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Preparation of 1-Aryl-5-hydroxy-Δ^2-1,2,3-triazolines

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A number of 1-aryl-5-hydroxy-Δ^2-1,2,3-triazolines have been prepared by reaction of ketones with aryl azides in the presence of potassium *tert*-butoxide. Some of the triazolines with two different substituents at C-4 exist in solution as a mixture of the two diastereomeric forms. In other cases, especially when two methyl groups are present at C-4, the triazoline ring is partly opened in solution to give a triazene. The structures of the triazolines and of the triazenes were determined by IR- and NMR-spectroscopy.

In the preceding paper a number of 1-methyl- and 1-benzyl-5-hydroxy-Δ^2-1,2,3-triazolines were described.[1] In the present paper the corresponding 1-aryl-compounds (I) are described and some of their properties are discussed.

It was found that phenyl azide reacted smoothly with ketones in the presence of potassium *tert*-butoxide to give high yields of 1-phenyl-5-hydroxy-Δ^2-1,2,3-triazolines (I) (Table 1). Phenyl azide reacts considerably faster than methyl or benzyl azide,[1] and the reaction times shown in Table 1 should be observed since lower yields and impure products may otherwise result. Similarly, *p*-nitrophenyl, *p*-bromophenyl, and *p*-methoxyphenyl azide yielded triazolines by reaction with ketones (Table 1). The triazolines (Iq,r,s, and t), which contain a *p*-aminophenyl group, were prepared by catalytic hydrogenation of the corresponding nitro-compounds.

The triazolines thus prepared are undoubtedly homogeneous compounds in the solid state as seen from the sharp melting points (Table 1). However, NMR spectra of these compounds in chloroform or in pyridine solution show, in many cases, that two isomeric compounds are present. When R_a^4 is different from R_b^4, the triazolines may exist in two diastereomeric forms, I′ and I″. These two are readily interconvertible, presumably *via* a ketotriazene (II) as discussed in the preceding paper. This type of isomerism was observed in many cases and structures were assigned to the two isomers on the basis of their NMR spectra (Tables 2 and 3) following the principles used previously.[1]

Triazolines in which R_a^4 and R_b^4 are identical cannot exhibit diastereoisomerism. Nevertheless, a number of compounds of this type were found to consist of a mixture of two products in chloroform or in pyridine solution, as

Table 1. 1-Aryl-5-hydroxy-Δ^2-1,2,3-triazolines (I).

I	R^1	R_b[4]	R_a[4]	R^5	Reaction time, min	Isolation method	Yield %	M.p. °C.	Formula	% C Calc.	% C Found	% H Calc.	% H Found	% N Calc.	% N Found
a	Ph	H	Me	Me	2	B	72	84–85	$C_{10}H_{13}N_3O$	62.81	62.99	6.85	6.82	21.98	22.43
b	Ph	H	Me	Et	3	B	85	119–20	$C_{11}H_{15}N_3O$	64.35	64.37	7.37	7.17	20.47	20.36
c	Ph	H	Me	i-Pr	7	A	50	147–48	$C_{12}H_{17}N_3O$	65.72	65.66	7.81	7.86	19.16	19.33
d	Ph	H	Me	*t*-Bu	15	A	35	124–25	$C_{13}H_{19}N_3O$	66.92	66.82	8.21	8.35	18.02	18.05
e	Ph	H	$-(CH_2)_4-$		8	B	87	106–8	$C_{12}H_{15}N_3O$	66.32	66.15	6.96	7.00	19.34	19.29
f	Ph	H	$PhCH_2$	Me	7	B	61	121–22	$C_{16}H_{17}N_3O$	71.89	71.88	6.41	6.41	15.72	15.82
g	Ph	Me	Me	i-Pr	180	C[a]	71	65–66	$C_{13}H_{19}N_3O$	66.92	66.92	8.21	8.00	18.02	18.17
h	Ph	Me	Me	*t*-Bu	50 days	C	58	57–59	$C_{14}H_{21}N_3O$	68.00	67.61	8.56	8.59	16.99	16.84
i	Ph	H	Me	Ph	5	A	87	149–50	$C_{15}H_{15}N_3O$	71.13	70.99	5.97	6.12	16.59	16.42
j	Ph	H	Et	Ph	15	A	86	153–54	$C_{16}H_{17}N_3O$	71.89	71.81	6.41	6.30	15.72	15.79
k	Ph	Me	Me	Ph	180	A	89	147–48	$C_{16}H_{17}N_3O$	71.89	71.78	6.41	6.40	15.72	15.91
l	*p*NO_2Ph	H	Me	Me			69	111–12	$C_{10}H_{12}N_4O_3$	50.86	50.85	5.12	4.98	23.72	23.86
m	*p*NO_2Ph	H	Me	i-Pr	4	A	79	125–26	$C_{12}H_{16}N_4O_3$	54.53	54.27	6.10	6.18	21.20	21.35
n	*p*NO_2Ph	H	Me	*t*-Bu	10	A	90	127–28	$C_{13}H_{18}N_4O_3$	56.10	55.92	6.52	6.68	20.14	19.92
o	*p*NO_2Ph	Me	Me	i-Pr	8	A	84	98–99	$C_{13}H_{18}N_4O_3$	56.10	56.01	6.52	6.51	20.14	20.22
p	*p*NO_2Ph	Me	Me	Ph	5	A	92	111–12	$C_{16}H_{16}N_4O_3$	61.53	61.41	5.16	5.41	17.94	17.67
q	*p*NH_2Ph	H	Me	Me				110–13	$C_{10}H_{14}N_4O$	58.24	57.97	6.84	7.02	27.17	26.38
r	*p*NH_2Ph	H	Me	i-Pr			100	142–43	$C_{12}H_{18}N_4O$	61.51	61.41	7.74	7.59	23.92	23.77
s	*p*NH_2Ph	H	Me	*t*-Bu			97	129–30	$C_{13}H_{20}N_4O$	62.88	62.73	8.12	7.91	22.56	22.75
t	*p*NH_2Ph	Me	Me	i-Pr			100	101–2	$C_{13}H_{20}N_4O$	62.88	62.73	8.12	8.14	22.56	22.45
u	*p*BrPh	Me	Me	i-Pr	240	A	93	104–5	$C_{13}H_{18}N_3OBr$	50.01	49.86	5.82	5.74	13.46	13.38
v	*p*MeOPh	Me	Me	i-Pr	2 days	C	60	69–71	$C_{14}H_{21}N_3O_2$	63.86	63.79	8.04	8.18	15.96	15.87

The 1-phenyl triazolines (a–k) are colourless compounds. All triazolines in this table melt with evolution of nitrogen. [a] Recrystallized from pentane.

Table 2. NMR data of 1-phenyl-5-hydroxy-Δ^2-1,2,3-triazolines (4 % w/v, $CDCl_3$, magnet temp.)

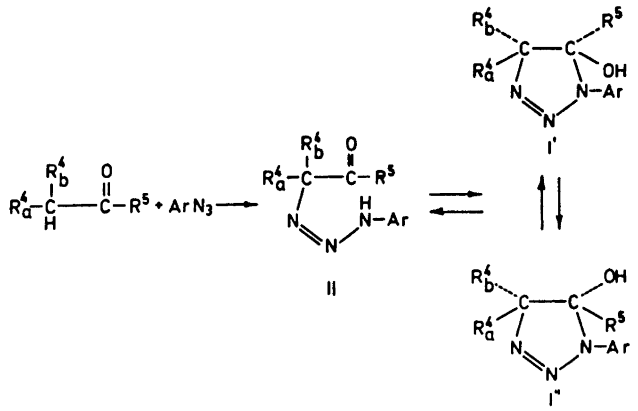
	R_b[4]	R_a[4]	R^5	Me-groups in 4-position *cis* δ	*cis* Δ	*trans* δ	*trans* Δ	H in 4-position *cis* δ	*cis* Δ	*trans* δ	*trans* Δ	Other signals
I'a				1.45d	−0.26							
	H	Me	Me							3.91q	−0.25	1.68(s,−0.15,3H)
I''a						1.12d	−0.16	4.33q				
I'b				1.44d	−0.28							1.51(s,−0.17,3H)
	H	Me	Et							4.10q	−0.24	
I''b						1.18d	−0.13					0.87("t",3H), 2.05("q",2H)
I'c	H	Me	i-Pr	1.42d	−0.30							
I'd	H	Me	*t*-Bu	1.44d	−0.23					4.18q	−0.27	1.03(d,3H),0.69(d,3H),2.63(sept,1H)
I''e	H	$-(CH_2)_4-$								4.42q	−0.26	0.91(s,9H)
I'f								4.31dd	−0.39			0.6−2.7(m,8H)
	H	$PhCH_2$	Me							4.10dd	−0.30	1.48(s,3H) 3.25(m,2H)
I''f								4.59dd				1.53(s,3H)
Ig	Me	Me	i-Pr	1.58s	−0.23	1.33s	−0.06					
Ih	Me	Me	*t*-Bu	1.67s	−0.17	1.42s	−0.07					1.06(d,3H),1.06(d,3H),2.41(sept,1H)
I'i				1.47d	−0.21							1.06(s,9H)
	H	Me	Ph							4.18q	−0.26	
I''i						0.68d	−0.22	4.62q	−0.46			
I'j	H	Et	Ph									
Ik	Me	Me	Ph	1.54s	−0.29	0.70s	−0.14			4.02"t"	−0.26	1.6−2.2(m,3H),1.87("q",2H)

$J_{H_4Me_4}$ = 7.2−7.5 cps. *cis* and *trans* refer to position relative to the hydroxy group at C-5.
The aromatic protons occur within the range 6.8−7.8. $\Delta = \delta_{CDCl_3} - \delta_{pyridine}$.

Table 3. NMR data of 1-aryl-5-hydroxy-Δ^2-1,2,3-triazolines (2 % in $CDCl_3$,[a] 4 % in pyridine, magnet temp.)

	p-substit. of 1-aryl group	R_b^4	R_a^4	R^5	Aromatic protons[b] *ortho*	*para*	Me-groups in 4-position *cis* δ	Δ	*trans* δ	Δ	H in 4-position *cis* δ	Δ	*trans* δ	Δ	Other signals
I'l	NO_2	H	Me	Me	7.65	8.24	1.53d	−0.18					4.14q	−0.17	1.80(s, −0.10,3H)
I''l	NO_2	H	Me	i-Pr	7.67	8.21	1.47d	−0.23	1.30d	−0.04	4.48q	−0.44			1.63(s, −0.11,3H)
I'm	NO_2	H	Me	*t*-Bu	7.79	8.20	1.44d	−0.18					4.35q	−0.23	0.63(d,3H),1.08(d,3H)2.77(sept,1H)
I'n	NO_2	H	Me	i-Pr	7.72		1.56s		1.44s				4.63q	−0.20	0.95(s,9H)
Io	NO_2	Me	Me	i-Pr	7.39	8.10	1.60s		0.77s						7.39("s",5H)
Ip	NO_2	Me	Me	Ph											
I'q	NH_2	H	Me	Me	6.69	7.19	1.53d	−0.20	1.21d	−0.05	4.41q		3.90q	−0.16	1.61(s, −0.15,3H)
I''q	NH_2	H	Me	i-Pr	6.67	7.22	1.49d	−0.26					4.15q	−0.22	1.45(s, −0.20,3H)
I'r	NH_2	H	Me	*t*-Bu	6.66	7.25	1.49d	−0.21					4.35q	−0.23	0.85(d,3H),1.04(d,3H)
I's	NH_2	H	Me	i-Pr	6.66	7.20	1.60s	−0.23	1.29s	−0.09					0.94(s,9H)
It	NH_2	Me	Me	i-Pr											
Iu	Br	Me	Me	i-Pr			1.58s	−0.21	1.33s	−0.05					0.99(d,3H),1.11(d,3H)2.26(sept,1H)
Iv	MeO	Me	Me	i-Pr	6.90	7.35	1.60s	−0.23	1.30s	−0.10					

$J_{H,Me_2} = 7.0 - 7.5$ cps.
cis and *trans* refer to position relative to the hydroxy group at C-5.
[a] Except Iu and Iv which were measured as 4 % solutions.
[b] The centres of the doublets are given. These do not, of course, represent the true δ-values.
$\Delta = \delta_{CDCl_3} - \delta_{pyridine}$.



seen from their NMR spectra. IR spectra of the chloroform solutions of these compounds were found to exhibit carbonyl group absorption at 1710 cm^{-1} and an NH band at 3330 cm^{-1}. This seems to indicate that the ketotriazene (II) is present in equilibrium with the hydroxytriazoline (I). The equilibration of (I′) and (I″) is assumed to take place *via* (II), but with 1-methyl- or 1-benzyl-substituted triazolines the ketotriazene (II) could not be detected.[1] With an aromatic substituent at N-1, on the other hand, appreciable amounts of (II) may apparently be present in solution in some cases. In the solid state only one of the compounds listed in Table 1 (namely I h) showed carbonyl absorption (in potassium bromide), indicating that the triazene (II) is usually only present in solution. Apart from (Ih), the solid products listed in Table 1 presumably all have the I′-form. When these products are dissolved in chloroform or in pyridine they may isomerize to give a mixture of the diastereomeric forms (I′) and (I″) or they may give a mixture of (I′) and the ketotriazene (II). In no cases were (I″) and (II) observed simultaneously.

In (Ia), which has one methyl group at C-4 and C-5, 70 % of the (I′) isomer is present (Table 4), showing that the two methyl groups tend to be as far apart

Table 4. Equilibrium content of I′ in $CDCl_3$ solution as determined from the NMR spectra. (Ia-j 4 %, Il-s 2 %, magnet temp.)

1-Ph							1-*p*NO_2-Ph			1-*p*NH_2-Ph		
a	b	c	d	f	i	j	l	m	n	q	r	s
70	~90	100	100	~80	82	?	70	100	100	70	100	100

as possible. The steric interactions become more pronounced in the 5-ethyl and the 5-isopropyl compounds (Ib) and (Ic), which contain 90 and 100 % of the (I′) isomer, respectively. None of these compounds gave detectable amounts of the triazenes (II). The *tert*-butyl derivative (Id) would not be ex-

Table 5. NMR data of β-keto-triazenes (II) in $CDCl_3$-solution. (Measuring conditions as in Tables 2 and 3).

	R^1	R_a^4	R_b^4	R^5
n	(7.3) – 8.20	1.45(d,3H)	5.30(1H)	1.25(s,9H)
d	7.1 – 7.8	1.40(d,3H)	5.27(q,1H)	1.24(s,9H)
s				1.26(s)
o	7.29 – 8.25	1.51(s,6H)		1.07(d,6H)3.07(sept,1H)
u	7.0 – 7.7	1.51(s,6H)		1.06(d,6H)3.10(sept,1H)
g	7.0 – 7.6	1.49(s,6H)		1.07(d,6H)
v	6.90 – 7.35	1.52(s,6H)		1.07(d,6H)
	3.83(s,3H)			
t	6.66 – 7.20	1.50(s,6H)		
h	6.8 – 7.6	1.49(s,6H)		1.21(s,9H)

Table 6. Equilibrium content of II in $CDCl_3$ and in pyridine solution as determined from the NMR spectra. (Measuring conditions as in Table 2).

R_b^4	H			Me					
R^5		*t*-Bu				i-Pr			*t*-Bu
	n	d	s	o	u	g	v	t	h
$CDCl_3$	42	24	11	70	56	53	37	34	91
Pyridine		< 5	< 2		11	8	5	5	71

pected to give any of the (I″) isomer when dissolved in chloroform, and this was indeed found to be the case. However, NMR spectra (Tables 5 and 6) showed that a solution of (Id) contained 24 % of the ketotriazene (IId). Apparently the steric hindrance in this case causes ring opening to some extent.

In the *p*-nitrophenyl derivatives (Il) and (Im) the same ratio between the diastereomeric forms (I′) and (I″) was found as between (Ia) and (Ic) (Table 4). However, the 5-*tert*-butyl derivative (In) gave 42 % of the triazene (IIn) when dissolved in deuteriochloroform. Since a *p*-nitro-group would not be expected to have any steric effects, the increased amounts of the triazene (IIn) over that of (IId) indicates that electronic factors are involved in the equilibrium between the hydroxy-triazolines (I) and the triazenes (II). This is further seen from the fact that the *p*-aminophenyl derivative (Is) gave only 11 % of the triazene (IIs) in chloroform solution.

In the 4,4-dimethyl derivatives only one isomer of the hydroxy-triazoline is possible. The 4,4-dimethyl-5-isopropyl derivative (Ig) was found to give 53 % of the triazene (IIg) in solution. Comparison of this with the corresponding 4-monomethyl derivative (Ic), which did not give any triazene, show again that steric factors play a part in the equilibrium between hydroxytriazolines and triazenes. This is further confirmed by the *tert*-butyl compound (Ih),

which gave 91 % of the triazene IIh at equilibrium in solution. It may be noted, that (Ih) is the only compound which contains the triazene isomer in the solid state as seen from the IR spectrum, which showed absorption at 1680 cm^{-1} (carbonyl) and at 3270 cm^{-1} (NH). The sharp melting point (Table 1) could indicate that it is completely in the (IIh) form.

The 4,4-dimethyl-5-isopropyl derivatives (It, v, g, u, and o), which have increasing electronegative substitution of the phenyl-group, contain increasing amounts of the triazenes (II) at equilibrium in solution (Table 6). This shows again that, besides steric factors, electronic factors have an effect on the equilibrium between hydroxy-triazolines and triazenes. It is therefore understandable why the 1-alkyl substituted triazolines, described in the preceding paper, do not yield detectable amounts of triazenes.

It may be noted that when a phenyl group is present at C-5 a triazene is not formed in solution (compounds Ii,j, and k), not even in case of the 1-(*p*-nitrophenyl) derivative (Ip). This may be explained by an enhanced electrophilicity of the carbonyl group in the triazene (II) due to the electronegativity of the phenyl group.

When pyridine or dimethyl sulfoxide was used as the solvent, smaller amounts of the triazenes (II) were formed. Nitrobenzene, on the other hand, did not affect the triazene formation. The increased formation of hydroxy-triazolines in pyridine or in dimethyl sulfoxide may therefore be due to a stabilization by hydrogen bonding of the solvent to the hydroxy group (*cf.* Ref. 2).

The ring-opening reaction (I→II) is rather rapid. Thus repeated integration of the range 1.20 – 1.70 ppm in the NMR spectrum of (Ig) immediately after it was dissolved showed that equilibrium was attained within a few seconds. The reaction is accelerated by base. A solution of (Ig) in dimethyl sulfoxide showed two separate signals for the methyl groups at C-4. On addition of a trace of potassium hydroxide these signals collapsed to a singlet. This indicates that (Ig⇌IIg) takes place at such a rate that the two methyl groups become magnetically equivalent.

Some methyl ketones react in a more complicated manner with azides, and this will be the subject of a forthcoming paper.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on Varian A-60 or HA-100 spectrometers. Unless otherwise stated deuteriochloroform was used as solvent. Chemical shifts are given in ppm (δ-values) relative to tetramethylsilane.

All ketones were commercially available with the exception of 2,2,4-trimethyl-3-pentanone.[1]

The organic azides were prepared by methods described in the literature: Phenyl azide,[3] *p*-nitrophenyl azide and *p*-bromophenyl azide,[4] and *p*-methoxyphenyl azide.[5]

General procedure for the preparation of 1-aryl-5hydroxy-Δ^2-1,2,3-triazolines

The appropriate azide (0.02 mol) (or when *p*-nitrophenyl azide is used, a suspension in 20 ml of *tert*-butyl alcohol) is added with stirring to a solution of potassium (1.0 g) in *tert*-butyl alcohol (20 ml). The mixture is cooled in ice-water until crystallization begins

and the ketone (0.02 mol) is then added. The reaction mixture usually turns dark, and a slight evolution of nitrogen is often observed. The temperature should not exceed 30°C, and permanent cooling in ice-water is frequently necessary for the first couple of minutes. After this first period only occasional cooling is employed. The reaction mixture is stirred magnetically or shaken vigorously by hand.

After the appropriate reaction time (Table 1) the product is isolated by one of the following procedures:

Procedure A. The reaction mixture is poured into ice-water (200 ml), and the crystalline product is filtered off and washed with water and pentane. Recrystallization from ethyl acetate-pentane gives the pure product.

Procedure B. If the product fails to crystallize when poured into ice-water, it is extracted with methylene chloride. Drying over sodium sulfate and removal of the solvent gives a syrup which crystallizes when treated with pentane. The product is recrystallized from ethyl acetate-pentane.

Procedure C. In some cases a potassium salt precipitates during the reaction, and a very pure product is obtained by the following procedure. The reaction mixture is diluted with ether (20 ml) and cooled to 0°C. The potassium salt is filtered off, washed rapidly with dry ether (moisture hydrolyses the salt), and transferred to a mixture of ice-water (20 ml) and ether (20 ml). After stirring for some time the hydrolysis of the potassium salt is complete, and the product is present in the ether phase. The aqueous phase is further extracted two or three times with ether, and the combined extracts are dried over sodium sulfate. Removal of the solvent leaves a syrup, which can be crystallized in ether-pentane at −70°C. Recrystallization from ethyl acetate-pentane gives the pure product.

*1-(*p*-Nitrophenyl)-4,5-dimethyl-5-hydroxy-Δ²-1,2,3-triazoline* (II). *p*-Nitrophenyl azide (0.82 g) in ether (25 ml) was added to a solution of potassium (0.5 g) in *tert*-butyl alcohol (10 ml). Butanone-2 (1.34 ml), previously dried over Drierite and diluted with ether (15 ml), was added and the mixture was shaken vigorously. The reaction mixture turned black at once, and fine, dark crystals separated. After 1 min the mixture was poured in a mixture of ice-water (100 ml) and ether (100 ml). The two phases were separated and the aqueous phase was extracted twice with ether. The combined ether-extracts were dried and evaporated. The residue was a mixture of 1-(*p*-nitrophenyl)-4,5-dimethyl-1,2,3-triazole and the triazoline (I l). Crystallization from ether (5 ml) at 0°C gave 151 mg (14 %) of the triazole, m.p. 202 – 203°C (reported [6] m.p. 206°C). Crystallization of the material in the mother liquor from ether-pentane at −76°C gave 815 mg (69 %) of (I l) as light brown crystals, m.p. 85 – 97°C (dec.). Recrystallization from ethyl acetate-pentane gave the pure product (Table 1).

*1-(*p*-Aminophenyl)-5-hydroxy-Δ²-1,2,3-triazolines.* These products were prepared from the corresponding 1-*p*-nitrophenyl compounds in the following way:

The 1-(*p*-nitrophenyl)-triazoline (*ca.* 300 mg) and platinum oxide (3 mg) was suspended in methanol (3 ml) and hydrogenated for 30 min at a hydrogen pressure of 2.5 atm. During this time the nitro compound dissolved. The catalyst was then filtered off and the solvent was evaporated giving the crystalline 1-(*p*-aminophenyl)-triazoline. Recrystallization from ethyl acetate-pentane gave the pure products (Table 1).

Microanalyses were performed by Dr. A. Bernhardt.

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