	 7, 58%
2	 2	 8, 61%
3	 3	 9, 69%
4	 4	 10, 70%
5	 5	 11, 60%
6	 6	 12, decomp

illustrates the attempted application of the method to a secondary aromatic amine in the presence of a primary aliphatic amine. Unfortunately, while the protocol was successful as judged by NMR and mass spectral investigation of the crude reaction mixture, the product **12** could not be isolated pure after silica gel chromatography owing to the slow decomposition of the diaryl triazene moiety.

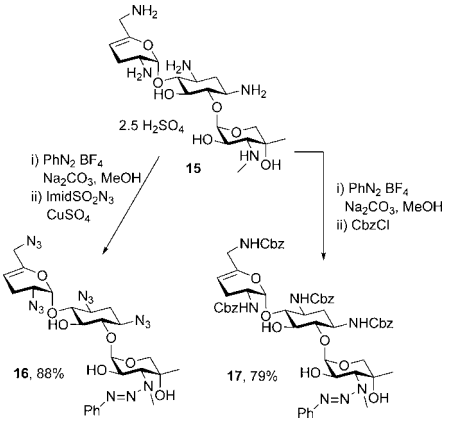
The method is not limited to the conversion of the primary amine functionality to azide groups: Scheme 1 illustrates the conversion of spermidine to a triazeno bis(benzyloxy carbamate) and of 4-aminopiperidine to a triazeno 9-fluorenylmethyl carbamate.

Scheme 1. Selective Protection of Polyamines as Triazeno Carbamates



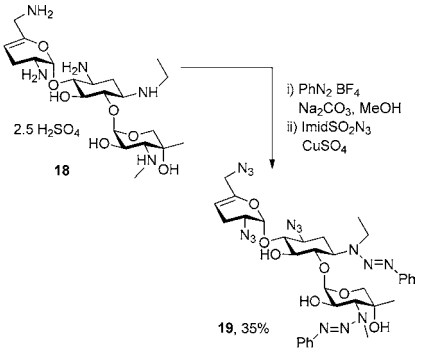
Having established the viability of the method, we explored its application to the aminoglycosides. First, we investigated sisomicin **15** with its single secondary and four primary amino groups. Reaction with 1 equiv of benzenediazonium tetrafluoroborate under the standard conditions was followed by treatment with either an excess of imidazolesulfonyl azide or benzyloxycarbonyl chloride resulting in the isolation of **16** and **17**, respectively, both in excellent yield (Scheme 2). Application to netilmicin **18**, with two secondary amino groups, was also successful, albeit only in moderate yield

Scheme 2. Application to Sisomicin



(Scheme 3). Finally, the method was applied to the monosubstituted deoxystreptamine aminoglycoside apramycin

Scheme 3. Application to Netilmicin



20, when the azido and carbamate-protected triazenes **21** and **22** both were obtained in moderate yield (Scheme 4).

The examples of Schemes 2–4 illustrate the potential of the method for the selective protection of secondary amino groups in complex substrates containing multiple primary amino groups. In addition to showing compatibility with ester functions (Table 1, entry 1), these examples reveal that the selective installation of the triazene moiety may be conducted in the presence of primary, secondary, and tertiary hydroxyl groups, glycosidic bonds, and enol ethers. The apramycin series also serves to illustrate the selective removal of the triazene moiety. Thus, brief treatment of either **21** or **22** with trifluoroacetic acid in a mixture of dichloromethane and ethanol at room temperature gave essentially quantitative yields of the azide- and carbamate-protected secondary amines **23** and **24**, respectively (Scheme 4). The conversion of apramycin to **23** by this simple two-step procedure is noteworthy; direct conversion of apramycin to **23** by copper sulfate catalyzed treatment with excess triflyl azide gave only a 50% yield and was complicated by the concomitant formation of a N7′-demethylated pentaazide in yields ranging from 10 to 20%.[14]

Consistent with expectations, the ^{1}H NMR spectra of the azido triazenes reported herein are mostly sharp in $CDCl_3$ and CD_3OD at room temperature (see the Supporting Information) with the exception of those compounds that contain multiple Cbz groups. The contrast between the ^{1}H NMR spectra of phenyl triazene protected dissymmetric

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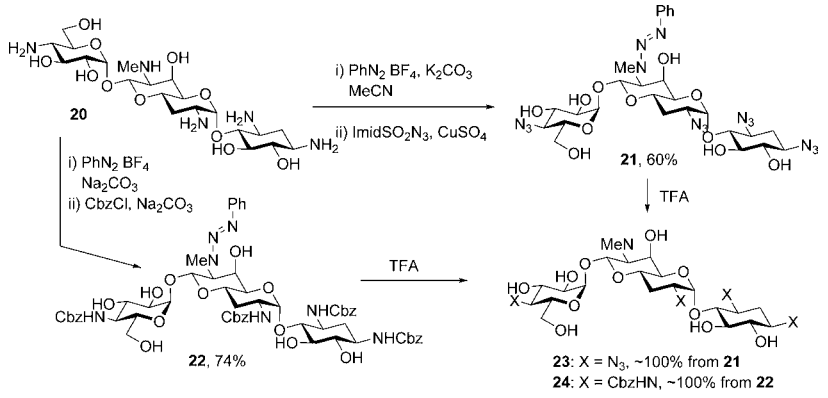
Scheme 4. Application to Apramycin and Deprotection



secondary amines and those of the corresponding carbamates is illustrated in Figure 1. The room-temperature ^{1}H NMR

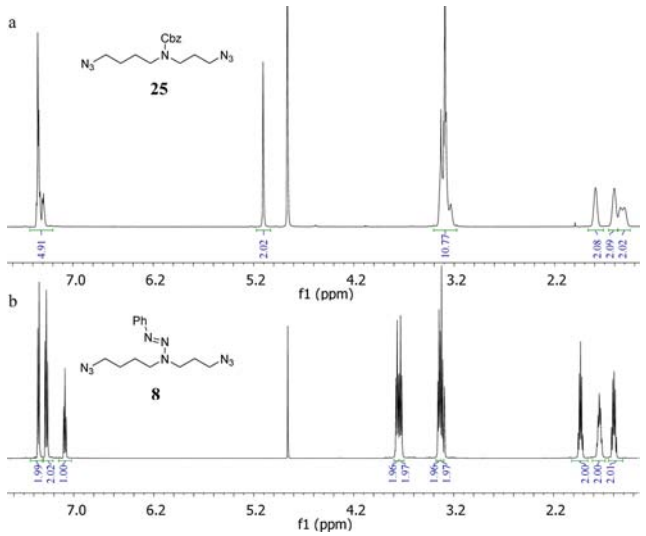


Figure 1. Room-temperature 600 MHz ^{1}H NMR spectra of **25** (a) and **8** (b) in CD_3OD.

spectrum of **25**, obtained by sequential treatment of spermidine with imidazole sulfonyl azide and benzyl chloroformate, displays significant broadening of all resonances in this pseudosymmetric secondary carbamate (Figure 1a). In contrast, the ^{1}H NMR spectrum of the corresponding diazido triazene **8** is sharp (Figure 1b). The ^{1}H NMR spectra of some azido triazenes, however, do show broadening of selected resonances (see the Supporting Information spectra), such as noted for other trizenes,[15] rather than for multiple resonances; as such, spectral interpretation is not significantly impaired.

The ability to selectively protect secondary amino groups in the presence of primary amino groups in high yield with only a 10% excess of the reagent suggests that the more basic secondary amino groups undergo electrophilic attack by the diazonium ion more rapidly than the primary amino groups. Alternatively, the primary amino groups react with the diazonium salt to give either a disubstituted triazene or other reactive intermediate either reversibly or such that the diazo moiety is rapidly transferred intermolecularly to the secondary amino group. Whichever pathway is correct, it is clear that a useful method for the selective protection of a secondary amine in the presence of a primary amine is at hand.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01902.

Full experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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