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v-TRIAZOLINES. PART XXVII.[1] ISOMERIZATION REACTIONS OF SUBSTITUTED [v-TRIAZOL-4-YL]METHYL-CYCLOPENTEN-3- AND -2-ONES.

MARIA LUISA GELMI*, DONATO POCAR and PASQUALINA TRIMARCO

Istituto di Chimica Organica, Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian, 21, 20133 MILANO, ITALY

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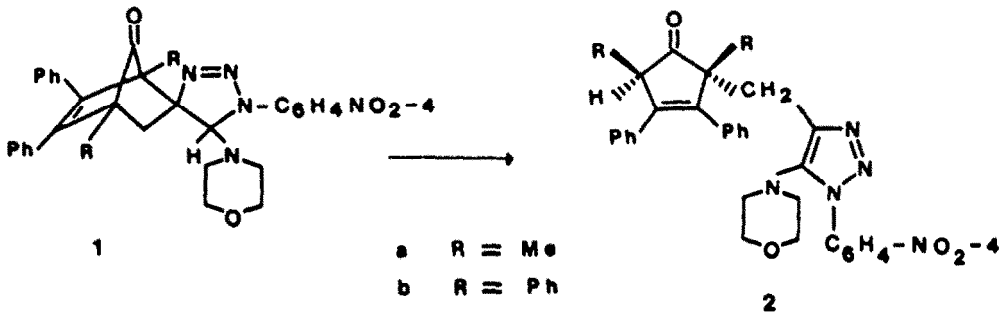
Abstract - Substituted 3-cyclopenten-1-ones 2a,b, derived from the rearrangement of 1, were isomerized under thermal conditions to afford the corresponding 2-cyclopenten-1-ones 4, 5b, respectively. When the isomerization was performed with basic catalysis, 2a afforded 2-cyclopenten-1-one 5a, whereas 5b was formed from 2b. Under acidic catalysis 4 and 5b were obtained from 2a and 2b, respectively. All transformations are characterized by a high stereoselectivity.

Previous work from our laboratory dealt with the synthesis of some substituted 7-keto-spiro[bicyclo[2.2.1]5-hept-2-en[2.4']-v-triazolines] 1 which were obtained both through (4+2)π-cycloaddition of tetrasubstituted cyclopentadienones to 5-amino-1-aryl-4-methylene-v-triazolines[2] and through (3+2)π-cycloaddition of arylazides to the enamines of the correspondingly substituted 7-keto-5-norbornene-2-carboxaldehydes.[3] The most interesting chemical feature of compounds 1 is their spontaneous rearrangement in polar aprotic solvent solution and at room temperature to 2-(triazolylmethyl)-substituted 3-cyclopenten-1-ones 2 which are formed as the sole reaction products, i.e. sterically pure (Scheme 1).

SCHEME 1

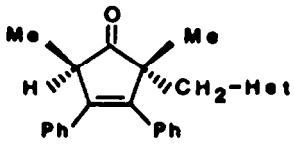


In an attempt to isomerize compound 2b to the corresponding α,β-unsaturated ketone for synthetic purposes the clean formation of a single stereoisomer was observed. This result prompted us to focus our attention on the chemical and the stereochemical features of the isomerization reactions of ketones 2. This study appeared worthy of interest since, notwithstanding the publication of some work

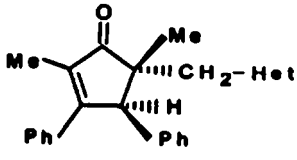
on this and related problems, several questions are still open, mainly in the field of highly substituted cyclopentenones. Several studies on the isomerization of β,γ- to α,β-unsaturated ketones have appeared,[4-7] but the effect of the substituents on the cyclopentenone ring and hence the stereochemistry of the isomerization have been only occasionally considered. In our case many bulky substituents were present making the molecules highly crowded and possibly contributing to favour one stereoisomer over another. A significant feature, too, was the presence of the basic morpholinotriazolyl substituent which could play a role in the catalyzed reactions.

RESULTS

All results which were obtained from catalyzed and thermal isomerization reactions of compounds 2a and 2b are summarized, separately for the sake of clarity, in Table 1 and Table 2. In both Tables indicated yields were determined on the crude reaction mixtures (^{1}H-NMR).



2a



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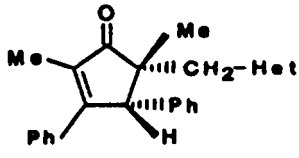
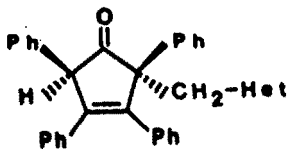


5a

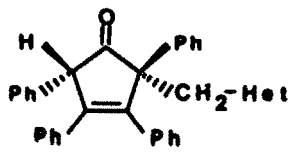
TABLE 1

Starting compound	Reaction conditions	% composition of the reaction mixture 2a	4	5a
2a	MeCN, 15h, 80°C	100	-	-
2a	xylene, 40h, 155°C	80	20	-
4	xylene, 35h, 155°C	-	100	-
5a	xylene, 35h, 155°C	-	-	100
2a	CH_2Cl_2, Et_3N, 20d, 25°C	100	-	-
2a	MeOH, NaOH, 24d, 25°C	-	-	100
4	MeOH, NaOH, 16d, 25°C	-	100	-
2a	CH_2Cl_2, pTSA, 32h, 25°C	-	100	-
5a	CH_2Cl_2, pTSA, 16d, 25°C	-	-	100

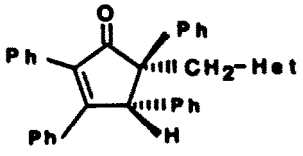
Thermal isomerizations. When a solution of 2b in acetonitrile was heated for 15 h a reaction mixture containing 2b, 3 and 5b was obtained, the ratio of compounds present being about 4:3:1. Further heating of the reaction solution yielded exclusively 5b. Similarly 5b was obtained as the sole reaction product by prolonged refluxing of a solution of isolated 3. A somewhat different behaviour was presented by the methyl-substituted analogue 2a. In this case a greater thermal stability of the compound was noticed, no conversion being observed after 15 h refluxing in acetonitrile. However at higher temperature (refluxing xylene) a 20% transformation of 2a into 4 occurred after 40 h. The isomeric α,β-unsaturated ketone 5a was not produced. Both 4 and 5a (produced as described later) were stable under the above conditions.



2b



3



5b

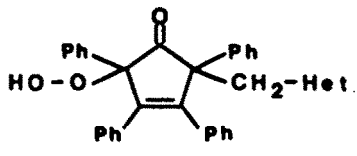


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TABLE 2

Starting compound	Reaction conditions	% composition of the reaction mixture			
		2b	3	5b	6
2b	MeCN, 15h, 80°C	50	37.5	12.5	-
2b	MeCN, 100h, 80°C	-	-	100	-
3	MeCN, 14h, 80°C	-	-	100	-
2b	CH_2Cl_2, Et_3N, 100h, 25°C	83	17	-	-
3	CH_2Cl_2, Et_3N, 20d; 25°C	-	-	100	-
2b	MeOH, NaOH, 24h, 25°C	-	-	18	82
5b	MeOH, NaOH, 7d, 25°C	-	-	100	-
2b	CH_2Cl_2, pTSA, 96h, 25°C	-	-	100	-

Base catalyzed isomerizations. At room temperature and in absence of catalysts both compounds 2a and 2b were found to be stable for long times in solution. However, when 2b was reacted at room temperature in presence of a catalytical amount of triethylamine a slow conversion into 3 was observed. Under the conditions employed this reaction is very slow since after 100 h the ratio of 2b with respect to 3 was only 5:1. On further action of the same catalyst for about 20 days, 5b was eventually produced as a result of the completion of the isomerization of 2b in 3 and further isomerization of 3 into the α,β-unsaturated ketone 5b. However, under the same conditions 2a was stable and remained unchanged even after 20 days.

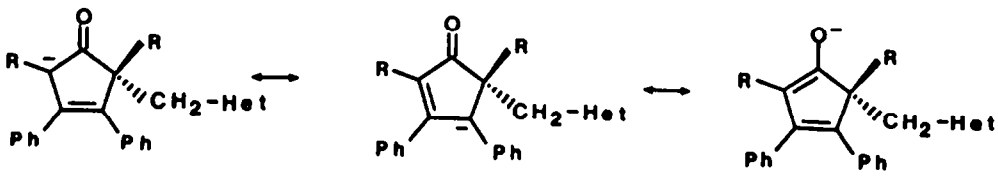
The effect of a stronger base was tested reacting 2a and 2b with sodium hydroxide in methanol. 5a and 5b were obtained, respectively, as isomerization products, other isomers being absent. Both 5a and 5b were stable in the above medium, no apparent change being observed even after several days. Similarly 4 was found to remain unchanged after 16 days reaction in MeOH/NaOH at room temperature. However, 2a and 2b behaved very differently since from 2a only 5a was obtained, whereas 2b afforded 5b only as the minor reaction product, the major being the hydroperoxide 6.[8]

Acid catalyzed isomerizations. The β,γ-unsaturated ketones 2a and 2b afforded the α,β-conjugated counterparts 4 and 5b, respectively, also by action of a catalytic amount of p-toluenesulfonic acid. The reaction was performed at room temperature and in aprotic solvent. 5a was not changed under the same conditions.

Structural assignment of cyclopentenones 2-5. The structures of 2a and 2b are firmly known.[2] The 3-cyclopenten-1-one and 2-cyclopenten-1-one structures were assigned on the basis of IR absorptions corresponding to expected values.[10] The structure of 2b being known, the 2S*, 5S* configuration for 3 is directly inferred. A confirmation is given by comparison of ^{1}H-NMR spectra. 2b shows a larger difference in the environment of the diastereotopic CH_2 protons. The lower field shift of the H-5 signal in 2b reflects the more rigid conformation due to the cis-standing phenyl groups. Comparison of molecular models of 4 and 5a shows that in 4 (Me and Ph cis) the methyl group is appreciably shielded by the phenyl group on the neighbouring carbon which must be in a conformation coplanar with the C-H_4 bond to avoid excessive steric hindrance. Accordingly, the H atom is deshielded both by the phenyl group and, to a lesser extent, by the Het residue on the same side. The conformational freedom of the CH_2Het group is high, allowing the nearly complete equivalence of the CH_2 protons. On the other hand, in 5a H-4 is shielded by the methyl group and corresponds to a higher field signal. The shielding of the Me-5 group is absent in 5a, the chemical shift being in the normal range. Both the lowered conformational freedom of the CH_2-Het group, caused by the large cis phenyl group and the effect of the phenyl group itself make the protons of CH_2 group less equivalent than in 4 (Δδ 0.4 ppm instead of 0.04 ppm). Taking into account the effect of the different substitution the spectrum of 5b fairly agrees with that of 5a in the difference of chemical shifts of the CH_2 hydrogens (Δδ 0.4 ppm).

DISCUSSION

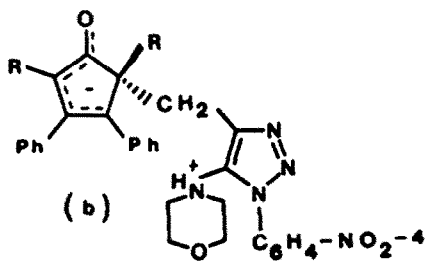
Generally speaking the previous results point out that a trend of the unconjugated ketones 2a, 2b, 3 toward isomerization to the conjugated counterparts, 4, 5a and 5b, respectively, is always present, thus showing that in any case the α,β-unsaturated compounds are the most stable ones. This result, through prima facie obvious,deserves some comments, taking into account that all isomerization reactions are highly stereoselective and that similar, but not identical, mechanisms should operate in the case of thermal, base-catalyzed and acid-catalyzed transformations. Notwithstanding the presence of a basic group - the morpholino residue - on the heterocyclic substituent, which could act as catalyst, compounds 2 are practically stable in solution for very long times at room temperature. Clearly, no enolization occurs under these conditions, preventing any change. However, using a relatively stronger base as triethylamine compound 2b is very slowly deprotonated at C-α forming the delocalized enolate (a) which can undergo both kinetic protonation[4-7] at C-α, probably both on the si*



(a)

and on the re* face forming again the starting isomer 2b and its stereoisomer 3, respectively, and thermodynamic protonation on C-γ producing the most stable α,β-unsaturated compound 5b. Obviously, at longer reaction times, 5b must become the sole reaction product. The formation of a single stereoisomer of the α,β-unsaturated cyclopentenone 5b is explained by observing that the severe interaction between phenyl groups that would characterize the other isomer would destabilize this latter compound. Not surprisingly, compound 2a shows a higher stability, being unaffected by triethylamine under the conditions used for 2b. Clearly in the methyl substituted compound the deprotonation of C-α is slower[11] making more difficult the enolization process. This view is confirmed by a comparison of the thermal behaviour of 2a and 2b. Here again 2a is only isomerized under far more severe conditions with respect to 2b.

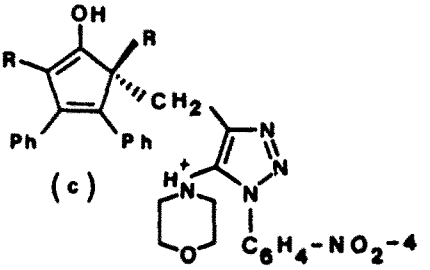
As far as the mechanism of the thermal isomerization is concerned, it has to be taken into consideration that the reaction must be a self-catalyzed one since no base or acid was deliberately added. However, at the high temperature involved, differently from low temperatures (see above) the morpholino group on the triazole ring can act as the deprotonating reagent producing the zwitterionic intermediate (b) in which the protonated amino group acts, intramolecularly or intermolecularly, as the protonating reagent of the enolate moiety. From 2b compounds 3 and 5b are formed as the kinetic and thermodynamic products, respectively. Owing to the more drastic conditions which were used in the case of 2a, which is more difficult to deprotonate, only the thermodynamic protonation leading to the α,β-unsaturated ketone was observed. Sterically pure products were always obtained. Compounds 4 and 5b do not have corresponding configurations but it is evident that the less hindered molecule was formed in both cases. Indeed, comparing 4 with its stereoisomer 5a, it is clear that both isomers are characterized by a remarkable crowding, but owing to the relatively low bulkiness of the methyl group, 4 should be less hindered because the bulkiest substituents (CH_2-Het and Ph) are trans. Similarly it is inferred from molecular models that the epimer at C-4 of 5b (not observed) would be more crowded than 5b, exhibiting a severe interaction between cis-standing phenyl groups on C-4 and C-5.



(b)

The same results of the thermal isomerization were obtained by the acid-catalyzed one, through the intermediacy of enol (c) which undergoes protonation in the same way as (b) (see above).

In presence of sodium hydroxide as catalyst enolization to give enolate (a) and protonation to form the α,β-unsaturated compounds 5a and 5b took place in good agreement with the foregoing and with the known fact that when strong bases are used to produce the enolate, the formation of the α,β-unsaturated ketone is favoured.[7] Here again a difference was observed between 2a and 2b. The tetraphenyl-substituted enolate was readily attacked by oxygen on C-α affording hydroperoxide 6 as the main product. This reaction did not occur appreciably on 2a, which is expected since the autoxidation mechanism involving the radical on C-2[12] should be favoured when a benzyl radi-



(c)

cal is formed. As far as the stereochemistry of the hydroxide-catalyzed isomerization is concerned, the following is noted. 2b behaved as in the thermal and acid-catalyzed reactions giving 5b in good agreement with the steric requirement described above. However, in the case of 2a, which is clearly less controlled by steric hindrance, the protonation of the enolate occured on the less hindered si* face, producing 5a. Somewhat surprisingly, the protonation reaction is irreversible under the conditions used. This is confirmed by the absence of deuterium exchange both in 5a and 5b when they were kept in a solution of CD_3OD with catalytic NaOD for 120 h at room temperature. Under similar conditions also 4 was found to be stable. Remarkably, 5a was not epimerized when reacted with CH_2Cl_2/pTSA under similar conditions to those used for the isomerization of 2a,b.

The above results point out that the highly substituted 3-cyclopenten-1-ones 2a,b can be isomerized with relative ease to the more stable 2-cyclopenten-1-ones which are stable to all epimerization reactions both under acidic and basic catalysis.

EXPERIMENTAL SECTION

Mp are not corrected. IR spectra were taken with a Perkin-Elmer Model 197 instrument and NMR spectra with Varian EM-390 and XL-200 spectrometers. Values are given in ppm from TMS. Column chromatography was run on silica gel with the eluant indicated and ready-to-use silica gel plates were employed for TLC. Mw of new compounds were confirmed by MS.

Isomerization of 2a with p.toluenesulfonic acid. Compound 2a (100 mg, 0.18 mmol) was stirred in CH_2Cl_2 (10 ml) with a catalytic amount of p-toluenesulfonic acid for 32 h. The solution was washed with H_2O, the organic layer was separated and after evaporation the crude residue was recrystallized yielding pure (4S*, 5R*)-3,4-diphenyl-2,5-dimethyl-5-[5-morpholino-1-(4-dinitrophenyl)-v-triazol-4-yl]methyl-2-cyclopenten-1-one 4 (90 mg, 91%). Found: C, 69.93; H, 5.69; N, 12.74. $C_{32}H_{31}N_5O_4$ requires: C, 69.55; H, 5.86; N, 12.60%.

Isomerization of 2b with p.toluenesulfonic acid. Compound 2b (300 mg, 0.44 mmol) was stirred with a catalytic amount of p.toluenesulfonic acid in CH_2Cl_2 (15 ml) for 96 h and then elaborated as described for 2a. After recrystallization pure (4R*,5R*)-5-[5-morpholino-1-(4-nitrophenyl)-v-triazol-4-yl]methyl-2,3,4,5-tetraphenyl-2-cyclopenten-1-one 5b (250 mg, 84.3%) was obtained. Found: C, 74.87; H, 5.24; N, 10.40. $C_{42}H_{55}N_5O_4$ requires: C, 75.23; H, 5.62; N,10.13%.

Isomerization of 2a with NaOH/MeOH. Compound 2a (1.5 g, 2.7 mmol) and NaOH (50 mg, 1.25 mmol) was stirred in MeOH (10 ml) for 24 h. A solid precipitate was formed and filtered. On recrystallization pure 5a (710 mg, 47.8%) was obtained. The filtrate was evaporated, the residue was washed with diluted HCl and chromatographed (PhH: AcEt, 4:1). As the main fraction (4R*, 5R*)-3,4-diphenyl-2,5-dimethyl-5-[5-morpholino-1-(4-nitrophenyl)-v-triazol-4-yl]methyl-2-cyclopenten-1-one 5a (150 mg, 10.1%) was obtained. Found: C, 69.93; H, 5.69; N, 12.74. $C_{32}H_{31}N_5O_4$ requires: C, 70.00; H, 5.83, N, 12.77%.

Isomerization of 2b with NaOH/MeOH. A solution of NaOH (85 mg, 2.13 mmol) and 2b (2.6 g, 3.86 mol) in MeOH (20 ml) was stirred for 24 h. The solid precipitate was filtered and dissolved in CH_2Cl_2 (10 ml). After washing with diluted HCl, the solution was evaporated and the residue crystallized yielding pure 5-hydroperoxy-2-[5-morpholino-1-(4-nitrophenyl)-v-triazol-4-yl]methyl-2,3,4,5-tetraphenyl-3-cyclopenten-1-one 6 (2.0 g, 73.5%). Found: C, 71.47; H, 5.00; N, 9.92. $C_{42}H_{35}N_5O_6$ requires: C, 71.09; H, 5.03; N, 9.81%. The mother liquors were chromatographed with CH_2Cl_2:AcOEt, 4:1, yielding two main fractions. The first contained a mixture of 2b and 5b (230 mg) in a 1:2 ratio according to ^1H NMR. The second fraction afforded a further crop of 6 (100 mg, 3.7%).

TABLE 3 - M.p. and spectroscopic data

Compd[a]	m.p. °C	ν_{max} (nujol)	^{1}H NMR (CDCl3)[b,c]
2a	185-186 (EtOH)	1738	δ 1.25 (d,J=8.0 Hz, 3, Me-5); 1.62 (s, 3, Me-2); 2.44-2.65 (m, 4, CH_2N); 2.66, 3.16 (dd,J=-15.5Hz, 2, CH_2); 3.50-3.52 (m, 4, CH_2O); 3.92 (q,J=8.0 Hz, 1, H-5)
2b	210-211 dec. (CH_2Cl_2/n-pentane	1747	δ 2.18-2.28, 2.40-2.50 (2m, 4, CH_2N); 3.20, 4.08 (dd,J=-15 Hz, 2, CH_2); 3.46-3.64 (m, 4, CH_2O); 5.53 (s, 1, H-5)
3	225-227 (CH_2Cl/iPr_2O)	1755	δ 2.50-2.65 (m, 4, CH_2N); 3.40-3.64 (m, 4, CH_2O); 3.65, 3.90 (dd,J=-15 Hz, 2, CH_2); 4.91 (s,1, H-5)
4	141-143 ($CHCl_3$/iPr_2O)	1680	δ 0.75 (s, 3, Me-5); 2.00 (d,J=1.9 Hz, 3, Me-2); 3.0-3.15 (m, 4, CH_2N); 3.06, 3.10 (dd,J=-14 Hz, 2, CH_2); 3.68-3.72 (m, 4, CH_2O); 5.42 (d,J=1.9 Hz, 1, H-4)
5	199-200 (CH_2Cl_2/iPr_2O)	1690	δ 1.72 (s, 3, Me-5); 2.11 (d,J=1.6 Hz, 3, Me-2); 2.46, 2.83 (dd,J=-16 Hz, 2, CH_2); 2.62-2.67 (m, 4, CH_2N); 3.54-3.59 (m, 4, CH_2O); 4.55 (q,J=1.6 Hz, 1, H-4)
5b	233-235 (CH_2Cl_2/iPr_2O)	1685	δ 2.56-2.60 (m, 4, CH_2N); 3.42-3.44 (m, 4, CH_2O); 3.55, 3.95 (dd,J=-14.5, 2, CH_2); 5.87 (s, 1, H-4)
6	167-168 ($CHCl_3$)	1755	δ 2.46-2.53 (m, 4, CH_2N); 3.49-3.54 (m, 4, CH_2O); 3.61, 3.87 (dd,J=-13.5 Hz, 2, CH_2); 7.96 (s, 1, exchang., OH)

[a] Complete data for compounds 2a and 2b are reported for discussion purposes from ref. 2

[b] 200 MHz for 2a, b, 4, 5a, b

[c] Aromatic signals in the expected range

Thermal rearrangement of 1b. Compound 1b[2] (1.44 g, 2.21 mmol) was dissolved in MeCN (30 ml) and refluxed for 7 h. The reaction mixture was evaporated and chromatographed with CH_2Cl_2-Et_2O (ratio 1:0 to 0:1). Three main fractions were isolated. Fraction 1 contained (2S*, 5S*)-2-[5-morpholino-1-(4-nitrophenyl)-v-triazol-4-yl]methyl-2,3,4,5-tetraphenyl-3-cyclopenten-1-one 3 (200 mg, 13.4%). Found: C, 74.87; H, 5.24; N, 10.40. $C_{42}H_{35}N_5O_4$ requires: C, 74.50, H, 5.01; N, 10.20%. From fraction 2 product 2b (700 mg, 47%) was isolated. Fraction 3 afforded a mixture of 2b and 5b in a 2:1 ratio (250 mg, 16.8%).

Thermal isomerization of 2b. Compound 2b (200 mg, 29.7 mmol) was refluxed for 15 h in MeCN (20 ml). The reaction mixture was analyzed by ^{1}H NMR and IR showing that it was a mixture of 2b, 3 and

5b (ratio 4:3:1).

Thermal isomerization of 3. Compound 3 (100 mg, 14.85 mmol) was refluxed for 14 h in MeCN (10 ml). After evaporation the crude residue was analyzed by IR and ^{1}N NMR showing the complete transformation into 5b.

Thermal isomerization of 2a. Compound 2a (100 mg, 18.2 mmol) was dissolved in xylene (10 ml) and refluxed for 40 h. After evaporation the crude residue was analyzed by ^{1}H NMR showing it was a mixture of 2a and 4 (ratio 4:1).

Tables 1 and 2. The data reported in the Tables were obtained using the following methods.

Thermal isomerization. The starting compound (0.15 mmol) was dissolved or suspended in the solvent indicated (10 ml) and the reaction mixture was refluxed for the time indicated. After evaporation the residue was analyzed by ^{1}H NMR and IR.

Acid-catalyzed isomerizations. The starting compound (0.15 mmol) was dissolved in CH_2Cl_2 (10 ml). p- Toluenesulfonic acid (0.015 mmol) was added and the reaction mixture was kept at room temperature for the time indicated. The reaction solution was washed with water, dried and evaporated. The residue was analyzed by ^{1}H NMR and IR.

Base-catalyzed isomerizations. Sodium hydroxide: the starting ketone (0.15 mmol) was suspended in MeOH (10 ml) and NaOH (0.015 mmol) was added. The mixture was stirred at room temperature for the time indicated, evaporated, taken up in CH_2Cl_2 and washed with water. The residue was analyzed by ^{1}H NMR and IR. Triethylamine: the starting ketone (0.15 mmol) was dissolved in CH_2Cl_2 (10 ml) and triethylamine (0.015 mmol) was added. After standing at room temperature for the time indicated the reaction solution was evaporated and the residue analyzed by ^{1}H NMR and IR.

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8 Other examples of hydroperoxidation of α-phenyl-2-cyclo-penten-1-ones have been described.[9] Further work in this field is in progress.

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