ACTA CHEMICA SCANDINAVICA 27 (1973) 2983–2988

Preparation of 1,2,3-Triazoles by Base-catalyzed Dehydration of 5-Hydroxy-Δ^2-1,2,3-triazolines

CARL ERIK OLSEN

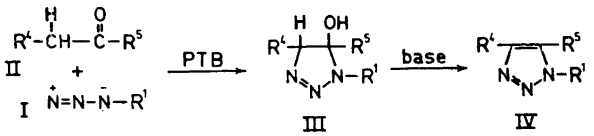
*Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark and Organic Chemical Laboratory, Royal Veterinary and Agricultural University, Thorvaldsensvej 40, DK-1871 Copenhagen, Denmark**

5-Hydroxy-Δ^2-1,2,3-triazolines are easily dehydrated to 1,2,3-triazoles on treatment with hot methanolic potassium hydroxide. The yield is very high when the substituent at the 1-position is an alkyl group, but rather low when it is a phenyl group. The potassium *tert*-butoxide catalyzed reactions of benzyl methyl ketone with organic azides give 1,2,3-triazoles directly. NMR spectra of the 1,2,3-triazoles are discussed.

The base-catalyzed reaction of organic azides with carbonyl compounds is a long known method for the preparation of 1,2,3-triazoles,[1–4] 5-hydroxy-Δ^2-1,2,3-triazolines being suspected intermediates (Scheme 1).[1,4,5] Using the particular base potassium *tert*-butoxide (PTB) we noted [6–8] that the reaction stopped at the stage of the triazoline. This could be due to either of two facts. First, the substituent R^4 is alkyl in our experiments, whereas it has been groups like RCO-, ROOC-, *etc.* in previous preparations. Assuming that the dehydration reaction (III→IV) is base-catalyzed, it is quite reasonably accelerated when R^4 is electronegative, since the adjacent proton, which is to be removed, is activated. Second, the lack of spontaneous dehydration could be due to the reaction conditions used. However, the PTB-catalyzed reactions of methyl benzyl ketone (R^4=Ph, R^5=Me) with methyl azide, benzyl azide, and phenyl azide, under conditions otherwise similar to those employed in the preparation of 5-hydroxy triazolines, resulted in the exclusive formation of 4-phenyl-5-methyl-1,2,3-triazoles, although R^4 in these cases is only moderately electronegative. The yields, which were very high in all three cases, appear from Table 2 in the experimental part.

Thus we conclude that in the presence of strong bases 5-hydroxy-Δ^2-1,2,3-triazolines may only be isolated if electronegative substituents are not present at the 4-position. Incidentally phenyl azide was also allowed to react

* Present address.



Scheme 1.

with benzyl phenyl ketone in the presence of sodium ethoxide. This resulted in a high yield of 1,4,5-triphenyl-1,2,3-triazole.

For R^4 being an alkyl group the proton at the 4-position of the hydroxy triazoline is not completely unactivated, however. There is still a proximate electron attracting azo group capable of activating it, and dehydration to 1,2,3-triazoles can be accomplished by treatment with hot methanolic potassium hydroxide (*cf.* Ref. 9). The results of a number of experiments are summarized in Table 3 in the experimental part. The yields of 1,2,3-triazoles are generally excellent for R^1 being alkyl but rather low for R^1 being phenyl. However, these yields are not necessarily the optimum obtainable, since a standard procedure, refluxing for 2 h, has been used all over, except in a few cases where an extension of the reaction time proved necessary to force the reaction to completion.

As to the mechanism of the dehydration reaction we can say safely only that the base-catalyzed removal of the proton at the 4-position is irreversible. When conducting the dehydration reaction in deuterated solvents (1,4,5-trimethyl-5-hydroxy-Δ^2-1,2,3-triazoline in deuterium oxide and 1-phenyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline in tetradeuteriomethanol) containing potassium hydroxide in such amounts as to make the reaction proceed with a rate convenient for an NMR study, the proton at the 4-position was not exchanged with deuterium (*cf.* Ref. 10 for experimental details). Consequently a 'preequilibrium' type E1cB mechanism[11] can be ruled out. It is more difficult to distinguish between an 'irreversible' type E1cB mechanism and an E2 mechanism. The preferred mode of elimination from the triazolines is apparently *trans*: dehydration of 1-benzyl-4,5-tetramethylene-5-hydroxy-Δ^2-1,2,3-triazoline, the only investigated hydroxy triazoline in which a *trans* orientation of the departing groups (H and OH) is impossible, required boiling for 30 h to go to completion, whereas 2 h was sufficient in almost all other cases (Table 3); but according to McLennan,[11] the stereochemistry of the elimination is a very unreliable criterion. The best means for deciding between the two possible mechanisms would probably be to determine the k_D/k_H isotope effect at the 4-position.[11,12].

Apparently a *tert*-butyl group at the 5-position retards the dehydration reaction (case c and l), possibly because a proper conformation of the triazoline ring is difficult to attain. A phenyl group seems to have the same effect.[8]

NMR spectra were recorded for all 1,2,3-triazoles prepared, and the data have been collected in Table 1. Some additional data for triazoles from the literature have also been included. The data in Table 1 (in conjunction with those for compounds IVd, XIIId, and XVIId of Ref. 8) confirm the observation

Table 1. Chemical shifts (δ-values) and coupling constants (cps) of some 1,2,3-triazoles (deuteriochloroform).

IV	R^1	R^4	R^5	R^1 [a]	R^4 [a]	R^5 [a]
a[13]	Me	H	H	4.10	7.74	7.59
b	Me	Me	Me	3.92s	2.22s 2.26s	
c	Me	Me	Bu^t	4.12s	2.44s	1.43s
d	Me	Me	Ph	3.97s	2.34s	7.2 – 7.7m
e	Me	Ph	Me	3.98s	7.2 – 7.9m	2.43s
f[14]	$PhCH_2$	H	H	7.33"s" 5.58s	7.50 7.70	(J = 1.0)
g[8]	$PhCH_2$	H	Me	7.0 – 7.5m 5.51s	7.48	2.19d (J = 0.8)
h[8]	$PhCH_2$	H	Bu^t	6.8 – 7.6m 5.71s	7.51s	1.28s
i[8]	$PhCH_2$	H	Ph	6.6 – 7.7m 5.52s	7.70	
j	$PhCH_2$	Me	Me	7.2 – 7.5m 5.45s	2.25s	2.08s
k	$PhCH_2$	Me	Et	7.0 – 7.5m 5.49s	2.29s	0.96t 2.55q
l	$PhCH_2$	Me	Bu^t	6.8 – 7.4m 5.70s	2.48s	1.29s
m	$PhCH_2$	Me	Ph	6.8 – 7.6m 5.46s	2.31s	
n	$PhCH_2$	$-(CH_2)_4-$		7.0 – 7.6m 5.44s	1.6 – 3.0m	
o	$PhCH_2$	Ph	Me	7.0 – 7.9m 5.55s		2.32s
p[15]	Ph	H	H	7.3 – 7.9m	7.86d 8.02d	(J = 1.0)
q[8]	Ph	H	Me	7.53"s"	7.60	2.38
r[9]	Ph	H	Ph	7.1 – 7.6m	7.86s	
s[15]	Ph	Me	H	7.3 – 7.9m	2.45d (J = 0.7)	7.74
t	Ph	Me	Me	7.50"s"	2.28 2.37	(J = 0.4)
u	Ph	Me	Et	7.53"s"	2.39s	1.08t 2.70q
ü	Ph	Me	Bu^t	7.2 – 7.7m	2.54s	1.23s
v	Ph	Me	Ph	7.0 – 7.6	2.46s	
w[15]	Ph	Et	H	7.2 – 7.9	1.36t 2.86q	7.74"s"
x[9]	Ph	Ph	H	7.2 – 8.1		8.19s
y	Ph	Ph	Me	7.55"s"	7.3 – 8.0m	2.49s
z	Ph	Ph	Ph	7.1 – 7.8		

[a] s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

by Begtrup [16] that a phenyl group attached at the 1-position of a 1,2,3-triazole ring generally appears as a rather sharp singlet if a methyl group is present at the 5-position. An ethyl group, but not a *tert*-butyl group, seems to have the same effect.

The considerable downfield displacement of two of the protons of phenyl groups at the 4-position, observed with the triazoles IVe, o, x, y, z, possibly originates in a mesomeric effect from the triazole nucleus. These easily recognizable protons lie within the range 7.6 – 7.9 ppm.

An interesting feature of the NMR spectra is that an alkyl group at the 5-position is shielded by a benzyl group at the 1-position, as appears from a comparison of IVj with IVb, IVl with IVc, or IVo with IVe. This shielding effect must be due to the ring current of the phenyl group, and the conformation necessary for a proper action of this long-range shielding effect (Fig. 1) might be favored by *n*-π electron repulsion [17–19] between the lone-pair of the middle nitrogen atom and the electron cloud around the benzylic phenyl group. A *tert*-butyl group at the 5-position seems to be long-range shielded by a phenyl group at the 1-position, as may be seen on comparing IVü with IVc.

Fig. 1.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 instrument, using TMS as an internal standard. Chemical shifts are given as δ-values. All starting materials have been described in Ref. 7 or are commercially available.

Reaction of methyl azide with methyl benzyl ketone. Methyl azide (0.02 – 0.03 mol as an approx. 25 % solution in *tert*-butyl alcohol and methyl benzyl ketone (2.67 ml, 0.02 mol) were added to 20 ml of PTB stock solution.[8] The reaction mixture gradually turned red, and heat evolution was observed. After standing for 4 h, the mixture was poured into 150 ml of ice-water. The product was extracted with methylene chloride. Evaporation of the solvent and crystallization of the residue from ethyl acetate – pentane gave 3.18 g of a pure product (Table 2).

Table 2. 1-Substituted 4-phenyl-5-methyl-1,2,3-triazoles prepared from methyl benzyl ketone and organic azides.

IV	R^1	React. time h	Yield %	m.p. °C	Formula	Analyses % C Calc.	% C Found	% H Calc.	% H Found	% N Calc.	% N Found
e	Me	4	92	97 – 98	$C_{10}H_{11}N_3$	69.34	69.19	6.40	6.50	24.26	23.88
o	$PhCH_2$	2	85	93 – 94	$C_{16}H_{15}N_3$	77.08	77.03	6.06	6.15	16.86	16.78
y	Ph	0.5	79	155 – 156	$C_{15}H_{13}N_3$	76.56	76.40	5.57	5.78	17.86	17.96

Table 3. 1,4,5-Trisubstituted 1,2,3-triazoles (IV) prepared from 5-hydroxy-Δ^2-1,2,3-triazolines. When referring to picrates experimental data (yield, melting point, and solvent of recrystallization) are put in parenthesis. EtAc = ethyl acetate, P = pentane, cyHex = cylohexane.

IV	R^1	R^4	R^5	Reaction time h	Yield %	M.p. °C	Recryst. solvent	Formula	% C Calc.	% C Found	% H Calc.	% H Found	% N Calc.	% N Found
b	Me	Me	Me	2	90	50–51	EtAc–P	$C_5H_9N_3$	54.05	53.97	8.16	8.30	37.83	37.63
c	Me	Me	Bu^t	8	93	68–69	EtAc–P	$C_8H_{15}N_3$	62.72	63.11	9.87	10.18	27.43	26.87
d	Me	Me	Ph	2	95	103–104	EtAc–P	$C_{10}H_{11}N_3$	69.34	69.36	6.40	6.44	24.26	24.33
j	$PhCH_2$	Me	Me	2	93	108–109	EtAc–P	$C_{11}H_{13}N_3$	70.57	70.51	7.00	6.89	22.45	22.36
k	$PhCH_2$	Me	Et	2	(70)[a]	(95–96)	(Benzene)	$(C_{18}H_{18}N_6O_7)$	50.23	50.23	4.22	4.29	19.53	19.38
l	$PhCH_2$	Me	Bu^t	3	91[b]	(87–88)[c]	(EtAc–P)	$(C_{20}H_{22}N_6O_7)$	52.40	52.48	4.84	5.01	18.33	18.51
m	$PhCH_2$	Me	Ph	2	93[b]	65–66[d]	EtAc–P	$C_{16}H_{15}N_3$	77.08	76.98	6.06	6.27	16.86	16.83
n	$PhCH_2$	$-(CH_2)_4-$		30	9[d]	79[e]	cyHex	$C_{13}H_{15}N_3$	73.23	73.17	7.09	7.15	19.71	19.63
t	Ph	Me	Me	2	(21)[a]	(144–145)[f] 85–86[g]	(Benzene) P							
u	Ph	Me	Et	2	7[b,d]	(143–144)[h,c]	(Benzene)	$(C_{17}H_{16}N_6O_7)$	49.04	48.89	3.88	4.01	20.19	20.08
ü	Ph	Me	Bu^t	2	10	106–108	P	$C_{13}H_{17}N_3$	72.52	72.41	7.96	8.11	19.52	19.50
v	Ph	Me	Ph	2	33	120–121	EtAc–P	$C_{15}H_{13}N_3$	76.56	76.55	5.57	5.59	17.86	17.77

[a] Picrate obtained by successive treatment with acetic anhydride and picric acid. [b] Oil, purity tested by NMR. [c] Picrate obtained by treatment with picric acid. [d] After purification by TLC. [e] Reported [21] m.p. 77°C. [f] Reported [22] m.p. 131°C. [g] The free triazole was recovered by the method of Nicolaus and Testa.[23] [h] Reported [9] m.p. 144–145.5°C.

Reaction of benzyl azide with methyl benzyl ketone. Benzyl azide (2.48 ml, 0.02 mol) and methyl benzyl ketone (2.67 ml, 0.02 mol) were added to 20 ml of PTB stock solution. The reaction mixture turned red, and heat evolution was observed after a few minutes. After 2 h, the mixture was poured into 150 ml of ice-water. The crystalline product was washed with water and pentane, yielding 4.22 g (85 %) of a crude product with m.p. 92 – 93°C. Recrystallization from ethyl acetate – pentane gave the pure product (Table 2).

Reaction of phenyl azide with methyl benzyl ketone. Phenyl azide (2.2 ml, 0.02 mol) and methyl benzyl ketone (2.67 ml, 0.02 mol) were added to 20 ml of PTB stock solution, which had been previously cooled to beginning crystallization. Cooling was continued during the first minute of reaction. The product separated after half a minute, causing the mixture to solidify. After 15 min, 30 g of ice was added, and the crystalline product was filtered off, washed with water and pentane, yielding 3.74 g (79 %) of a product with m.p. 154 – 155°C. Recrystallization from ethyl acetate gave the pure product (Table 2).

Reaction of phenyl azide with benzyl phenyl ketone. Phenyl azide (2.2 ml, 0.02 mol) and benzyl phenyl ketone (3.9 g, 0.02 mol) were dissolved in a solution of 0.7 g of sodium in 15 ml of ethanol. Heat evolution occurred, and the mixture solidified after some minutes. After standing for 20 hours, the product was filtered off, washed with ethanol and water, leaving 5.0 g (84 %) of crude 1,4,5-triphenyl-1,2,3-triazole. After recrystallization from toluene the m.p. was 228 – 229°C (reported 230.5 – 231°C [20]).

General procedure for the conversion of 5-hydroxy-Δ^2-1,2,3-triazolines into 1,2,3-triazoles. The hydroxy triazoline [7] (*ca.* 2 mmol) and 1 g of potassium hydroxide are dissolved in 15 ml of methanol. The mixture is refluxed for a few hours (*cf.* Table 3). The solvent is removed, and 10 ml of water is added. Extraction with methylene chloride, drying over Na_2SO_4, and evaporation of the solvent gives the crude product, which can be purified by recrystallization, TLC, and/or by conversion into the picrate, eventually after treatment with acetic anhydride in order to avoid co-precipitation of amine picrate (*cf.* Table 3).

Acknowledgements. The author thanks Professor C. Pedersen for advice and inspiration and Dr. M. Begtrup for many fruitful discussions.

Microanalyses were performed by Dr. A. Bernhardt.

REFERENCES

1. Grundmann, C. In *Methoden der org. Chemie*, 4. Ed., Vol. 10/3, p. 813 (1965).
2. Benson, F. R. and Savell, W. L. *Chem. Rev.* **46** (1950) 1.
3. Boyer, J. H. In *Heterocyclic Compounds*, Wiley, New York 1961, Vol. 7, p. 384.
4. L'Abbe, G. *Ind. Chim. Belge* **36** (1971) 3.
5. Regitz, M. *Angew. Chem.* **79** (1967) 786.
6. Olsen, C. E. and Pedersen, C. *Tetrahedron Letters* **1968** 3805.
7. Olsen, C. E. and Pedersen, C. *Acta Chem. Scand.* **27** (1973) 2279.
8. Olsen, C. E. *Acta Chem. Scand.* **27** (1973) 1987.
9. Munk, M. E. and Kim, Y. K. *J. Am. Chem. Soc.* **86** (1964) 2213.
10. Olsen, C. E. *Acta Chem. Scand.* **27** (1973) 2989.
11. McLennan, D. J. *Quart. Rev.* **21** (1967) 490.
12. Crosby, J. and Stirling, C. J. M. *J. Am. Chem. Soc.* **90** (1968) 6869.
13. Elguero, J., Gonzalez, E. and Jacquier, R. *Bull. Soc. Chim. France* **1967** 2998.
14. Wiley, R. H., Hussung, K. F. and Moffat, J. *J. Org. Chem.* **21** (1956) 190.
15. Bertho, A. *Ber.* **58** (1925) 859.
16. Begtrup, M. *Unpublished results.*
17. Yonezawa, T., Morishima, I. and Fukuta, K. *Bull. Chem. Soc. Japan* **41** (1968) 2297.
18. Karabatsos, G. J. and Taller, R. A. *Tetrahedron* **24** (1968) 3923.
19. Bjørgo, J., Boyd, D. R., Watson, C. G. and Jennings, W. B. *Tetrahedron Letters* **1972** 1747.
20. Moulin, F. *Helv. Chim. Acta* **35** (1952) 177.
21. Bianchetti, G., Croce, P. D., Pocar D. and Vigevani, A. *Gazz. Chim. Ital.* **97** (1967) 301.
22. Rojahn, C. A. and Trieloff, H. *Ann.* **445** (1925) 302.
23. Nicolaus, B. J. R. and Testa, E. *Angew. Chem.* **73** (1961) 655.

Received May 2, 1973.