Stable Monosubstituted Triazenes by Reduction of Some Tertiary Azides

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Monosubstituted triazenes are transiently produced during the reduction of azides, followed by elimination of nitrogen spontaneously to yield the amine products (eq 1). While aromatic triazenes have been isolated as un-

$$RN_3 \rightarrow RN{=}NNH_2 \rightarrow RNH_2 \qquad (1)$$

stable compounds, aliphatic monosubstituted triazenes have not been reported.[1,2a] Indirect evidence of their formation was first provided by the isolation of triazoles resulting from intramolecular interaction of a triazene with geminal nitrile or carboxylic ester groups.[2]

We now report on a series of isolable, stable triazenes (**2**), obtained by catalytic hydrogenation of a number of tertiary azides of the general structure **1** (Chart 1). The azides, particularly **1a**, were originally synthesized and reduced with a view toward preparation of biologically active cyclobutane amino acids.[3]

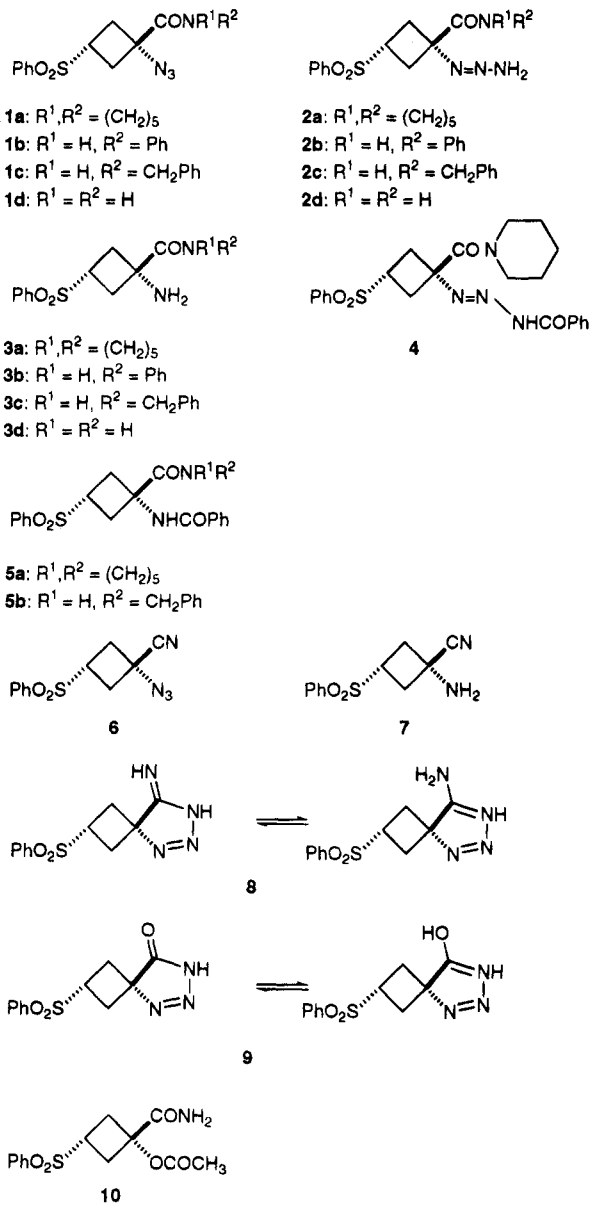
During the catalytic hydrogenation of **1a**,[3] the formation of a product of intermediate polarity between that of the starting material and that of the desired amine **3a** was observed by TLC. This product was first isolated as the benzoyl derivative **4** by chromatographic separation of the benzoylated total hydrogenation mixture. X-ray analysis revealed the triazene structure of **4**.[4,5] It showed, among other things, a trans N=N double bond, 1.246 Å long, and an N–NH(COPh) bond, 1.369 Å long. Triazene **2a** itself was later isolated as a stable, recrystallizable solid by chromatography of the hydrogenation mixture on silica gel. Upon its melting at 124–125 °C, gas evolution was observed, and **2a** was cleanly converted into **3a**.

In order to explore the scope of the reaction in regard to the amide function, azido amides **1b–d**, representing secondary and primary amides, were prepared by the route described for **1a**[3] and submitted to catalytic hydrogenation. Triazenes **2b–d** were thus isolated and characterized.

All hydrogenations were carried out in ethyl acetate over 10% palladium on activated carbon catalyst at room temperature and under normal pressure of hydrogen. The reactions were stopped when TLC showed triazene to be the major component, with an indication of some remaining azide and some formed amine. This usually took from 4 to 7 h. In the case of **1d**, an additional component was observed by TLC, later identified as a triazole derivative (see below). Separation of the reaction components was carried out by chromatography on silica gel, which did, however, cause some decomposition of the less stable triazenes, particularly **2d**. All triazenes were obtained as crystalline solids, except for **2c** which was obtained as a solid foam, not completely free of **3c**. Benzoylation of this product produced only the benzoylamine derivative **5b**.

The yields of the triazenes were variable, depending on the hydrogenation conditions, the duration of hydrogenation, and the extent of decomposition on silica gel, but were typically 30–40%. The overall yield, including starting azide and amine, was high. When the desired product of reduction was the amine, the reaction mixture, after disappearance of the azide, was refluxed under air atmosphere until total conversion of the triazene to the amine was achieved.

Chart 1



(1) (a) Smith, P. A. S. *Open-Chain Nitrogen Compounds*; A. Benjamin, Inc.: New York–Amsterdam, 1966; Vol. II, pp 336–340. (b) Sheradsky, T. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience Publishers: London–New York–Sydney–Toronto, 1971; pp 382–395.

(2) (a) Hohenlohe–Oehringen, K. *Monatsh. Chem.* **1958**, *89*, 557–561. (b) Hohenlohe-Oehringen, K. *Monatsh. Chem.* **1958**, *89*, 562–569.

(3) Gaoni, Y.; Chapman, A. G.; Parvez, N.; Pook, P. C.-K.; Jane, D. E.; Watkins, J. C. *J. Med. Chem.* In press.

(4) The X-ray structure determination was performed by Dr. Felix Frolow of this institute.

(5) Atomic coordinates for compound **4** have been deposited with the Cambridge Crystallographic Data Center and can be obtained, on request, from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

(6) Gaoni, Y. *Tetrahedron* **1989**, *45*, 2819–2840.

(7) For general remarks concerning chromatography and NMR procedures, see ref 3.

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The triazenes were characterized by their clean conversion to the amines and by their ^{1}H NMR spectra. A good elemental analysis was obtained only for **2a**. Except for **2c**, which contained about 7% of the amine, the NMR spectra showed the presence of one compound only and were closely related to the spectra of the starting azides or of the amines, as well as to the spectra of a large number of other cyclobutyl sulfones.[6] These spectra would typically show two distinct multiplets for the α and β protons of the ring methylenes, a quintuplet for the ring tertiary proton, resulting from almost equal coupling with the four adjacent ring protons, and the signals of the side groups. The IR spectra of the triazenes did not show any common absorptions which could be ascribed to N=N stretching vibrations. The ^{1}H NMR and IR spectra of all compounds mentioned in this work are available as supplementary material.

The relative stability of the triazenes was roughly determined by following the formation of the amine in the solids, kept at 6 °C. The amount of amine formed could be readily determined by ^{1}H NMR. Triazenes **2a** and **2b** were thus found to be unchanged after a period of 12 weeks, while **2c** and **2d** contained, by then, about 25% and 40%, respectively, of the corresponding amines. The stability of the triazenes seems thus to be directly related to the bulkiness of radical R (eq 1), which might suggest that a 1,3-shift is involved in the nitrogen elimination step.

A measure of the relative stabilities of the triazenes was also carried out in a deuteriochloroform solution kept at room temperature. These measures were less reliable, probably as a result of an uncontrollable change in the acidity of the solution. Thus, half-lives of 27 and 18 days were found for **2b** in two different experiments. The half-life of **2c** was approximately 35 days and that of **2d**, 14 days. The amine was here again the sole degradation product, except for **2a** which showed less than 3% of amine formation after 8 days in solution, but which was degraded to a complex mixture after 21 days (TLC, NMR).

As mentioned above, an intramolecular reaction may occur during hydrogenation of tertiary azides carrying a reactive adjacent group such as a nitrile or a carboxyl.[2] Such reactions occur, to some extent, in the case of azido nitrile **6** and of the primary amide **1d**.

Hydrogenation of **6**, prepared by dehydration of **1d**, produced mainly **7**, as well as a small proportion of **8**. Compound **8** was isolated by chromatography as a very polar substance. The triazole structure was assigned to it by analogy with the literature[2a] and on the basis of its analytical and physical properties, including high polarity and low solubility.

Hydrogenation of **1d** produced, besides triazene **2d** and amine **3d**, a small amount of a relatively non-polar product, identified as **9** by analytical and spectral data. In particular, the chemical shifts of the α and β cyclobutane ring protons resemble those of **8** in being, relatively, more widely spaced ($\Delta\delta$ ~1 ppm) than in any of the monocyclic compounds described above ($\Delta\delta$ usually 0.1–0.3 ppm, with up to 0.6 ppm for the amines). A chemical transformation of **9** to **10** by treatment with acetic acid[2b] confirmed the assigned structure.

Experimental Section[7]

Amides 1. Amides **1b** and **1c** were prepared from *cis*-1-azido-3-(phenylsulfonyl)cyclobutane-1-carboxylic acid (**11**) via the acid chloride by reaction with 2 equiv of the corresponding amine in CH_2Cl_2 as described earlier for the preparation of **1a**.[3] Amide **1d** was prepared by passing ammonia into a solution of the acid chloride in THF (see below).

***cis*-1-Azido-*N*,*N*-pentamethylene-3-(phenylsulfonyl)cyclobutane-1-carboxamide (1a).** See ref 3.

***cis*-1-Azido-*N*-phenyl-3-(phenylsulfonyl)cyclobutane-1-carboxamide (1b)** was obtained in 82% yield by direct crystallization of the crude reaction product from ethanol, mp 113–114 °C. Anal. ($C_{17}H_{16}N_4O_3S$) C, H, N.

***cis*-1-Azido-*N*-benzyl-3-(phenylsulfonyl)cyclobutane-1-carboxamide (1c)** was isolated in 85% yield by chromatography of the crude reaction product on silica gel (20 g of silica gel for the crude from 2 g of **11**;[3] CH_2Cl_2–hexane–EtOAc 2:2:1): mp 94–95 °C (EtOH). Anal. ($C_{18}H_{18}N_4O_3S$) C, H, N.

***cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-carboxamide (1d).** The acid chloride obtained from 5 g of **11**[3] was dissolved in THF (100 mL) and cooled to 0 °C. Gaseous NH_3 was bubbled into the solution for 0.25 h. After the solution was warmed to room temperature, most of the solvent was evaporated at reduced pressure and the residue was taken in water and filtered. The solid product was thoroughly washed with water and air dried to yield pure **1d** (4.45 g, 89%): mp 131–132 °C (EtOH). Anal. ($C_{11}H_{12}N_4O_3S$) C, H, N.

Catalytic Hydrogenation of Azides 1. The azides were dissolved in ethyl acetate (10 mL per mmol of azide) and stirred under hydrogen over 10% Pd on activated carbon catalyst (10% of the weight of the azide) until TLC showed triazene, situated between the least polar spot of the azide and the more polar spot of the amine, to be the major component (usually 4 to 7 h). After filtration of the catalyst, the solvent was evaporated under reduced pressure at 40 °C, and the residue was chromatographed on silica gel, as detailed below.

***N*,*N*-Pentamethylene-*cis*-3-(phenylsulfonyl)-1-triazenocyclobutane-1-carboxamide (2a) and *cis*-1-(3-Benzoyltriazeno)-*N*-phenyl-3-(phenylsulfonyl)cyclobutane-1-carboxamide (4).** The product of reduction of 1.7 g of **1a** was chromatographed on silica gel (35 g; CH_2Cl_2–ether–EtOAc 5:4:1), yielding 0.51 g of **2a**, which was recrystallized from CH_2Cl_2–hexane, mp 124–125 °C decomposing into **3a**; for the preparation of **3a**, see ref 3).

For the separation of **4**, the total hydrogenation product from 2.5 g of **1a** was benzoylated in pyridine (10 mL) with benzoyl chloride (0.85 mL) at ice bath temperature (gas evolution during addition of the benzoyl chloride), and the total product was chromatographed (40 g; CH_2Cl_2–hexane–EtOAc 1:1:1). The following were thus obtained: some recovered **1a** (0.75 g, 30%), **4** (1.25 g, 38%), and **5a**[3] (0.45 g, 15%). Product **4** was recrystallized from ethanol, mp 156–157 °C. Anal. ($C_{23}H_{26}N_4O_4S$), C, H, N.

A prismatic crystal of **4** was used for the X-ray analysis.[4,5]

***N*-Phenyl-*cis*-3-(phenylsulfonyl)-1-triazenocyclobutane-1-carboxamide (2b) and *cis*-1-Amino-*N*-phenyl-3-(phenylsulfonyl)cyclobutane-1-carboxamide (3b).** The reduction mixture from 0.5 g of **1b** was chromatographed on silica gel (30 g; CH_2Cl_2–hexane–EtOAc 4:2:1), yielding 0.06 g of starting azide (12%), 0.22 g of **2b** (44%), and 0.14 g of **3b** (30%). Triazene **2b** was recrystallized from ethyl acetate–hexane, mp 97–98 °C (decomposing into **3b**). Amine **3b** was recrystallized from EtOAc–hexane or from CH_2Cl_2–hexane and showed in both cases a double melting point, first 137–138 °C and then resolidifying to melt at 146–147 °C. Anal. ($C_{17}H_{18}N_2O_3S$) C, H, N.

***N*-Benzyl-*cis*-3-(phenylsulfonyl)-1-triazenocyclobutane-1-carboxamide (2c) and *cis*-1-Amino-*N*-benzyl-3-(phenylsulfonyl)cyclobutane-1-carboxamide (3c).** The total reduction product from 1.73 g of **1c** was chromatographed on silica gel (35 g; CH_2Cl_2–EtOAc–ether 4:3:1) to yield 0.80 g of starting azide **1c** (46%), 0.56 g of **2c** (32%), and 0.19 g of **3c** (12%). Triazene **2c** did not solidify and was obtained as a solid foam which proved to contain 7% of **3c** by ^{1}H NMR. The powdered solid foam was used to obtain an IR spectrum in KBr. Amine **3c** was recrystallized from EtOAc–hexane, mp 114–115 °C. Anal. ($C_{18}H_{20}N_2O_3S$) C, H, N.

Benzoylation of **2c** containing ca. 7% of **3c** furnished exclusively ***N*-benzyl-*cis*-3-(phenylsulfonyl)-1-(benzoylamino)-cyclobutane-1-carboxamide (5b)**, mp 254–255 °C (EtOH). Anal. ($C_{25}H_{24}N_2O_4S$) C, H, N.

***cis*-3-(Phenylsulfonyl)-1-triazenocyclobutane-1-carboxamide (2d), *cis*-1-Amino-3-(phenylsulfonyl)cyclobutane-1-carboxamide (3d), and 8-Hydroxy-*cis*-2-(phenylsulfonyl)-5,6,7-triazaspiro[4.5]octa-5,7-diene (9).** The total reduction product from 1.85 g of **1d** was chromatographed on silica gel (35 g; elution EtOAc–2% MeOH; no triazene could be eluted when Florisil was used instead of silica gel). Decomposition with gas evolution was observed to occur on the column. Eluted from the column were 0.35 g of **9** (25%), 0.55 g of starting azide **1d** (30%), 0.25 g of triazene **2d** (13%), and 0.2 g of amine **3d** (12%). The triazene was recrystallized from CH_2Cl_2–hexane to yield pure **2d**, mp 71–72 °C (decomposing to the amine). Amine **3d** was recrystallized from CH_2Cl_2–hexane, mp 130–131 °C. Anal. ($C_{11}H_{14}N_2O_3S$) C, H, N.

Triazole **9** was recrystallized from ethyl acetate–hexane, mp 120–121 °C. Anal. ($C_{11}H_{11}N_3O_3S$) C, H, N.

***cis*-1-Azido-3-(phenylsulfonyl)cyclobutane-1-carbonitrile (6).** To a solution of amide **1d** (4.45 g, 15.9 mmol) in dioxane (110 mL) were added at room temperature pyridine and trifluoroacetic anhydride (2.6 mL each). The slightly warmed up solution, through an exothermal reaction, was then kept at 90 °C for 3 h and overnight at room temperature. After addition of water (50 mL) and removing most of the dioxane at reduced pressure, the residue was extracted with ethyl acetate to yield a solid crude product. Recrystallization from ethyl acetate–hexane provided pure **6** (3.5 g, 84%), mp 81–82 °C. Anal. ($C_{11}H_{10}N_4O_2S$) C, H, N.

***cis*-1-Amino-3-(phenylsulfonyl)cyclobutane-1-carbonitrile (7) and 8-Amino-*cis*-2-(phenylsulfonyl)-5,6,7-triazaspiro[4.5]octa-5,7-diene (8).** Azide **6** (3.17 g) was reduced in ethyl acetate (75 mL) by stirring under hydrogen, over 10% Pd/C catalyst (0.4 g), for 16 h. After filtration of the catalyst and evaporation of the solvent, the residue was chromatographed on silica gel (60 g). Elution with CH_2Cl_2–ether–EtOAc (40:40:15) provided some recovered starting material (0.65 g, 20%) and then amine **7** (1.6 g, 56%). Further elution with CH_2Cl_2–15% MeOH then provided compound **8** (0.53 g, 16%).

Amine **7** was recrystallized from CH_2Cl_2–hexane, mp 92–93 °C. Anal. ($C_{11}H_{12}N_2O_2S$) C, H, N.

Triazole **8** was recrystallized from MeOH–EtOAc, mp 169–170 °C dec. Anal. ($C_{11}H_{12}N_4O_2S$) C, H, N.

***cis*-1-Acetoxy-3-(phenylsulfonyl)cyclobutane-1-carboxamide (10).** Triazole **9** (60 mg) was warmed in acetic acid (1 mL) at ca. 100 °C until gas evolution had ceased (ca. 20 min). The acetic acid was evaporated are reduced pressure and the residue was chromatographed on silica gel (7 g; CH_2Cl_2–ether–EtOAc 6:3:1) to yield **10** (50 mg, 74%), mp 185–6 °C (EtOAc). Anal. ($C_{13}H_{15}NO_5S$) C, H, N.

Supplementary Material Available: Spectroscopic and analytical data and copies of ^1H NMR spectra of **2a–d** and **3a–d** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.