# Triazenes: A Useful Protecting Strategy for Sensitive Secondary Amines

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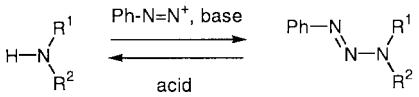
**Abstract:** The application of aryl triazene as a protecting group for sensitive secondary amines such as 4-piperidone (**2**) is described. The triazene protected amine is compatible with oxidative and reductive conditions as well as with lithiating and alkylating reagents. The free amine is regenerated by treatment with trifluoroacetic acid.

**Key words:** amines, piperidones, protecting groups, triazenes

The secondary amine is a functional group which is often found in natural products and biologically active substances (*N*-methylamino acids, alkaloids). Although many methods exist for protecting amino groups, few are compatible with metal hydride reductions, organolithium bases and alkylating agents.[1,2] During our work with 4-piperidones as potential building blocks for combinatorial asymmetric drug discovery on solid support we were faced with the sensitivity of these compounds in deprotonation and reduction reactions. Because neither an established linker nor a protecting group served our needs for the planed transformations, our search for unusual protecting groups led us to the idea of using the diazenyl group.[3] In this letter, we describe our observations on the preparation, stability and cleavage of triazene moieties containing the base sensitive amine 4-piperidone (**2**). Triazenes are well known substances which have been applied for the protection of primary aromatic amines.[4–9] However, less attention has been focussed on the use of triazenes as suitable amine protecting groups[10] and only two reports dealt with piperidone or piperidinol based triazenes.[4,11]

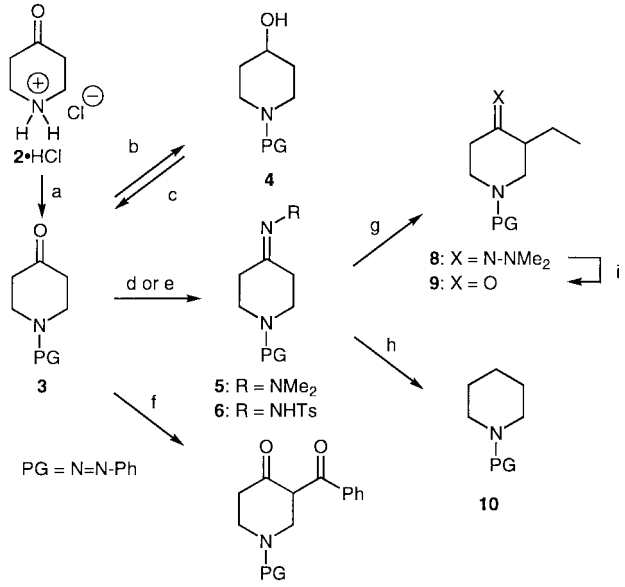



**1**

**Scheme 1**

## Protection of amine

The secondary amine functionality was protected by adoption of the method of Gross et al.[5] as the phenyl triazene **1** by mixing a cold solution of phenyl diazonium salts with a cooled mixture of the secondary amine, triethylamine and aqueous THF.[12] *p*-Toluidine or *p*-chloroaniline as diazonium precursors are in some cases beneficial because the resulting products show a higher tendency to crystallize. The crude products were purified by treatment with charcoal and chromatography (yields 60–90%). The triazenes **3** and **12** are stable in contact with air and at elevated temperatures (boiling ethanol). We have also observed that the triazenes were stable to *m*-CPBA and ethyl iodide for several hours at r.t. However carboxylic acids (e.g. *m*-chlorobenzoic acid) will cause slow cleavage of the triazene group. Chromatography on silica gel is possible.



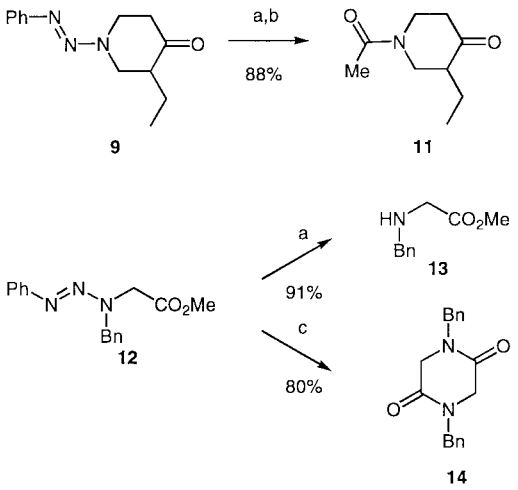

**Scheme 2** (a) $PhN_2BF_4$, $Et_3N$, −10 °C then r.t., 60%; b) $LiAlH_4$, THF, 95%; c) PDC, $CH_2Cl_2$, 75%; d) $Me_2NNH_2$, 95%, e) $TsNHNH_2$, EtOH, 70%, f) 1. LDA, THF, −78 °C; 2. BzCN, 65%; g) 1. *t*-BuLi, THF, -78 °C, 2. EtI, 85%; h) $NaBH_4$, EtOH, reflux, 70%; i) $CuCl_2$, aq THF, 50%.

## Reactions

The triazene protected 4-piperidone **3** was reduced with $LiAlH_4$ in THF at r.t. in excellent yield (Scheme 2). The resulting alcohol **4** was oxidized with pyridinium dichromate (PDC) in good yield showing that the triazene provides suitable protection for amines against chromium based oxidants and prevents strong coordination of amines to chromium by-products.[13] Ketone **3** was easily acylated to give dione **7** (LDA, THF, followed by PhCOCN at −78 °C). Furthermore, it reacted readily with dimethylhydrazine or tosylhydrazine to give the corresponding hydrazones **5** and **6**, respectively. Dimethylhydrazone **5** was lithiated with *t*-BuLi in THF at −78 °C

and alkylated with ethyl iodide to give hydrazone **8**. Cleavage of the hydrazone group in **8** with aqueous $CuCl_2$ was clean and gave piperidone **9**.[14] Reduction of tosylhydrazone **6** with $NaBH_4$ in boiling ethanol gave triazene protected piperidine **10** in good yield. A triazene protected *N*-benzylglycine prepared by hydrolysis of the corresponding ester **12** with a hydrogen peroxide/lithium hydroxide mixture, was coupled with *N*-benzylglycine using BOP-Cl. Cleavage of the protecting group under usual acidic conditions furnished the diketopiperazine **14** in good overall yield.

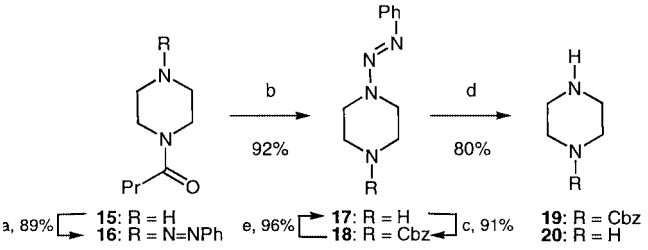
The triazene-protected products, e.g. **9**, could be converted back to the corresponding amines under mild acidic conditions (50% TFA in $CH_2Cl_2$, r.t., 1-10 h). The arene functionality of the protecting group decomposes cleanly under this conditions to give benzene, which is readily removed by evaporation. The secondary amines were usually isolated after conversion into acetamides with $Ac_2O$ by an one-pot-procedure.[15] Moreover, amides can be obtained directly by treatment of the triazenes with aliphatic acid chlorides in dichloromethane at room temperature.[16,17] Under these conditions, the arene moiety is converted to the corresponding chloroarene, whereas the amine gives rise to the *N*,*N*-dialkyl amide.



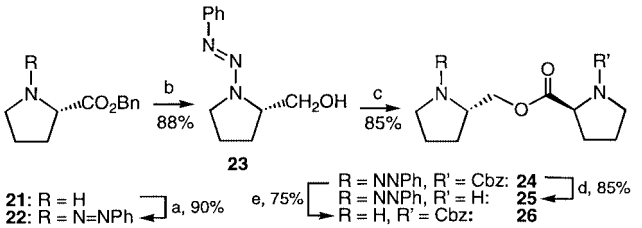

**Scheme 3** a) 50% TFA in $CH_2Cl_2$, r.t., 10 h; b) $Ac_2O$, $Et_3N$, r.t., 8 h; c) 1. LiOH, $H_2O_2$, 0 °C; 2. *N*-BnGlyOMe, BO*P*-Cl, 3. 50% TFA in $CH_2Cl_2$, r.t., 10 h

In order to determine the potential orthogonality with the Cbz based protecting group, a sequence of protection/deprotection steps were conducted on piperazine and proline derivatives (Scheme 4). First, *N*-butoyl piperazine (**15**) was protected with the diazenyl group (**16**, 89% yield), the amide hydrolyzed (**17**, 92% yield) and finally the free amine functionality protected with the Cbz group (**18**, 91% yield). The two different protecting groups could be cleaved off selectively. The diazenyl group under acidic conditions (to give **19**, 80% yield) or the carbobenzyloxy group by hydrogenolysis (to give **17**, 96%). Mono protected piperazine **17** were also prepared directly from piperazine (**20**) in 60% yield (1 equiv of diazonium salt) or in 93% yield based on $PhN_2BF_4$ (10 excess of diamine).

Similarly, benzyl proline has served as a starting material for a sequence of protection, reduction and esterification (Scheme 5). The selective cleavage of the Cbz group in **24** to give the triazene derivative of proline prolinol ester **25** was achieved under typical hydrogenolysis conditions. The acidolysis of triazenyl group was also selective. The somewhat lower yield of the product is due to unstable nature of the amino esters **25** and **26** which renders isolation difficult.




**Scheme 4** a) $PhN_2BF_4$, $CH_2Cl_2$, $Et_3N$, −10 °C to r.t.; b) KOH, EtOH, 12 h, Δ; c) CbzCl, aq $K_2CO_3$, $CH_2Cl_2$, 12 h; d) 1. TFA, $CH_2Cl_2$, −10 °C to r.t., 1 h; 2. aq $K_2CO_3$; e) $H_2$, Pd/C, MeOH, 1h.




**Scheme 5** a) $PhN_2BF_4$, $CH_2Cl_2$, $Et_3N$, −10 °C to r.t.; b) $LiAlH_4$, THF; c) Cbz-Pro-OH, DCC, DCM; d) $H_2$, Pd/C, MeOH, 1 h; e) 1. TFA, $CH_2Cl_2$, −10 °C to r.t., 1 h; 2. aq $K_2CO_3$.

In conclusion, we have demonstrated that the phenyl triazene moiety can serve as a useful protecting group for secondary amines. This acids cleavable (TFA) protecting group, combines extreme resistance to basic hydrolysis with resistance to oxidants (PDC, $H_2O_2$, peracids), metal hydrides ($LiAlH_4$, $NaBH_4$) and hydrogenation (Pd/C in methanol), alkylating agents (methyl iodide at room temperature), alkyl lithium and lithium amide bases (*t*-BuLi, LDA). Moreover Lewis acids such as Ti(O*i*-Pr)$_4$ are also compatible, however, Brønsted acids give rise to cleavage.

So far we observed orthogonality with ester, amide, Cbz and other benzyl based protecting groups. This protecting group can also serve as a linker for solid-phase organic synthesis.[3]

## Acknowledgement

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(12) Procedure for the protection of the secondary amine group to give **3**: To a cooled (0 °C) solution of aniline (1.86 g, 20 mmol) in a mixture of conc. HCl (12 mL) and water (10 mL) was added cold solution of $NaNO_2$ (1.38 g, 20 mmol). After stirring for 30 min at 0 °C 4-piperidone hydrochloride (25 mmol) was added, the mixture was cooled to −10 °C and added to a cooled and stirred solution of triethylamine in aq THF. Then the mixture was warmed up to rt and stirred for 2 h. Extractive work-up (ether), treatment with charcoal and chromatography gave **3** (2.45 g, 60% yield). Alternatively, the reaction can be run in organic solvents: To a stirred mixture of **2**•HCl (0.70 g, 4.54 mmol) at rt and wet THF (15 mL) was added PhN = $NBF_4$ (0.79 g, 4.11 mmol) followed by excess of triethylamine. Extractive work-up and purification gave **3** (0.54 g, 65%). The triazene protected *N*-benzylglycine methylester **12** was prepared by adding a phenyldiazonium solution to a cooled mixture of substrate and triethylamine. All new compounds have been characterized by $^1H$ and $^{13}C$ NMR, MS, IR and elemental analysis or HRMS, respectively. Selected NMR data: **3**:$^1H$ NMR: 2.50−2.68 (m, 4 H), 4.05−4.20 (m, 4 H), 7.10-7.25 (m, 1 H), 7.28−7.55 (m, 4 H).$^{13}C$ NMR: 40.08, 45.61 br, 120.83, 126.60, 128.93, 149.94, 207.17. **5**:$^1H$ NMR: 2.45 (s, 6 H), 2.50−2.59 (m, 2 H), 2.75-2.83 (m, 2 H), 3.85−4.01 (m, 4 H) 7.08−720 (m, 1 H), 7.25-7.50 (m, 4 H).$^{13}C$ NMR: 27.70, 33.64, 45.86 br, 46.96 br, 47.31, 47.35, 120.70, 126.18, 128.84, 150.25, 165.45. **6**:$^1H$ NMR: 2.44 (d, 3 H), 2.48−2.57 (m, 2 H), 2.58−2.70 (m, 2 H), 7.18−7.45 (m, 4 H), 7.80−7.90 (m,1 H).
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(15) Typical procedure for the deprotection of amines and subsequent acylation: To a cooled (0 °C) solution of the triazene in dichloromethane (1.0 mmol), trifluoroacetic acid (10 mmol, 10 equiv) was added. After 5 h, the excess of TFA and solvent were removed under vacuum. The residue was dissolved in a $CH_2Cl_2/Et_3N$ mixture and treated with $Ac_2O$
(16) Strict exclusion of moisture is not necessary. Water reacts with acid chlorides yielding the corresponding acid and as well as HCl. Both acids increase the cleavage rate of the triazene prior to acylation rather than disturbing the reaction sequence.
(17) Typical procedure for the deprotection of amines and in situ acylation: To a cooled (0 °C) solution of the triazene in dichloromethane (1.0 mmol), the acid chloride (4.0 mmol, 4 equivalents) was added. After 24 h, the excess of acid chloride and the solvent were removed under vacuum.

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