Triazenes by Acid-Mediated Opening of the Dihydro-1,2,3-triazole Ring of 1,3-Dipolar Cycloadducts of Organic Azides to Cyclic Ketene N,N-Acetals[‡]

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Dedicated to Professor Paul Rademacher on the occasion of his 65th birthday

Keywords: Nitrogen heterocycles / Triazenes / Cleavage reactions / Protonation / Spiro compounds / Tautomerism

Spirocyclic 1,3-dipolar cycloadducts **1** and **4** of azides to heterocyclic ketene N,N-acetals open their dihydro-1,2,3-triazole ring in the presence of weak Brønsted acids to afford novel 1,3-substituted triazenes **2**X and **5**X, respectively, which form colorless, crystallized tetrafluoroborates (X = BF_4) and hexafluorophosphates (X = PF_6). Ring-opening is reversed in alkaline solutions. Methyl triflate methylates the dihydro-1,2,3-triazole ring of **1a** and **4** at *N*-3 and thus induces ring-cleavage to 1,3,3-trialkyltriazenes **3** and **6**, respectively. The 1,3-substituted triazenes **2a**X, **2b**BF_4, **2d**X and **5**X exist as tautomers that have the larger substituents, which include the heterocyclic rings, connected with the azo group (*N*-1). By contrast, triazene **2c**PF**6** has a bulky alkyl group at each terminal nitrogen and hence forms two rapidly equilibrating tautomers of similar stability.

Introduction

Alkyltriazenes have attracted considerable interest as synthetic reagents[1,2] and candidates for the development of anticancer drugs.[2,3] Various aspects of triazenes have been reviewed.[2–5] Besides the most common formation of triazenes from diazonium ions or organic azides, rare cases have been reported in which triazenes arise by ring-opening of heterocycles that contain an array of three nitrogen atoms.[6–8] 4-Hydroxy-3,4-dihydrobenzo-1,2,3-triazines[7] and 5-hydroxy-4,5-dihydro-1*H*-1,2,3-triazoles[8] may equilibrate with triazene isomers. Here we report formation of novel, water-soluble triazenes **2**X, **3**, **5**X, and **6** by ring-opening of 1,3-dipolar cycloadducts **1**, **4** of azides to cyclic ketene N,N-acetals.

Results and Discussion

Cyclic ketene N,N-acetals that are derived from tetrazole and benzimidazole belong to the most electron-rich dipolarophiles and thus undergo 1,3-dipolar cycloadditions even with alkyl azides to afford cycloadducts **1** and **4**, respectively.[9,10] Those cycloadducts **1** that have a proton attached to their triazole carbon (R^3 = H), e. g. **1d**, are prone to base-induced cleavage of the dihydrotetrazole ring yielding methyl azide and 5-amino-1*H*-1,2,3-triazoles, which occasionally are undesired byproducts. Attempts at separation by extracting a benzene solution of a mixture containing **1d** with a saturated aqueous solution of potassium dihydrogen phosphate afforded a surprising result: Not the 5-amino-1*H*-1,2,3-triazole as intended but **1d** was extracted into the aqueous layer from which it could be recovered quantitatively after addition of concentrated sodium hydroxide solution.[9]

NMR spectra of solutions in potassium [D_2]dihydrogen phosphate/deuterium oxide that were obtained from **1a** and **d** showed that protonation drastically changes the spirocyclic structures. The spiro carbon-13 signals at 100–105 ppm[9,10] are no longer observed while ^{1}H and ^{13}C NMR signals that are characteristic of 5-alkyl-1,4-dimethyltetrazolium ions make their appearance.[11] These results indicate that the dihydrotriazole ring of **1a** and **d** was opened to yield a triazene. Addition of one equivalent of [D]hydrochloric acid to a solution of **1d** in [D_4]methanol transformed **1d** in the same way as the dihydrogen phosphate buffer. A small excess of [D]hydrochloric acid induced decomposition with concomitant gas evolution as known for alkyltriazenes.[12,13] Analogous results were observed for solutions of **4** in [D_4]acetic acid while [D]trifluoroacetic acid induced decomposition and evolution of gas.

[‡] The results are part of the dissertations by M. Ach (1992) and D. Regnat (1990), University of Würzburg.

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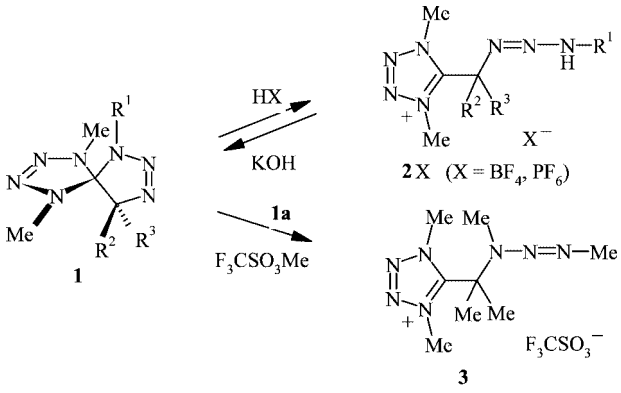
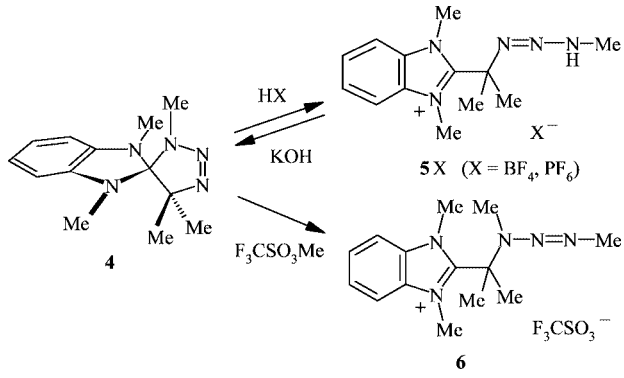


			R^1	R^2	R^3
1a,	**2a**BF_4,	**2a**PF_6	Me	Me	Me
1b,	**2b**BF_4		Ph	Me	Me
1c,		**2c**PF_6	*t*Bu	Me	Me
1d,	**2d**BF_4,	**2d**PF_6	Me	*t*Bu	H



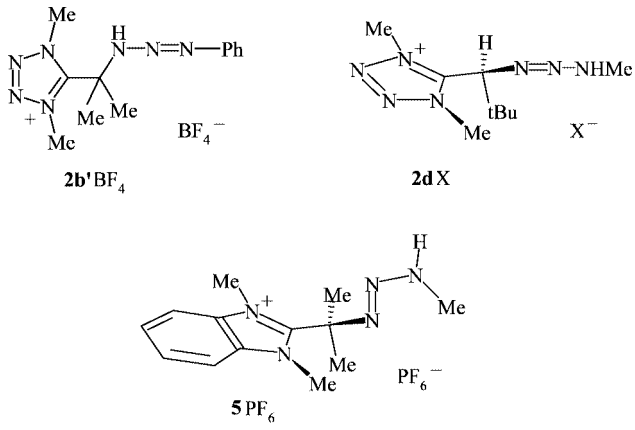
Two different procedures furnished the protonation products of **1** in high yields as colorless, nicely crystallized tetrafluoroborates **2**BF_4 and hexafluorophosphates **2**PF_6 (Table 1), which melted with decomposition but were shelf-stable. Addition of somewhat less than one equivalent of tetrafluoroboric acid in diethyl ether to a solution of **1** in diethyl ether at low temperatures immediately gave rise to the formation of crystals. They dissolved again with gas evolution when the amount of acid exceeded one equivalent even only slightly. In the second procedure, crystals appeared slowly when a solution of ammonium hexafluorophosphate and two equivalents of acetic acid in aqueous ethanol was added to solutions of **1**. Both methods converted the benzimidazole derivative **4** into the triazenes **5**X. Small-scale experiments, performed in NMR sample tubes, demonstrated that the acid-induced transformation was completely reversible on addition of one equivalent of potassium hydroxide to solutions of **2**X and **5**X in [D_4]methanol.

It was intriguing to exchange the Brønstedt acids for alkylating reagents. Methyl iodide in [D]trichloromethane solution failed to react with **1a** even within extended periods of time. Methyl tosylate required heating at 60 °C for slow reaction with **1a** but decomposition of the product prevailed before the conversion was complete. By contrast, methyl triflate reacted with **1a** and **4** at room temperature to afford colorless crystals (**3** and **6**, respectively) in high yields (Table 1).

Table 1. Yields of triazenes, melting points (with decomposition and gas evolution), and IR data.

	Yield [%]	M.p. [°C]	IR [cm^{-1}] (KBr) C=N, C=C	(Nujol) NH (br.)
2aBF_4	91	74–76	1538	3430
2aPF_6	70	91–93	1539	3285
2bBF_4	95	113–115	1603, 1520	3280
2cPF_6	76	100–102	1633, 1501	3285
2dBF_4	quant.	131–133	1625, 1510	3420
2dPF_6	91	167–169	1625, 1512	3450
3	83	73–75	1633, 1534	
5BF_4	97	187–190	1625, 1505	3430
5PF_6	86	175–178	1505	3445
6	95	100–102	1632, 1507	

The structures of the products were based on elemental analyses, and spectroscopic and crystallographic evidence. An X-ray diffraction analysis of **5**PF_6, whose parameters have already been reported in a communication,[14] not only confirmed the triazene structure but also revealed the nature of the tautomer existing in the solid state, viz. *NH*-methyl tautomer **5**PF_6 with (*E*)-configuration of the azo group and *s-cis* conformation of the N–NHMe bond. Both configuration and conformation are identical with those found for 3-methyl-1-(*p*-tolyl)triazene in the solid state.[15] The *cis*-conformation apparently reflects the importance of intermolecular hydrogen bonding. The requirements of conjugation impose considerable degrees of planarity on the triazene moieties of both molecules. We note that each of the geminal methyl groups of **5**PF_6 exists in a different environment.



Proton and carbon-13 NMR spectra (Table 2 and Table 3) show that only a single tautomer exists in solutions of **2a**X, **2b**BF_4, **2d**X, and **5**X. The ^{1}H NMR spectra taken

Table 2. Chemical shifts (δ [ppm]) and N*H*–C*H*$_3$ coupling constants ($|^3J|$ [Hz]) in 200 or 250 MHz proton spectra; shifts of broad signals are printed in *italics*.

Cpd.	Me_2C—N=N—NH—Me			^3J	NMe	Ar-H[a]	Solvent
2aX	1.75	*10.4*	2.91	3.8	4.39		[D$_6$]DMSO
	1.85	–	3.02	–	4.43		CD_3OD
5X	1.88	*10.1*	2.93	3.9	4.11	7.69 8.03	[D$_6$]DMSO
	1.94	–	3.03	–	4.15	7.7 7.9	CD_3OD
	Me_2C—N=N—NH—Ph						
2bBF_4	1.86	*12.4*	7.0–7.4		4.43		[D$_6$]DMSO
	Me_2C—N=N—NH—*t*Bu					*T* [K]	
(A)	1.78	*10.5*	0.91		4.28	298	[D$_6$]DMSO
	1.81	–	0.99		4.27	297[b]	CD_3OD
2cPF_6	*1.84*	–	0.95		*4.16 4.35*	198[c]	CD_3OD
	Me_2C—NH—N=N—*t*Bu						
(B)	1.74 10.01		1.24		4.36	298	[D$_6$]DMSO
	1.81 –		1.31		4.38	297[b]	CD_3OD
	1.76 –		1.32		4.26	198[c]	CD_3OD
	*t*Bu—CH–N=N–NH—Me						
2dX	1.02 5.22	*10.5*	2.93	3.9	*4.45*		[D$_6$]DMSO
	1.12 5.18	–	3.06	–	*4.50*	298	CD_3OD
	1.10 5.20	–	3.03	–	4.40 4.62	263	CD_3OD
	Me_2C–NMe—N=N—Me					Ar-H[a]	
3	1.93 3.13		3.30		4.33		$CDCl_3$
6	2.00 3.09		3.29		4.13	7.65 7.72	$CDCl_3$

[a] Centres of an AA′BB′ spectrum. [b] 400 MHz spectrum. [c] The signal of CHD_2OD (δ = 3.30 ppm, 298 K) was taken as standard.

from solutions of **2a**BF_4, **2b**BF_4, and **5**BF_4 in [D$_4$]methanol remain unchanged down to the lowest accessible temperature (228 K). The tautomeric structures **2a**X, **2d**X, and **5**X that exist in [D$_6$]dimethyl sulfoxide solutions of *N*-methyltriazenes are proven by a 3.8–3.9 Hz coupling between the *N*-proton and the methyl protons.[12] The *N*-methyl carbon-13 shifts (ca. 30 ppm) support the position of the methyl groups at *N*-3, in agreement with known preference of un-

Table 3. Chemical shifts (δ [ppm]) in 50 MHz carbon-13 spectra.

Cpd.	Me_2C—N=N—NH—Me				NMe	C=N	ArCH	Solvent
2aX	25.3	62.8		30.3	40.5	156.2		[D$_6$]DMSO
	26.0	64.0		30.7	41.3	158.1		CD_3OD
5X	27.1	64.5		30.0	35.2	156.3	113.2 126.7 132.2[a]	[D$_6$]DMSO
	MeC—N=N—NH—Ph							
2bBF_4	24.7	64.2	114.3 129.5	122.8 141.5[a]	40.7	155.4		[D$_6$]DMSO
	Me_2C—N=N—NH—*t*Bu						*T* [K]	
(A)	23.8	60.4	51.7	28.1	[b]	156.7	298	[D$_6$]DMSO
	23.9	61.4	52.6	28.1	39.9	158.0	297[c]	CD_3OD
2cPF_6	23.2	61.4	53.3	27.9	39.1	155.7	198[d]	CD_3OD
	Me_2C—NH—N=N—*t*Bu							
(B)	25.3	63.7	54.5	29.5	[b]	156.7	298	[D$_6$]DMSO
	25.3	64.7	55.2	29.4	41.3	158.0	297[c]	CD_3OD
	24.8	64.6	54.8	29.5	41.2	157.2	198[d]	CD_3OD
	*t*Bu—CH—N=N—NH—Me							
2dX	27.2	41.2 73.4		31.2	39.9[e]	154.7		CD_3OD
	Me_2C—NMe—N=N—Me						ArCH	
3	22.1	59.3	31.2	47.9	39.5	155.2		$CDCl_3$
6	24.7	62.2	30.9	48.5	34.9	154.3	112.7 127.2 132.1[a]	$CDCl_3$

[a] Quaternary carbon atom. [b] The signal is obscured by the signal of the solvent. [c] 100 MHz spectrum. [d] The signal of CHD_2OD (δ = 49.0 ppm, 298 K) was taken as standard. [e] Broadened signal.

symmetrical 1,3-dialkyltriazenes for the tautomers that have the smaller group attached to the amino nitrogen.[16]

The singlet for the two ring methyl groups in the 200 MHz ^{1}H NMR spectrum of **2d**X in [D_4]methanol is broadened at room temperature. Cooling increases the width at half height until the signal is split into two signals of equal intensity at a coalescence temperature of (284 ± 2) K at which the free enthalpy of activation is calculated[17] at (58.5 ± 0.5)kJ·mol^{-1} from a signal splitting of 45.2 Hz at 263 K (Supporting Information; see also the footnote on the first page of this article). The observed dynamic phenomenon is due to restricted rotation around the C(5)–CH*t*Bu bond. In comparable zwitterions that differ from **2d**X only by a triazenide side chain instead of the 3-methyltriazen-1-yl group, rotation around the C(5)–CH*t*Bu bond is even completely frozen on the ^{1}H, ^{13}C, and ^{15}N NMR time scales employed,[10,18] and the *tert*-butyl groups adopt a conformation perpendicular below (or above) the ring planes in the solid state.[18]

N-Alkyl-*N*′-phenyltriazenes prefer the 3-alkyl-1-phenyl tautomer, in which the phenyl group is conjugated with the azo group.[12,19] Accordingly, the triazene obtained from **1b** might be anticipated to possess the 1-phenyl structure **2b**′BF_4. However, the observed ^{13}C chemical shifts for the *ipso*-carbon (δ =141.5 ppm) and *ortho* carbons (δ =114.3 ppm), are not compatible with this tautomer whose *ipso*-carbon and *ortho*-carbons are expected to resonate around 150 and 120 ppm, respectively, as in 3,3-dialkyl-1-phenyltriazenes.[20] Instead, the observed ^{13}C shifts closely resemble those of 3-phenyltriazenes.[21] Furthermore, the *N*-proton resonates at very low field (δ =12.4 ppm, in [D_6]dimethyl sulfoxide) as expected for tautomer **2b**BF_4 (12.2–12.8 ppm) while the signal of the *N*-proton of tautomer **2b**′BF_4 is expected to appear at 10.9–11.6 ppm.[22] These results leave no room for doubt that the product of **1b** exists as unconjugated tautomer **2b**BF_4.

The NMR spectra of triazene **2c**PF_6 indicated the presence of two equilibrating isomers, **A** and **B** (Figure 1 and Figure 2). While, at room temperature, two sharp ^{1}H signals are observed for the *tert*-butyl groups of **A** and **B** at 400 MHz, rapid equilibration gives rise to a single broad signal at 200 MHz. Cooling results in splitting of all signals, at first of the *tert*-butyl signals due to their largest shift difference. At low temperatures, isomer **A** is somewhat more stable than isomer **B** (**A**/**B** = ca. 3:2 at 198 K). Both isomers are degenerate with respect to their free energies at the coalescence temperature of the *tert*-butyl signals, (281 ± 2) K, at which $\Delta G^{\neq}$ was calculated[17] at (56.8 ± 0.5)kJ·mol^{-1} from a signal splitting of 72.1 Hz at 222 K. At the lowest accessible temperature (198 K), rotation around the C(5)–CMe_2 bond of **A** becomes slow as is seen from broadening of both the ^{1}H and ^{13}C signal of the geminal methyl groups, splitting of the *N*-methyl ^{1}H signal, and disappearance of the *N*-methyl ^{13}C signal in the noise.

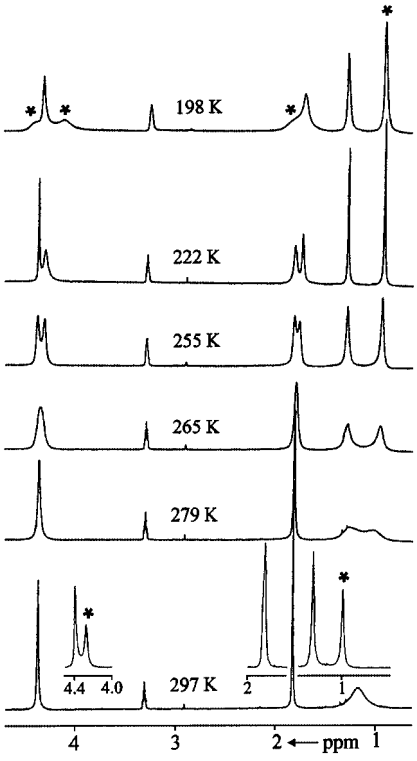


Figure 1. Variable-temperature 200 MHz ^{1}H NMR spectra recorded for **2c**PF_6 in [D_4]methanol; insert: 400 MHz spectrum. Signals of tautomer **A** are labelled with an asterisk.

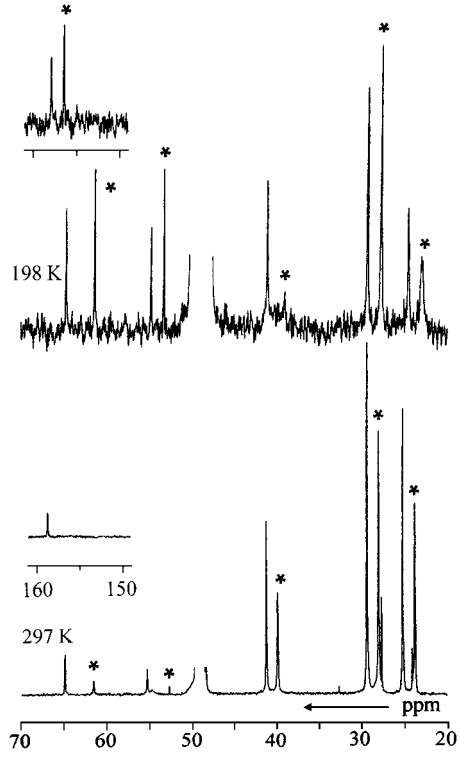
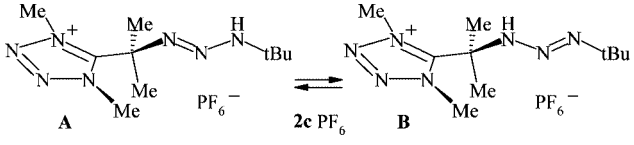


Figure 2. Carbon-13 NMR spectra of **2c**PF_6 in [D_4]methanol at 297 K (100 MHz, below) and 198 K (50 MHz, above); the solvent signal has been omitted. Signals of tautomer **A** are labelled with an asterisk.

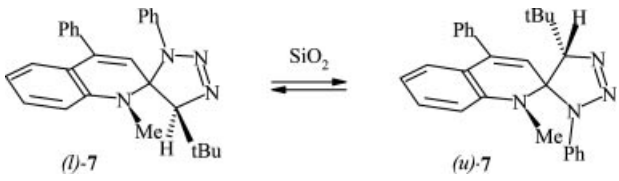
At room temperature, each pair of proton signals due to **A** and **B** (250 MHz), except for the NH signal of **A**, is quite sharp in [D_6]dimethyl sulfoxide, indicating slower equilibration compared to [D_4]methanol. As in [D_4]methanol at low temperatures, isomer **A** is preferred over **B** (**A**/**B** ≈ 3:2). Heating results in coalescence of each signal pair, except for that of the NH groups. Decomposition occurs at 340 K as was concluded from gas evolution and formation of 2-methylpropene which was identified with the help of its characteristic ^{1}H NMR multiplets[23] and the ^{13}C NMR spectrum.[24]

N,*N*′-substituted triazenes may form two tautomers, each of which may exist, in principle, as *E*/*Z* diastereomers and *s-cis*/*s-trans* conformers. As both terminal alkyl groups of **2c**PF_6 are very bulky it is highly unlikely, however, that hopelessly crowded *Z* diastereomers and *s-cis* conformers are involved in the present isomerism. Therefore, we assume that the equilibration is due to tautomerism. This hypothesis is supported by the observed deceleration of the equilibration by the use of [D_6]dimethyl sulfoxide compared to [D_4]methanol.[12c]

The relative stabilities of tautomeric 1,3-substituted triazenes are determined, in the first place, by the accessibility to the NH groups by hydrogen acceptor solvents, which depends on the size of the terminal *N*-substituents.[25] As the *N*-*tert*-butyl group is smaller than the other *tert*-alkyl group, which includes the heterocyclic ring, we tentatively assign structure **2c**PF_6(**A**) to the tautomer for which stabilization by hydrogen bonding is more effective and structure **2c**PF_6(**B**) to the other tautomer. This assignment is corroborated by the chemical shifts, except that the ^{13}C shifts of the CMe_2 groups appear to be exchanged.



The 1,3-dimethyltriazene structures **3** and **6** of the methylation products are based on the observation of two temperature-independent *N*-methyl NMR signals with a ^{13}C shift difference (**3**: 16.7 ppm; **6**: 17.6 ppm) that is much larger than expected for *N*,*N*-dimethylamino groups of 3,3-dimethyltriazenes (6.6–6.7 ppm at –60 °C). In addition, 3,3-dimethyltriazenes show temperature-dependent NMR spectra due to restricted rotation around the N–NMe_2 bond.[20b] A nuclear Overhauser experiment confirmed structure **6**. Irradiation at the frequency of the *N*-methyl protons that resonate at highest field enhanced the signal of the geminal methyl groups (2%) but not the signal of the other *N*-methyl group, which, therefore, cannot be attached to the same nitrogen atom.



Conclusions

The ring-opening products, described in this paper, of 1,3-dipolar cycloadducts of azides to cyclic ketene N,N-acetals represent novel substitution pattern for triazenes. We expect that similar spirocycles that are derived from other *N*-heterocycles will also give this ring-opening reaction. For example, a triazene intermediate is certainly involved in the diastereomerization (*l*)-**7** ⇋ (*u*)-**7** which occurs in the presence of silica gel.[26] As the acid-induced ring-opening is reversibel at higher pH values we predict pH ranges where significant fractions coexist of both, spirocycles and triazenes. Furthermore, the biological properties of the triazenes described here remain to be explored. Their solubility in water will facilitate this task. It is tempting to speculate about the development of spirocycles of type **1**, **4**, or similar systems as selective antitumor pro-drugs which are stable in normal tissues but yield cytotoxic triazenes at the relatively low pH values that exist in tumor tissues in the presence of a high level of serum glucose.[27]

Experimental Section

General Remarks: Yields, melting points, and IR: Table 1. ^{1}H NMR: Table 2. ^{13}C NMR: Table 3. Molecular formulae and masses, and elemental analyses: Table 4. ^{1}H and ^{13}C NMR: Bruker AC 200, AC 250 and WM 400. Assignments of ^{13}C NMR signals were supported by DEPT spectra. The NOE experiment was performed with a sample that had been degassed at 10^{-2} Torr and sealed under vacuum. IR: Perkin–Elmer 1420. The spirocycles **1a**, **d**,[10] **1b**, **c**, and **4**[11] were prepared according to known procedures. Tetrafluoroboric acid in diethyl ether (54%, d = 1.19 g mL^{-1}) was purchased from Merck, Darmstadt.

Table 4. Molecular formulae, masses, and elemental analyses.

		Mol. mass	Elemental analysis	C	H	N
2aPF_6	$C_7H_{16}F_6N_7P$	343.2	calcd.	24.50	4.70	28.57
			found	24.79	4.72	28.15
2bBF_4	$C_{12}H_{18}BF_4N_7$	347.1	calcd.	41.52	5.23	28.25
			found	41.41	5.30	28.14
2cPF_6	$C_{10}H_{22}F_6N_7P$	385.3	calcd.	31.17	5.75	25.45
			found	31.27	5.95	25.26
2dPF_6	$C_9H_{20}F_6N_7P$	371.3	calcd.	29.12	5.43	26.41
			found	29.47	5.67	26.02
3	$C_9H_{18}F_3N_7O_3S$	361.3	calcd.	29.92	5.02	27.14
			found	29.80	5.05	26.78
5PF_6	$C_{13}H_{20}F_6N_5P$	391.3	calcd.	39.90	5.15	17.90
			found	40.27	5.25	17.74
6	$C_{15}H_{22}F_3N_5O_3S$	409.4	calcd.	44.01	5.42	17.11
			found	44.39	5.38	16.90

Triazenes by Protonation of 1 and 4. General Procedures

A. Tetrafluoroboric acid in diethyl ether (1.30 mL, 9.5 mmol) was diluted with dry diethyl ether (140 mL). The dilute solution was

added dropwise to a stirred solution of **1a**, **b**, **d**, or **4** (10.0 mmol) in 100 mL dry diethyl ether kept at –10 °C. A colorless precipitate formed immediately. The suspension was cooled to –20 to –40 °C for 1 d. The colorless powder was isolated by filtration, washed with diethyl ether and dried i. vac.

2bBF_4: M.p. 110–115 °C (dec.). Recrystallization from methanol/diethyl ether (1:1) at –20 °C afforded colorless needles.

5BF_4: M.p. 180–190 °C (dec., darkening above 150 °C). Recrystallization from methanol at –30 °C afforded colorless needles.

B. A solution of acetic acid (1.20 g, 20 mmol) and ammonium hexafluorophosphate (1.79 g, 11 mmol) in a mixture of ethanol/water (5:1, 200 mL) was added dropwise to a stirred solution of **1a**, **c**, **d**, or **4** (10.0 mmol) in ethanol (50 mL) kept at 0 °C. Cooling at 0 °C was continued for 1 d followed by isolation of the colorless needles.

2dPF_6: 45%, m.p. 168–171 °C (dec.). Cooling of the mother liquor for 3 d at –30 °C yielded a second crop, 46%, m.p. 167–169 °C (dec.).

5PF_6: 86%, m.p. 170–173 °C (dec.). Recrystallization from methanol at –20 °C afforded colorless prisms.

Triazenes by Methylation of the Spirocycles 1a and 4 with Methyl Triflate. General Procedure: Methyl triflate (0.82 g, 5.0 mmol) was added dropwise to a stirred solution of **1a** or **4** (5.5 mmol) in [D] trichloromethane (5 mL). The components reacted immediately (^{1}H NMR). Addition of diethyl ether (1 mL) was followed by cooling of the mixture at –20 °C for 2 d and isolation of colorless plates (**3**) or powder (**6**).

Acknowledgments

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie, Frankfurt am Main, is gratefully acknowledged. D. R. is endebted to the Fonds der Chemischen Industrie for a doctoral stipend.

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Received: May 24, 2005
Published Online: September 5, 2005

