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Base Induced Conversions of 5-Hydroxy-Δ^2-1,2,3-triazolines, Intermediates in the Reaction of Organic Azides with Carbonyl Compounds

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Treatment of 1-phenyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline with potassium hydroxide in methanol gives a mixture of 3-diazobutanone, aniline, and 1-phenyl-4,5-dimethyl-1,2,3-triazole. Anions of 5-hydroxy-Δ^2-1,2,3-triazolines are shown to be capable of existing in either a closed or an open form depending on substituents.

A unifying scheme for reactions of organic azides and carbonyl compounds is discussed with emphasis on the relation between reaction course, substituents, and medium.

In a previous paper[1] it was shown that 1-phenyl-5-hydroxy-Δ^2-1,2,3-triazolines gave much lower yields of 1,2,3-triazoles on treatment with potassium hydroxide in hot methanol than did the corresponding 1-alkyl triazolines. An explanation to this has now been found by using more gentle reaction conditions and by following the reaction by NMR spectroscopy. 1-Phenyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline[2] (IX, R^1=Ph, R_a^4=R^5=Me, R_b^4=H) (Scheme 1) was dissolved in tetradeuteriomethanol, a trace of potassium hydroxide was added, and NMR spectra were recorded at intervals. The results are shown in Fig. 1. The first spectrum (Fig. 1a) shows the two diastereomeric triazolines at equilibrium[2] prior to addition of KOH. Addition of a trace of KOH (Fig. 1b) accelerates the equilibration to such an extent that a time-averaged spectrum results (*cf.* Ref. 2). One day later (Fig. 1c) it is obvious that a conversion has begun to take place. This conversion is complete after three days (Fig. 1d). By adding a small amount of reference material, the signals at 2.26, 2.33, and 7.57 ppm were shown to be due to the expected[1] dehydration product, 1-phenyl-4,5-dimethyl-1,2,3-triazole (XVI). In a similar way the multiplet at 6.5–7.3 ppm was found to be due

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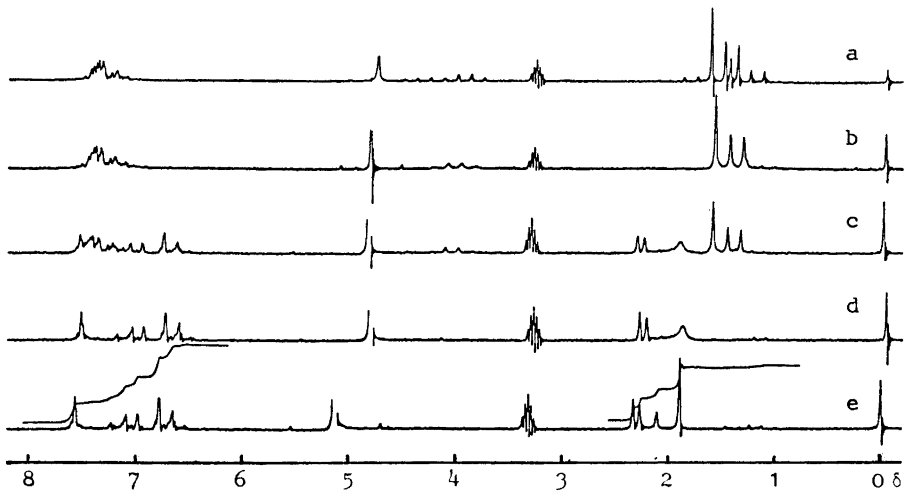


Fig. 1. NMR spectra showing conversions of 1-phenyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline (in CD_3OD). (a) prior to addition of KOH; (b) after addition of a trace of KOH; (c) one day later; (d) three days later; (e) after lowering the temperature to 0°C.

to aniline, a result that was confirmed by TLC. The molar ratio between these two compounds was measured to be 0.36.

Elimination of aniline from the triazoline or its ring-chain tautomer, the α-triazeno ketone IV, could result in 3-diazobutanone (V, $R_a^4 = R^5 = Me$), and the development of a yellow color supported this assumption. However, the broad signal at 1.92 ppm seemed unconsistent with this at first glance; but lowering the temperature to 0°C (Fig. 1e) caused the signal to split into two signals owing to the reduced rate of rotation about the partial double bond between the two carbon atoms in the grouping $N=N-C-C=O$.[3] The two signals stem from the methyl group adjacent to the diazo group in two conformers. The methyl group adjacent to the carbonyl group does not show up, because the hydrogen atoms have been exchanged with deuterium in the slightly alkaline deuteriomethanolic solution. It is to be noted that $R_b^4 = H$ is not exchanged with deuterium (Fig. 1b and c) in accordance with the statement made earlier[1] that there is no preequilibration between IV and its enol-anion. Undeuterated 3-diazobutanone resulted on carrying out a preparative scale experiment in regular methanol.

The overall conversion from butanone and phenyl azide[2] constitutes a diazo group transfer[4] from phenyl azide to a ketone, to our knowledge the first documented one. Tosyl azide is normally used as the donor of the diazo group in this kind of reaction.[4]

The experiment also illustrates that the use of phenyl azide from a synthetic point of view may be advantageous in cases where isomeric diazo compounds will result from the use of tosyl azide. In fact, the IR spectrum of the above diazobutanone showed one diazo band only, whereas that produced

using tosyl azide exhibits two.[5] The reason for this lies in the fact that the intermediate hydroxy triazoline in the phenyl case, in contrast to the tosyl case, is stable enough to be isolated; it may thus be purified before being converted into the diazo compound.

Using reaction conditions similar to those above, the corresponding reaction of 1-(*p*-nitrophenyl)-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline [2] was completed within an hour.

As described earlier,[2] 5-hydroxy-Δ^2-1,2,3-triazolines are in solution in equilibrium with α-triazeno ketones. But so far there has been no discussion of the structure of the anions of these compounds. A few potassium salts were mentioned in connection with the preparation of the triazolines, where they separated spontaneously.[2] A more general way of preparing them is to add the appropriate triazoline (or triazene) to a suspension of potassium *tert*-butoxide (PTB) in ether. The triazoline then dissolves, and after a few minutes the potassium salt precipitates. The salts are very sensitive to moisture, and many of them are relatively unstable, particularly those with $R_b^4 = H$.

The potassium salt of 1,5-diphenyl-4,4-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline [2] dissolved in dimethyl sulfoxide (DMSO) is clearly in the ring-closed form (alkoxide form, VIII), the NMR spectrum showing the two methyl groups at C-4 as two distinct, although a little broadened, signals at 1.2 and 0.48 ppm (the free triazoline in DMSO shows these signals at 1.47 and 0.58 ppm, respectively). The latter signal stems from that methyl group oriented *cis* to the phenyl group at C-5 (*cf.* Ref. 2). The enhanced shielding in the anion is probably due to the overall increased electron density in the molecule. In agreement with the above conclusion the IR spectrum does not show any C=O band (nujol).

In contrast, the potassium salt obtained by treatment of 1-phenyl-4,4-dimethyl-5-isopropyl-5-hydroxy-Δ^2-1,2,3-triazoline [2] with PTB in ether must be present in the ring-opened form (III), since the IR spectrum (nujol) shows a rather strong C=O band at 1695 cm^{-1}. The NMR spectrum taken in DMSO-d_6 (Fig. 2) is in agreement with this interpretation, the two methyl groups at C-4 now being equivalent (located at 1.23 ppm). The two isopropyl methyl

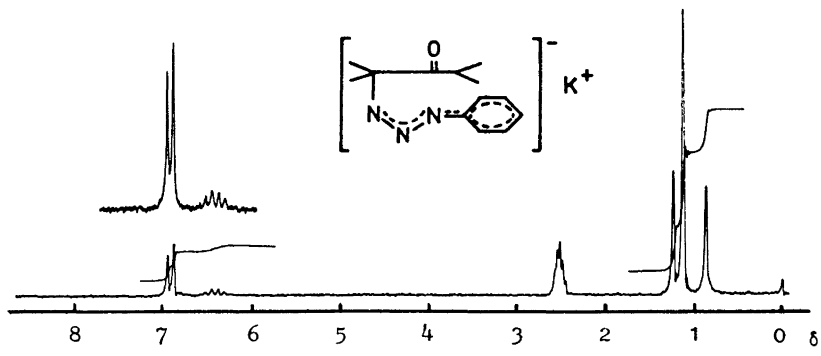


Fig. 2. NMR spectrum of the potassium salt obtained from 1-phenyl-4,4-dimethyl-5-isopropyl-5-hydroxy-Δ^2-1,2,3-triazoline (in DMSO-d_6).

groups are also equivalent as expected; but the signal from them is not split into a doublet, because the methine proton,which is adjacent to the carbonyl group, has been exchanged with deuterium from the solvent. Using undeuterated DMSO the signal appears as a doublet. The singlet at 1.13 ppm presumably comes from *tert*-butyl alcohol of crystallization; it persisted even after the K-salt had been thoroughly washed with ether. Perhaps the most interesting feature of the NMR spectrum (Fig. 2) is the appearance of the aromatic protons. Resonance considerations would predict high electron densities at both *ortho* and *para* positions, but seemingly only the *para* proton is being influenced, suffering an upfield shift of *ca.* 0.5 ppm relative to the other aromatic protons. This is presumably the effect of inter-electron repulsion,[6] which tends to disperse the charge to the extremities of the system, *i.e.* the *para* carbon atom and the Me_2C-N nitrogen atom. This effect was not observed with the corresponding 5-phenyl-triazoline anion in accordance with the assumed alkoxide structure (VIII) of this compound. The NMR spectrum of the analogous 5-*tert*-butyl triazoline potassium salt is almost identical to that shown in Fig. 2, the only major difference being that the signal at 0.86 ppm is replaced by a singlet at 1.08 ppm (*tert*-butyl).

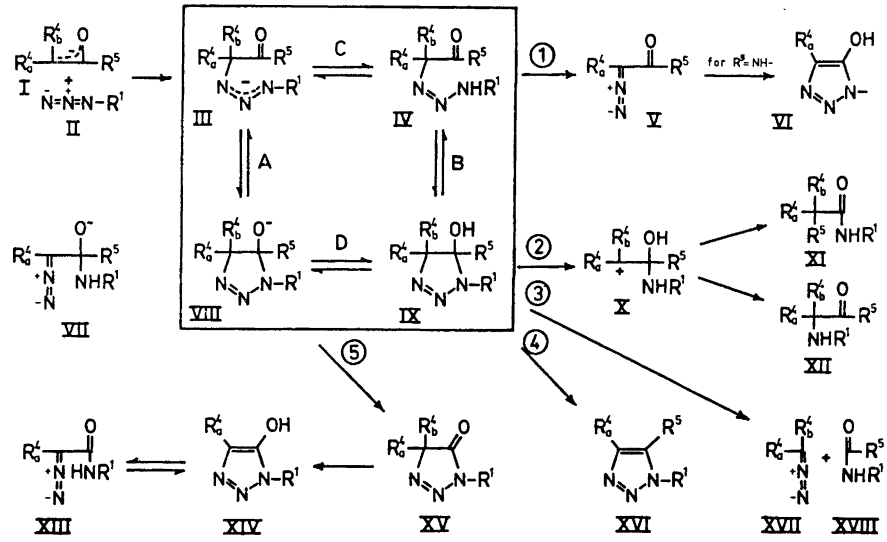
Phenylallylpotassium, a salt containing a grouping isosteric with the phenyltriazene system, also shows the effect of inter-electron repulsion.[7] In passing, the amazing resemblance between the spectrum shown in Fig. 2 and that of diphenylmethyllithium (in tetrahydrofuran) [6] must be mentioned.

We conclude that anions of 5-hydroxy-Δ^2-1,2,3-triazolines, as well as the triazolines themselves, may exist in both an open and a closed form, III and VIII. In addition, since only a slight modification of R^5 (changing from Ph to iPr) is enough to change the state completely, it is reasonable to assume the existence of a very mobile equilibrium, A, between the two forms in solution, and that the position of this equilibrium is governed largely by the same effects that determine the triazoline/triazene equilibrium B.[2] However, there is no reason to expect the closed form, VIII, to be favored over III by solvents with high acceptor abilities in hydrogen bonding, as was the case with IX relative to IV.[2]

Regitz [8,9] also recognized the possibility of two structures, assigning closed and open structures to the potassium salts obtained from tosyl azide and desoxybenzoin ($R_a^4 = R^5 = Ph$) and trimethyldesoxybenzoin ($R_a^4 = Ph$, $R^5 = Me_3Ph$), respectively.

GENERAL CONSIDERATIONS ON BASE-CATALYZED REACTIONS OF ORGANIC AZIDES WITH CARBONYL COMPOUNDS (Scheme 1)

In the light of recent results with 5-hydroxy-Δ^2-1,2,3-triazolines [1,2,10,11] we believe there is a new basis for rationalizing the various known pathways that may be followed in base-catalyzed reactions of organic azides with carbonyl compounds as functions of substituents and medium used. The following is not claimed to be a comprehensive review for which the reader is referred to the existing ones;[4,12–15] rather only a few pertinent examples and references have been drawn out for purposes of illustration.



Scheme 1.

The principal feature of Scheme 1 is the four boxed equilibria A, B, C, and D, for which we have argued above and in previous papers. The existence of these equilibria implies that the species III, IV, VIII, and IX potentially are present in any reaction mixture. In addition the triazene IV is capable of existing in two tautomeric forms.[16] The relative concentrations of these species may vary with substituents and medium, and this in conjunction with differing reactivities gives variety to the product distribution.

The initial reaction (I + II→III) is presumably a one step nucleophilic attack on the terminal nitrogen atom of the azide by the appropriately generated carbanion.[15] Subsequent adjustment of the boxed equilibria is assumed to be fast relative to the reactions leading out from the box. The following examination of these irreversible reactions has been divided into sections according to substituents.

R^1 = alkyl or aryl; R_b^4 = H; R^5 = alkyl or aryl

Routes *1* and *4* are available, *4* being predominant for R^1 being alkyl.[1] Changing R^1 to aryl makes route *1* more favorable, at least as long as R_a^4 is an alkyl group. This is partly because ArNH is a better leaving group than RNH, and partly because equilibrium B is shifted upwards. A phenyl group at position 5 tends to neutralize this latter effect[2,10] and hence enhances *4* at the expense of *1*.[1,10]

The effect of R_a^4 being an electronegative group (aryl,[1] acyl, or alkoxycarbonyl[13]) is more straightforward. Now route *4* becomes the only passable,

irrespective of R^1 being aliphatic or aromatic. There are two reasons for this. First, an electronegative R_a^4 must be expected to exert a greater electron withdrawing effect on C-5 than on N-1, resulting in a downward shift of B.[2] Second, the kinetic acidity of $R_b^4 = H$ must increase much more in IX than in IV, because in IV the hydrogen atom is already activated by one carbonyl group (*cf.* Ref. 17). The reaction of acetoacetic ester with phenyl azide, known to produce XVI ($R^1 = Ph$, $R_a^4 = EtOOC$, $R^5 = Me$)[18] may serve as an example. This reaction also illustrates a situation where there are two possible directions of ring-closing III and IV, using either the keto C=O group or the ester C=O group. The former is the more electrophilic though, and the further reaction entirely follows route *4* rather than *5*, which would have become available if the ester C=O group were used (*vide infra*).

R^1 = aryl or alkyl; $R_b^4 = H$; $R^5 = OR$ or NHR (potential leaving groups)

Routes *1* and *5* may be used as exits from the box, the former only for R^1 being aryl, though. Reaction along route *4* has not been observed.

Working in strongly basic media it is conceivable that route *5*, if available, often gets preference over *1* and that XIV or its rearrangement product, XIII, then becomes the main product.[13] An example is the reaction of malonic ester with phenyl azide.[19] Base treatment of triazenes (IV), obtained by coupling esters of α-amino acids with benzene diazonium salts, also gives XIV as the major product.[20]

As pictured in Scheme 1 the formation of the postulated intermediate XV is analogous to a two step "olysis" of an ester group (Ref. 21, Ch. 12 and Ref. 22, Sect. 2.4), but a one step reaction (III→XV) cannot be excluded. On the other hand the route VIII→VII→XIII(⇌XIV) seems unlikely, since compounds of type XIV are formed irrespectively of the electronic character of R_a^4, which may be ROOC as well as Me or H.[19] Base-catalyzed ring-opening of triazolines to diazo compounds (VIII→VII) presumably requires that R_a^4 be electronegative.[23]

Reaction along route *1* may be increased at the expense of *5* by changing R^5 to a relatively poor leaving group, *e.g.* an amino group.[24,25] This may be because the conversion VIII→XV, in contrast to IV→V, will be slowed down, and possibly also because A and B are displaced upwards.[2]

We believe that the conversion IV→V is a one step reaction without intervention of an enol-anion;[24,26] the removal of $R_b^4 = H$ is involved in the rate limiting step. Therefore it is reasonable that the relative importance of *1* and *5* depends on the acidifying ability[17] of R_a^4. Thus the relatively poor acidifying phenyl group is observed to disfavor *1* relative to *5* when R^5 is NH_2.[24] For $R^5 = NHMe$ the effect is swamped by the much more important effect of a very poor leaving ability of NHMe and by a supposed upward shift of A; here route *1* becomes the only observed one.

For $R^5 = OR$ use of exit *1* has been inferred indirectly from observations on the reaction of malonic ester with phenyl azide;[27] but as mentioned above, *5* is most important.

R^1=aryl; R_a^4=alkyl or aryl; R_b^4=R'CO; R^5=OR or NHR

Assuming the triazene anion III to be the first intermediate, the formation of 1,2,3-triazoles requires an acyl cleavage to take place (R' may be an alkyl or alkoxy group). The predominant formation of products of type XIV in the reaction of phenyl azide with phenyl or methyl malonamides [24] (particularly for R^5=NHMe) suggests that the acyl cleavage mainly takes place under formation of some species that is not in equilibrium with the boxed ones in Scheme 1. If this were the case, we should get products of type VI (*cf.* the previous section, where R^5 being an amino group is mentioned to retard *5* in relation to *1*). Indeed an acyl cleavage is well possible in the assumed intermediate XV (XV(R_b^4=R'CO)→XV(R_b^4=H)), since three electronegative groups (two carbonyls and one azo group) are attached to the same carbon atom (*cf.* Refs. 28 and 21, Ch. 13). However, with the malonamides some acyl cleavage probably also takes place in IV [IV(R_b^4=R'CO)→IV(R_b^4=H)], since small amounts of VI are formed, particularly if R_a^4=Ph.[24]

For R^5=OR route *5* should be even more feasible, OR being a better leaving group than NHR. Subsequent acyl cleavage should lead to products of type XIV or XIII. This has been observed using diethyl α-methylmalonate and ethyl α-methylacetoacetate as starting materials.[19]

R^1=Tosyl (or other benzenesulfonyl derivatives)

In this case route *1* is highly favored for two reasons, namely the high leaving ability of NHTos [29] as compared with NHAr or NHR and an upward shift of B (and A). Actually, the reaction may often (when R_a^4 is R'CO) be carried out under conditions mild enough (aliphatic amines as catalysts [26,30]) to prevent the relatively sensitive diazo compounds V from undergoing subsequent reactions. Hence the reaction of tosyl azide with carbonyl compounds provides an excellent method for the preparation of α-diazocarbonyl compounds.[4]

Stronger bases (alkali metal bases) must be used as catalysts if R_a^4 differs from R'CO, and products of type V may then undergo further reactions. In some cases, however, such a change of base may have another effect, because it shifts C and D to the left and thus opens up for route *5* if R^5 is a potential leaving group, *e.g.*, OR. In fact, this reaction course then often becomes dominating,[8,9,30,31] unless R^5 is very bulky, *e.g.*, Bu^t–O.[30] NHR is too poor a leaving group, and with carboxamides one expectedly gets conversion *1*.[32]

In general 1-tosyl-Δ^2-1,2,3-triazolines are unstable compounds,[33,34] the conversions *2* and *3* taking place spontaneously. These reactions are expected to take place in weakly basic media,[26,35] in strongly protic media,[8,9] if B is shifted downward for one reason or another (R^5=H or Ph [5,26]), or simply if *1*, *4*, and *5* are precluded (R_b^4≠H).

EXPERIMENTAL

NMR spectra were recorded on a Varian A-60 instrument, using TMS as an internal standard. Chemical shifts are given as δ-values. IR spectra were recorded on a Perkin-Elmer model 421 instrument.

Treatment of 1-phenyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline with potassium hydroxide. To a solution of 0.34 g of the triazoline [2] in 5 ml of methanol was added 4 mg of KOH, and the mixture was let stand for two days at 35°C. It was then poured into 50 ml of water and extracted with methylene chloride. Drying (Na_2SO_4) and evaporation on a rotary evaporator (25°C, 60 mmHg) gave a mixture of 1-phenyl-4,5-dimethyl-1,2,3-triazole, aniline, and 3-diazobutanone. The latter compound was distilled at 1 mmHg (temp. of water bath: 25 – 35°C), giving 78 mg of a thin yellow liquid. NMR showed that it consisted of 3-diazobutanone and aniline in a molar ratio of 9:2. The NMR spectrum ($CDCl_3$) at 25°C showed broad singlets of equal integrals at 1.97 and 2.22 ppm. At – 20°C two conformers were observable. The preponderating form exhibited signals at 1.98 and 2.29 ppm, and the other form at 2.16 and 2.18 ppm. The IR spectrum showed the diazo band at 2075 cm^{-1}.

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