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C- vs. N-Oxidations of Benzyltriazanes: Selective Access to Triazones, Azimines, and Triazenes

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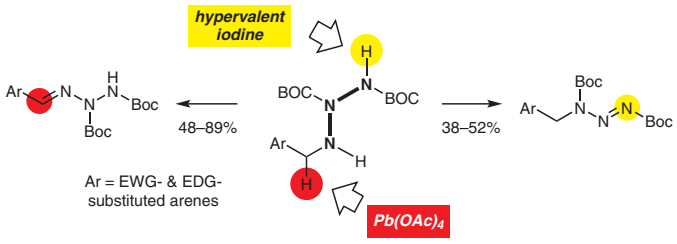

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Abstract The oxidation of several benzyltriazanes has been studied. Routes to the selective formation of triazenes, azimines, and triazones via C- or N-oxidation (and rearrangement) were devised. The rich reactivity of triazanes shows that trinitrogen chains are interesting functions, whose reactivity has been overlooked despite their interest as 3-N building blocks.

Key words hydrazines, hypervalent iodine, oxidation, azimines, triazanes

Hydrazines form a fascinating family of compounds with an extraordinary rich chemistry.[1] The single N–N bond is indeed the source of a very peculiar reactivity that makes hydrazines both good nucleophiles and reducing agents. In addition, the two nitrogen atoms can complex metals, adding to the reactivity. As a consequence, hydrazines are used in various fields, such as asymmetric synthesis[2] and as peptidomimetics.[3] They are also ubiquitous building blocks for heterocyclic synthesis.[4]

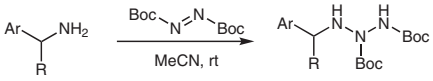
A subset of the latter, carbon-poor, low-molecular weight hydrazines are energetic compounds,[5] whose oxidation generates dinitrogen and has been applied in propulsion systems, particularly as fuels for space propulsion. In particular, our department has devised an industrial process for the production of monomethyl hydrazine (MMH), which is still in use.[6]

Unfortunately, some of the same properties that make hydrazines appealing reagents are also responsible for problems. In particular, hydrazines are usually carcinogenic and this means that strict precautions must be used when handling all hydrazines, and their use on an industrial scale is subject to strict regulations, compliance which significantly adds to the costs of the end products.

As a consequence, there is a need for alternatives to hydrazines. Given that efficiency in space propulsion is a direct consequence of the presence of N–N single bonds and a minimal amount of carbon in the materials used, we decided to investigate the potential of triazanes, hydrazine homologues with three singly bonded nitrogen atoms.

Surprisingly, the chemistry (including bioactivity) of triazanes has not been widely investigated.[7] There is thus still a need for new data on the properties of triazanes. We therefore initiated a program devoted to the chemistry of singly bonded polynitrogen compounds. We report herein that, upon choosing appropriate conditions, it is possible to direct the oxidation of benzyltriazanes selectively toward C- or N-oxidation and access varied polynitrogenated structures.

Table 1 Preparation of the N-Benzyl-Triazanes



Entry	Ar	R	Product, yield (%)
1	Ph	H	**1a**, 60
2	*p*-MeC$_6$H$_4$	H	**1b**, 38
3	*p*-ClC$_6$H$_4$	H	**1c**, 41
4	*p*-MeOC$_6$H$_4$	H	**1d**, 33[a]
5	2-Py	H	**1e**, 28
6	*o*-ClC$_6$H$_4$	H	**1f**, 33
7	*p*-CNC$_6$H$_4$	H	**1i**, 18
8	Ph	Me	**1g**, 31
9[b]	Ph	Ph	**1h**, 11

[a] Triazane **1d** was obtained as a mixture with the reduced DTBAD (**1d**/**R** = 65:35).
[b] Ethanol was used as solvent.

The route to triazanes involves the addition of an amine to an electron-poor diazene.[7c,d,8] We prepared an array of nine *N*-benzyl-triazanes from di-*tert*-butyl azodicarboxylate (DTBAD) and a range of benzylamines (Table 1). The amines were chosen in order to vary electronic effects on the aromatic ring, as well as steric hindrance at the benzylic carbon. All reactions were performed in acetonitrile at room temperature, except for benzhydrylamine, which required ethanol to give a satisfactory yield (Table 1, entry 9). The triazanes were isolated in yields ranging from 11% (Table 1, entry 9) to 60% (Table 1, entry 1). The lower yields are due to an undesired oxidation of the benzylamine, which reduces the DTBAD to the corresponding hydrazine, and probably generates an imine. The putative imines are not stable and their hydrolysis leads to the corresponding aldehydes or ketones, which could be observed by ^{1}H NMR spectroscopy. The byproducts were eliminated by column chromatography, except for in the case of *p*-methoxybenzylamine, where they eluted with the same R_f as the desired product (Table 1, entry 4). The latter was thus taken forward as a mixture in the oxidation.

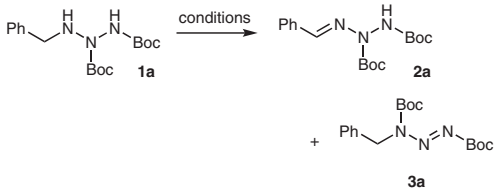
We next investigated the oxidation of the benzyltriazanes with different oxidants. The only report on this comes from Dreiding and co-workers, who showed that lead(IV) acetate induced the oxidation of three aryl-triazanes to the corresponding azimines, which are 1,3-dipoles with a $N^{(-)}$–$N^{(+)}$=N connectivity.[8] Our systems are more complex because the benzylic position can also potentially be oxidized, opening chemoselectivity issues. In other words, benzyltriazanes could lead to either C-oxidation (to the corresponding hydrazone-type compounds) or N-oxidation to the azimines. In addition, the 3-N chain could also fragment, owing to its intrinsic fragility.

In stark contrast to the single precedent, the reaction of triazane **1a** with $Pb(OAc)_4$ in cold dichloromethane and in the presence of a base to buffer the reaction mixture selectively delivered triazone **2a** in 89% yield (Table 2, entry 1). When the reaction was carried out in the absence of base, some triazene **3a** was isolated (19%, Table 2, entry 2), but the triazone remained the main product of the reaction; albeit the overall yield decreased. We next considered less toxic iodine(III) reagents as greener alternatives to the toxic lead derivative. Nicolaou and co-workers had shown that IBX converts benzylamines into benzylimines. However, benzylhydrazines behaved in a much more complex way, as the reaction delivered bimolecular coupled adducts, with overall loss of two nitrogens.[9]

For the oxidation of the higher order triazane **1a**, we considered Dess–Martin periodinane (DMP), phenyliodine(III) bis(trifluoroacetate) (PIFA), and phenyliodine(III) diacetate (PIDA). DMP delivered mostly unreacted triazane, with the triazone as the main oxidized product (Table 2, entry 3). In contrast, PIFA led to degradation (Table 2, entry 4). Interestingly, when **1a** was treated with PIDA at 0 °C in the presence of a base, triazene **3a** became the major product,[10] although a significant amount of triazone **2a** was also isolated (40 vs. 31%, Table 2, entry 5). Of note, a migration of the Boc group also took place, and therefore no azimine was obtained. The structure of **3a** was confirmed by X-ray analysis (Figure 1). We presume that the azimine formed first, but rearranged to the observed product via a 1,2-Boc shift, owing to the close proximity of the negatively charged nitrogen to the carbonyl of the Boc. Lowering the temperature to –20 °C resulted in a dramatic reactivity loss (68% recovered starting material, Table 2, entry 6), while running the reaction at 20 °C resulted in no change relative to the reaction at 0 °C (Table 2, entry 7). In the absence of a base, the ratio of N- vs. C-oxidation increased to 1.5:1 (Table 2, entry 8), suggesting that oxidation to the triazone was again slightly favored by the base. When an excess of oxidant was used (Table 2, entry 9), only the triazene **3a** was isolated but its overall yield was not improved.

To conclude, we have established conditions to favor either C-oxidation or N-oxidation of benzyl-triazanes. In both cases, the overall trinitrogen architecture is retained but the reactivity is significantly different from that of aryl-triazanes. The use of basic reagents seems to favor C-oxidation. The triazones are also less stable to the reaction conditions, which permits the triazenes to be obtained selectively.

Table 2 Optimization of the Triazane Oxidation



Entry	Conditions[a]	**2a** (%[b])	**3a** (%[b])
1	$Pb(OAc)_4$, K_2CO_3, –78 °C, CH_2Cl_2	89	–
2	$Pb(OAc)_4$, CH_2Cl_2, –78 °C	41	19
3	DMP, K_2CO_3, EtOH, 0 °C	23	5[c]
4	PIFA, K_2CO_3, EtOH, 0 °C	–	6
5	PIDA, K_2CO_3, EtOH, 0 °C	31	40
6	PIDA, K_2CO_3, –20 °C, EtOH,	20	11[d]
7	PIDA, K_2CO_3, EtOH, 20 °C	26	41
8	PIDA, EtOH, 0 °C	37	62
9	PIDA (2 equiv), EtOH, 0 °C	–	52

[a] All reactions were stopped after 0.5 h. The yields were determined by ^{1}H NMR spectroscopy using 1,2-dichloroethane as internal standard.
[b] isolated yields unless otherwise specified.
[c] 72% of starting material was recovered.
[d] 68% of starting material was recovered.

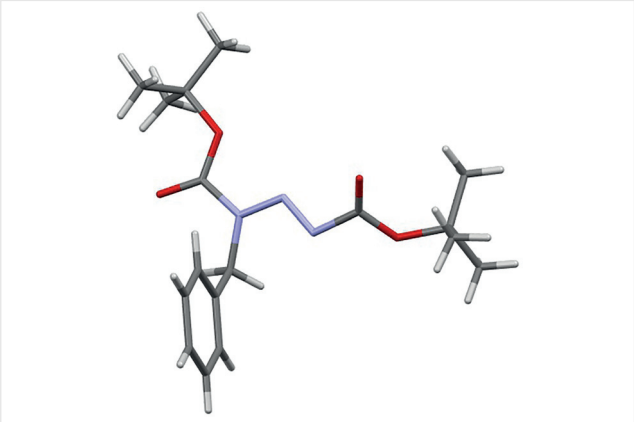
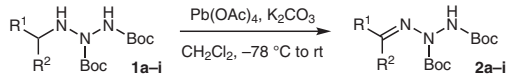


Figure 1 Structure of **3a**

Table 3 Scope of the Formation of Triazones



Entry	S. M.	R^1	R^2	Product, yield (%)[a]
1	**1a**	Ph	H	**2a**, 89
2	**1b**	*p*-MeC_6H_4	H	**2b**, 86
3	**1c**	*p*-ClC_6H_4	H	**2c**, 60
4	**1d**	*p*-$MeOC_6H_4$	H	**2d**, 48[b]
5	**1e**	2-Py	H	**2e**, 10
6	**1f**	*o*-ClC_6H_4	H	**2f**, 65
7	**1i**	*p*-CNC_6H_4	H	**2i**, 79
8	**1g**	Ph	Me	–
9	**1h**	Ph	Ph	**2h**, 87

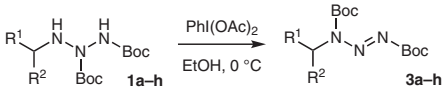
[a] Yields were determined by ^1H NMR spectroscopy using 1,2-dichloroethane as internal standard.
[b] **1d** was reacted further as a mixture with a byproduct (see Table 1); 48% of starting material was recovered.

With these two sets of conditions in hands we looked to establish the scope of these oxidations with regard to the benzyl moiety. We started with the lead-mediated formation of hydrazones of triazanes (triazones).

As deprotonation of the benzylic position is a crucial feature of the oxidation (see below), we first looked at how substituents on the aryl ring affected the reaction. The oxidation worked well with a substrate with an additional alkyl group (Table 3, compare entries 1 and 2). A chlorine atom either in the *para* or *ortho* position was accepted, but it was accompanied by some degradation (60% yield for **2c**, Table 3, entry 3; 65% yield for **2f**, Table 3, entry 6). The electron-withdrawing *p*-CN substituent was also conducive to the oxidation conditions (79%, Table 3, entry 7). On the contrary, a *p*-methoxy derivative gave a lower 48% NMR yield (Table 3, entry 4), together with 48% of recovered starting material. However, **2d** was not separable from **1d**. The oxidation was carried out on the purified mixture of **1d** and the hydrazine byproduct. The hydrazine may complex the $Pb(OAc)_4$ blocking the reaction at about 50% conversion; while more equivalents of the reagent led to degradation. Nonetheless, the yield, calculated based on the recovered starting material, is 96%, suggesting the oxidation is very efficient in that case. On the other hand, using a pyridine heteroaromatic ring was completely detrimental, as most of **1e** was destroyed in the reaction and only 10% of **2e** was isolated (Table 3, entry 5). Finally, the reaction can be compatible with increased substitution at the benzylic position (87% of **2h**, which features an additional phenyl substituent, Table 3, entry 9). Surprisingly, though, the α-methyl benzylamine derived triazane **1g** was completely decomposed under the oxidation conditions (Table 3, entry 8). It is not clear why, though we propose that the activated allylic proton in **2g** might be deprotonated under the reaction conditions, leading to degradation.

With the synthesis of the triazones in hands, we then tried to direct the oxidation to the other end of the triazane. To do this we selected the conditions of Table 2, entry 9, with the hypervalent iodine reagent $PhI(OAc)_2$ as the oxidant.

Table 4 Scope of the Formation of the Triazenes

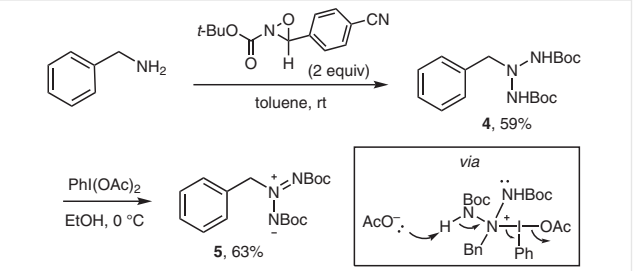


Entry	S. M.	R^1	R^2	**3**, yield (%)	**2**, yield (%)
1	**1a**	Ph	H	**3a**, 52	–
2	**1b**	*p*-MeC_6H_4	H	**3b**, 48	**2b**, 24
3	**1c**	*p*-ClC_6H_4	H	**3c**, 47	**2c**, 15
4	**1d**	*p*-$MeOC_6H_4$	H	**3d**, 56	**2d**, 19
5	**1e**	2-Py	H	**3e**, 29	–
6	**1f**	*o*-ClC_6H_4	H	**3f**, 44	**2f**, 19
7	**1g**	Ph	Me	**3g**, 38	C_6H_4
8	**1h**	Ph	Ph	**3h**, 10	C_6H_4

In all cases, where the starting materials feature functionalized benzyl substituents, the corresponding triazenes were obtained in similar yields: 52% to the parent benzyl substrate (Table 4, entry 1); 48% for a *p*-methyl (Table 4, entry 2), 47% for a *p*-chloro (Table 4, entry 3), 56% for a *p*-methoxy (Table 4, entry 4), and 44% for an *o*-chloro substituent (Table 4, entry 6). This was accompanied by various amounts of triazones. It is very likely that the substituents affect the stability of the latter, resulting in more or less degradation. However, in all cases, the triazenes were the major products of the reactions. Although 2-pyridyl triazane **1e** delivered a low yield of **3e** (and no triazone, Table 4, entry 5) probably because the pyridine ring interacts with the hypervalent iodine reagent. Finally, steric

hindrance at the benzylic position proved highly detrimental (Table 4, entries 7 and 8). Given that an additional phenyl led to a much lower yield (10%, Table 4, entry 8) than a methyl (38%, Table 4, entry 7), we believe that steric hindrance is the governing factor in this case.

Finally, we considered whether the protecting group pattern on the triazane might block the rearrangement. If the benzyl substituent were in the 2-position (hence a tertiary nitrogen), with one Boc protecting group on each side, then the only path open to the molecule would be the oxidation to an azimine (see Scheme 1).



Scheme 1 Access to azimine **5**

To generate the corresponding triazane **4**, we started from a report by Collet et al. who introduced a method to generate hydrazines by electrophilic amination of amines.[11] The N^+ source was an oxaziridine. The authors observed that symmetric triaziridines were also obtained as minor byproducts, which they sought to eliminate. Thus we re-optimized the conditions toward the formation of **4**. This was achieved by using two equivalents of oxaziridine oxidant and toluene as solvent. In this way, **4** was obtained in 59% yield. Triazane **4** was then oxidized using the conditions in Table 4, and azimine **5** was obtained in 63% yield. An X-ray structure was obtained for **5**, which confirmed our initial structural attribution (Figure 2).

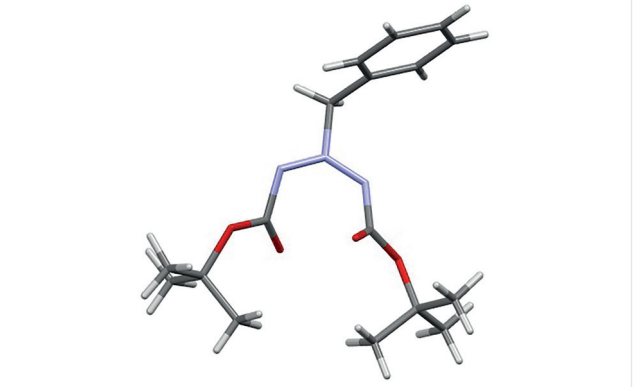


Figure 2 Structure of **5**

To conclude, we have studied the oxidation of several benzyl-triazanes. Depending on the reaction conditions, it is possible to oxidize selectively either the α-carbon or the trinitrogen chain. In the latter case, the substitution pattern on the triazane directs the oxidation toward further rearrangement to triazenes[12] (with 2,3-bisprotected triazanes), or toward the formation of azimines (1,3-bisprotected triazanes). The rich reactivity of triazanes shows that trinitrogen chains are interesting functions, whose reactivity has been overlooked. The triazones could be interesting new ligands for transition metals, while the triazenes may lead to nitrogen-centered radicals and/or serve as radical initiators.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591865.

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(12) **General Procedure for the Formation of Triazones**

The triazane (0.5 mmol) was dissolved in CH_2Cl_2 (4 mL) under N_2 at rt K_2CO_3 (10 equiv) and lead(IV) acetate (1 equiv, 85%) were added at –78 °C. The cold bath was removed, and the reaction mixture was stirred for 30 min. The precipitate was filtered off and washed several times with CH_2Cl_2. The combined organics extracts were concentrated in vacuo and purified by column chromatography.

Compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 and 1.58 (bs + s, 18H, *t*-Bu), 6.45 (s, 1H, NH), 7.35–7.39 (m, 3H, Ar), 7.71–7.75 (m, 2H, Ar), 7.92 (s, 1H, CH=N). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (Me), 82.3 (C-N), 82.9 (C-N), 127.6 (CH), 128.4 (CH), 129.6 (CH), 134.0 (C), 139.5 (CH=N), 151.6 (C=O), 153.8 (C=O). ESI-HRMS: *m*/*z* calcd $[M+H]^+$: 336.1918; found: 336.1924 (1.8 ppm). IR (neat): ν = 1450, 1479, 1720, 2979, 3287 cm^{-1}; mp 106°C, decomp: 159°C.

General Procedure for the Formation of Triazenes or Azimines

The triazane (0.5 mmol) was dissolved in EtOH (10 mL) under N_2 at rt $PhI(OAc)_2$ (2.2 equiv) was added at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. Water was then added, and the mixture was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent removed. The triazenes (or azimine) were purified by chromatography.

Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 18 H, t-Bu), 5.50 (s, CH_2), 7.36–7.38 (m, 3 H, Ar), 7.48–7.51 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 (Me, t-Bu), 74.3 (CH_2), 82.8 (C, t-Bu), 128.8 (CH, Ar), 129.0 (CH, Ar), 129.2 (CH, Ar), 132.3 (C, Ar), 156.7 (C=O). ESI-HRMS: *m*/*z* calcd $[M + Na]^+$: 358.1737; found: 358.1720 (4.8 ppm). IR (neat): ν = 1467, 1690, 1704, 2927, 2975 cm^{-1}; mp 145–146 °C, decomp.: 150 °C.