Reaction of Ketenes with Three Membered Heterocyclic Rings

IV. Addition of *tert*-butylcyanoketene to optically active styreneoxide and 1,1-diphenylethylenoxide

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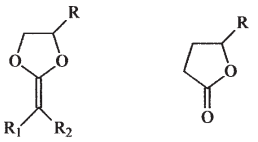
Addition of tert-butylcyanoketene to optically active styreneoxide and 1,1-diphenyletyleneoxide are presented. Loss of optical activity during the addition reaction of TBCK to optically active styrene oxide (R (-)) proves that the process is a stepwise one involving an open intermediate allowing free rotation around the σC-C s bond adjacent to the aromatic ring. The identified products for the addition of TBCK to 1,1-diphenyletyleneoxide are two isomeric acetals and an unsaturated ester. All structure attributions are based on IR, ^{1}H and ^{13}C NMR and MS data.

Keywords: cyanoketenes, TBCK, CCK, oxiranes

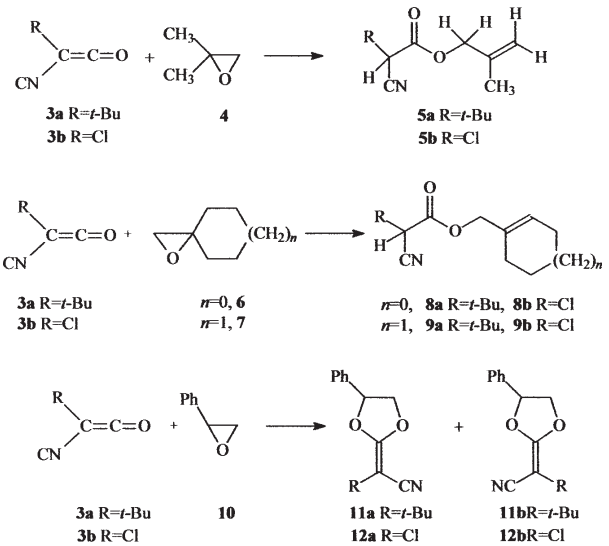
Depending on the structure of the reagents and the type of catalyst used, the addition reactions of epoxides to ketenes can lead to ketene acetals **1** [1, 2], five membered cyclic lactones **2** [3] or mixtures of these two types of products [4]. The presence of catalysts promotes the ring opening of the oxirane with generation of a nucleophile center at the oxygen atom, followed by the addition to the ketene [2-4].



1 **2**

In previous papers we reported the reactions of *tert*-butylcyanoketene **3a** (TBCK) and chlorocyanoketene **3b** (CCK) with isobutyleneoxide **4** [5], spiranic epoxides (1-oxaspiro[2.5]-heptane **6** and 1-oxaspiro[2.5]-octane **7**) [6] and styreneoxide **10** [7].

Isobutyleneoxide **4** or spiranic epoxides **6** and **7,** when reacting with cyanoketenes **3** in absence of catalysts**,** will follow a route involving an "ene"- like process, leading to the unsaturated esters (**5a**,**b**, **8a**,**b** and **9a**,**b**) of the acids corresponding to the used ketene [5,6].

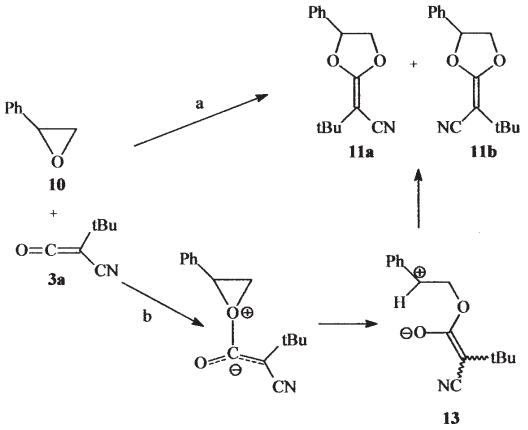


3a R=*t*-Bu **3b** R=Cl **4** **5a** R=*t*-Bu **5b** R=Cl

3a R=*t*-Bu **3b** R=Cl *n*=0, **6** *n*=1, **7** *n*=0, **8a** R=*t*-Bu, **8b** R=Cl *n*=1, **9a** R=*t*-Bu, **9b** R=Cl

3a R=*t*-Bu **3b** R=Cl **10** **11a** R=*t*-Bu **12a** R=Cl **11b**R=*t*-Bu **12b**R=Cl

For the reaction of styreneoxide **10** with TBCK **3a** or CCK **3b** performed in the absence of catalysts and leading exclusively to cyclic acetals (**11a**,**b** and **12a**,**b**) [7], we can take into account different mechanistic pathway: concerted insertion of the ketene C=O double bond on one of the oxirane's C-O σ bond (a) or an electrophylic attack of the ketene central carbon atom at the oxirane's oxigen atom followed by ring opening to zwitterionic intermediate **13** and then ring closure with formation of cyclic acetals (b).



10 **3a** **11a** **11b** **13**

Using an optically active styreneoxide could discriminate between these routes. Also attaching a second phenyl group at the same position in the oxirane ring, as in 1,1-diphenyletyleneoxide, could further stabilize the cationic center in **13**, eventually revealing details of the reaction mechanism.

Experimental part

All infrared spectra were recorded with a Bruker Vertex 70 FTIR-ATR instrument. The NMR data were obtained using a Gemini 300 Varian instrument (^{1}H at 300MHz and ^{13}C at 75 MHz). The GC-MS experiments were done using a GC 6890N Agilent Technologies gas-chromatograph coupled with a MS 5975 B quadrupole mass spectrometer, using the 70 eV standard ionization energy.

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The reaction of TBCK with optically active styreneoxide (R (-))

In a round bottomed flask fitted with magnetic agitation and reflux condenser were added 0.970 g (0.0032 moles) 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone and 0.684 mL (0.720g; 0.006 moles) optically active styreneoxide (R (-)) in 16.4 mL dry CCl_4. The mixture was refluxed for 2.5 hours, until the complete decomposition of the precursor and ketene disappearance, as confirmed by the IR spectrum (the bands at 2110 cm^{-1} (N_3), 2220 cm^{-1} (C≡N) and at 2130 cm^{-1}(C=C=O)).

Part of the yielded solution was analyzed by GC on a chiral column in the following conditions:

- capillary column: Φ_{int} = 0.25 mm and l = 25 m
- stationary phase: di-methyl-pentyl-β-cyclodextrine; film thickness 0.25μm
- vaporizer temperature: 250 °C
- FID detector: detector temperature 210 °C
- temperature program: 50°→ 230 °C (2 °/ min)
- carrier gas: H_2, 2mL/min flow.

The use of this technique has shown that the diastereoisomers corresponding to each geometric isomer are formed in equal proportions, corresponding to a racemic mixture. This result was also confirmed by polarimetry measurements showing a complete loss of optical activity.

The remainder of the reaction product, after removing the solvent, was analyzed by IR, ^{1}H-NMR, ^{13}C-NMR and GC-MS spectrometry, confirming the formation of a mixture of 1-cyano-1-*tert*-butyl-2-(3-phenyl-2,5-dioxo-cyclopentylidene)-ethylene **11a** and 1-cyano-1-*tert*-butyl-2-(4-phenyl-2,5-dioxo-cyclopentylidene)-ethylene **11b** in a ration of ~1:7, in concordance with the ratio determined by GC. These compounds are identical to the two isomeric acetals obtained in the reaction between TBCK and styreneoxide, as described in the literature [7].

The reaction of in situ generated TBCK with 1,1-diphenylethyleneoxide

A solution of 0.5 g (1.65 mmoles) 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone and 0.65 g (3.30 mmoles) 1,1-diphenylethyleneoxide in 15 mL dry benzene was refluxed for 1.5 h until the reaction was completed (IR control). After solvent evaporation under vacuum, 1.60 g of a dark orange liquid were obtained and analyzed by IR, NMR and GC-MS spectroscopy.

The IR spectra of the crude reaction mixture revealed a very strong band at 1642 cm^{-1}, a weak band at 1750 cm^{-1} and a strong band at 2198 cm^{-1}.

GC-MS analysis of the crude reaction mixture showed the formation of three 1:1 ketene-epoxide adducts: two of them had an almost identical fragmentation pattern, a situation consistent with two geometric isomers, while the third had a different fragmentation pattern.

The ^{1}H-NMR spectra of the crude reaction product showed, besides the multiplet for the aromatic protons (δ 7.25-7.40 ppm), two series of signals with different intensities: at δ 1.26 ppm and at 4.78 ppm in the case of strong signals, and at δ 1.17 ppm and at 4.89 ppm in the case of weak signals. The spectra also show other very low intensity signals at δ 1.10, 3.31 and at 7.59 ppm belonging to the third adduct.

After solvent evaporation, one of the adducts crystallized under cooling. After washing with methanol, we obtained a colorless crystalline compound with m.p.=137°C. The IR, NMR and GC-MS analysis showed that the crystallized product is 1-cyano-1-*tert*-butyl-2-(4,4-diphenyl-2,5-dioxo-cyclopentylidene)-ethylene (compound **17a** obtained in greater amount).

Using NMR and GC-MS spectroscopy we also identified and characterized compound **17b** (obtained in smaller amount) as 1-cyano-1-*tert*-butyl-2-(3,3-diphenyl-2,5-dioxo-cyclopentylidene)-ethylene.

The third adduct obtained in this reaction was isolated using column chromatography (silicagel, petroleum ether/ diethyl ether, 19/1) and identified by IR, NMR and GC-MS analysis as 1,1-diphenyl-1-ethenyl-*tert*-butyl-cyanoacetate (**18**).

17a: **IR** (solid in ATR, cm^{-1}): 1642 vs., 2198 s. **^{1}H- NMR** ($CDCl_3$ δ ppm): 1.26 (s, 9H, H^{11}); 4.78 (s, 2H, H^1); 7.25-7.40 (m, 10H, H-arom). - **^{13}C- NMR** ($CDCl_3$ δ ppm): 30.05 (C^{11}); 30.56 (C^{10}); 70.06 (C^2); 75.51 (C^1); 91.62 (C^8); 118.97 (C^9); 128.57 (C^5); 125.48 (C^4); 128.00 (C^6); 139.16 (C^3); 166.48 (C^7). **MS** (m/z, (relative abundance, %)): 41 (3.07); 53 (5.99); 57 (5.20); 77 (5.72); 105 (4.33); 108 (27.76); 124 (4.36); 152 (11.90); 165 (35.77); 166 (8.82); 167 (B.P.100); 168 (49.57); 169 (6.08); 178 (35.30); 179 (38.29); 180 (10.74); 196 (40.51); 197 (16.48); 304 (7.84); 319 (M.P. 19.87).

17b: **IR** (solid in ATR, cm^{-1}): 1642 vs., 2198 s. **^{1}H- NMR** ($CDCl_3$ δ ppm): 1.17 (s, 9H, H^{11}); 4.89 (s, 2H, H^1); 7.25-7.40 (m, 10H, H-arom). **^{13}C- NMR** ($CDCl_3$ δ ppm): 29.74 (C^{11}); 30.41 (C^{10}); 70.08 (C^2); 78.02 (C^1); 88.52 (C^8); 118.99 (C^9); 128.40 (C^5); 125.35 (C^4); 127.99 (C^6); 139.16 (C^3); 166.67 (C^7). **MS** (m/z, (relative abundance, %)): 41 (6.24); 53 (3.99); 57 (10.54); 77 (5.71); 105 (4.20); 108 (24.43); 124 (5.58); 152 (9.49); 165 (21.53); 166 (6.23); 167 (B.P.100); 168 (54.27); 169 (6.93); 178 (24.16); 179 (28.14); 180 (6.41); 196 (27.41); 197 (18.46); 304 (8.37); 319 (M.P. 27.12).

18: **IR** (solid ATR, cm^{-1})**:** 1750 vs., 2251 w. **^{1}H- NMR** ($CDCl_3$, δ ppm): 1.10 (s, 9H, H^1); 3.31 (s,1H, H^4); 7.59 (s, 1H, H^6); 7.25-7.40 (m, 10H, H-arom). **^{13}C- NMR** ($CDCl_3$ δ ppm): 27.96 (C^1); 35.75 (C^2); 49.70 (C^4); 115.45 (C^3); 128.49 ($C^{9'}$); 128.54 (C^9); 128.27 ($C^{11'}$); 128.38 (C^{11}); 128.80 ($C^{10'}$); 130.25 (C^{10}); 131.84 (C^6); 136.17 (C^7); 138.40 (C^8); 163.00 (C^5). **MS** (m/z, (relative abundance, %)): 41 (5.05); 57 (17.64); 77 (2.34); 89 (4.70); 102 (2.95); 105 (2.45); 108 (4.28); 115 (10.73); 128 (4.15); 139 (4.88); 152 (15.87); 165 (28.48); 166 (10.53); 167 (19.14); 168 (2.29); 169 (6.93); 178 (5.13); 179 (3.18); 196 (B.P. 100); 197 (20.38); 319 (M.P. 15.18).

The reaction of pre-generated TBCK with 1,1-diphenylethyleneoxide

A solution of 1.62 g (5.37 mmols) 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone in 30 mL dry benzene was refluxed for one hour until the disappearance from the IR spectrum of the 2110 cm^{-1} band characteristic for N_3 vinylic groups. The ketene solution was left to cool down at room temperature (25°C), then 2 g (1.02 mmoles) of 1,1-diphenylethyleneoxide were added and stirred until the total consumption of the ketene (approx. twenty hours). Benzene evaporation yielded 3.35 g of a dark-orange oil.

The IR, NMR and GC-MS analysis indicated the formation of two isomeric acetals (**17a** and **17b**) and of diphenylvinylic ester (**18).**

The reaction of 1-cyano-1-tert-butyl-2-(4,4-diphenyl-2,5-dioxo-cyclopentylidene)-ethylene with CF_3COOD

To a solution of 30 mg (0.094 mmols) 1-cyano-1-*tert*-butyl-2-(4,4-diphenyl-2,5-dioxo-cyclopentylidene)-ethylene (**17a**) in 0.7 mL $CDCl_3$ we added 0.02 mL (0.0299 mg, 0.00026 mmols) CF_3COOD and the reaction was allowed to proceed at room temperature for 4.5 h. ^{1}H-NMR analysis

showed the formation of deuterated 1,1-diphenyl-1-ethenyl-*tert*-butyl-cyanoacetate (**20**) with 75% yield accompanied by 25% nondeuterated ester **18**.

20: **^{1}H- NMR** ($CDCl_3$, δ ppm): 1.10 (s, 9H, H^1); 7.59 (s, 1H, H^6); 7.25-7.40 (m, 10H, H-arom).

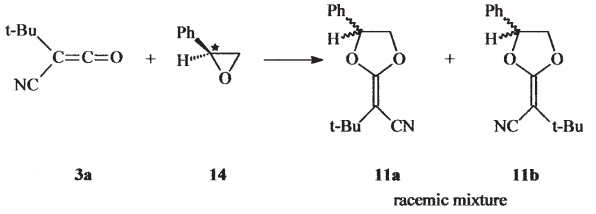
Results and discussions

The reaction between TBCK **3a** and optically active styreneoxide (R(-)) **14** was done generating the ketene *in situ* in carbon tetrachloride, in the presence of epoxide (ketene/epoxide ratio=1). Reflux was maintained until the total consumption of the ketene.

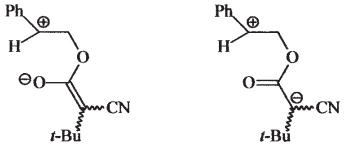
The reaction product was a racemic mixture of ketene acetals **11a,b**, the loss of optical activity proving that the reaction does not follow a concerted path, but a step-wise heterolytic one, and that the C-O σ bond of the oxirane adjacent to the aromatic ring is cleaved during the reaction.

The reaction intermediate in this case is the open zwitterion **13** where the optical activity is lost due to the free rotation around the C-C σ bond adjacent to the aromatic ring.

Taking into consideration the absence of the lactones from the reaction products, we can assume that the weight of structure **15**, with the negative charge localized at the carbon atom adjacent to the cyan group, is almost insignificant. Also if structures **13** and **15** would be in equilibrium, then, due to the free rotation around the C-C bond adjacent to the nitrile group, the two isomeric acetals **11a** and **11b** would have been formed in similar amounts. In all cases, however, an asymmetry is observed, acetal **11b** resulting in significantly greater amounts than **11a** [7].



3a 14 11a 11b



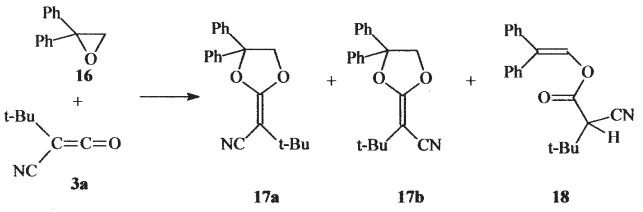
13 15

The reaction between TBCK **3a** and 1,1-diphenyl-etyleneoxide **16** was performed in anhydrous benzene both with *in situ* generation or pre-generation of the ketene and no differences have been observed in the products distribution. Ketene/epoxide ratio of 1/1 was used in all cases and after solvent removal the crude reaction product was analyzed by IR, NMR and GC-MS spectrometry.

The IR spectra of the crude reaction mixture revealed the presence of three absorption bands: one at 1642 cm^{-1} (characteristic for exocyclic C=C bonds), one at 1750 cm^{-1} (characteristic for esteric or lactonic C=O bonds) and another at 2198 cm^{-1} (characteristic for a C≡N group attached to a double bond).

GC-MS analysis of the crude reaction mixture showed the formation of three 1:1 ketene-epoxide adducts (M=319), two of them having identical fragmentation pattern.

After solvent removal and cooling a colorless crystalline compound has been isolated. GC-MS data showed that this was the major compound from the two with identical fragmentation pattern.



16 3a 17a 17b 18

Based on IR, MS and NMR data, structure **17a** has been attributed to this compound and **17b** to his geometric isomer. For the third adduct, a 1,1-diphenyl-1-ethenyl-*tert*-butyl-cyanoacetate structure **18** has been assigned based on spectral data, as will be shown further on.

The fragmentation pattern of the two geometric isomers can be rationalized accepting the three main fragmentation pathways proposed in figure 1. This scheme is based on the observation that the MS spectra of acetals **17a**,**b** includes the full fragmentation patterns of 1,1-diphenyletyleneoxide and 1,1-diphenylethene [8].

In the case of the third adduct, the proposed fragmentation scheme is shown in figure 2. The main pathway in this scheme (b) involves the elimination of one neutral *tert*-butylcyanoketene fragment from the primary radical-cation, leading to the formation of the radical-cation corresponding to diphenylacetaldehyde (m/z=196).

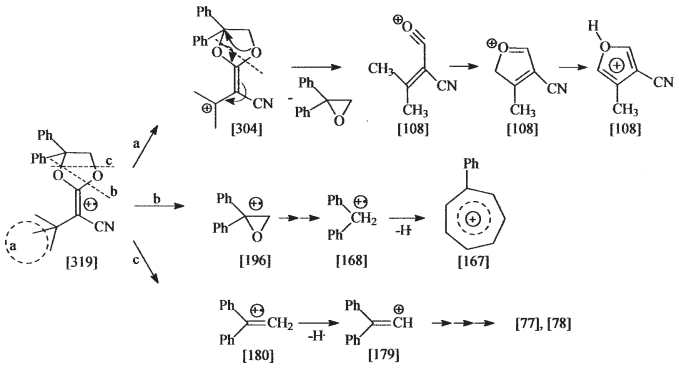


Fig. 1. MS fragmentation routes of the acetals **17a,b**

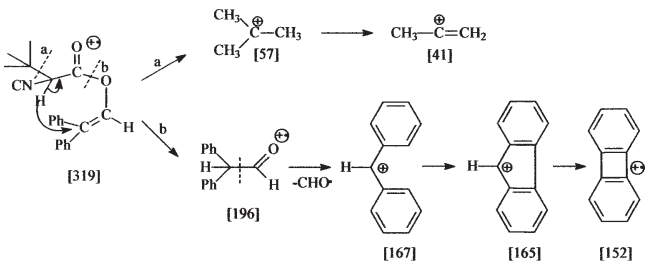


Fig. 2. MS fragmentation routes of the unsaturated ester **18**

The ^{1}H-NMR spectra of the crude reaction product shows three main groups of signals:

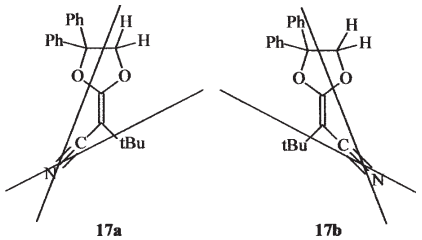
-two singlet signals in a region specific for the methyl protons of *tert*-butyl groups, located at d 1.17 ppm (weak signal) and at 1.26 ppm (strong signal)

-two singlet peaks of different intensities, centered at δ 4.78 ppm (strong signal) and at 4.89 ppm (weak signal),

-a multiplet signal for the aromatic protons at δ 7.25-7.40 ppm.

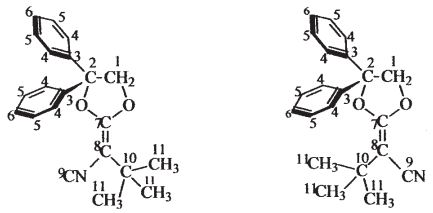
The presence of the two series of singlet signals of different intensities was in agreement with the formation in different proportions of two adducts with similar structures, namely the acetals **17a** and **17b**. In order to assign correctly the signals from the NMR spectra to the two isomeric molecules, some details of the structures have to be taken into account. The difference in chemical shifts (Δδ=0.1 ppm) of the CH_2 protons in the two isomers can be explained by the magnetic anisotropy induced by

the cyano group, as follows: in the case of one isomer, the two CH_2 protons lie inside the shielding cone of the cyano group and are more shielded, while for the other isomer the CH_2 protons are outside the cone and consequently less shielded.



17a **17b**

Thus, the isomer with the *tert*-butyl protons at δ 1.26 ppm and the CH_2 protons at δ 4.78 ppm is the **17a** compound, while the one with the *tert*-butyl protons at δ 1.17 ppm and the CH_2 protons at δ 4.89 ppm is the **17b** compound.



17a **17b**

Table 1

^{1}H NMR DATA FOR COMPOUND 17a AND 17b ($CDCl_3$, δ, ppm)

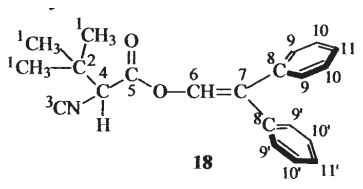
Compound	H^1	H^{11} (*t*-Bu)	Ph
17a	4,78	1,26	7.25-7.40
17b	4.89	1.17	7.25-7.40

In table 1 and 2 the ^{1}H- and ^{13}C-NMR data of the acetals **17a** and **17b** are presented.

In order to get a precise structure attribution for the third adduct, we have separated the compound by column chromatography (silicagel, petroleum ether/diethyl ether, 19/1) and further analysed it using IR, NMR and GC-MS spectrometry.

The IR spectra presents two absorption bands at 1750 cm^{-1} (characteristic for the C=O bonds of esters or lactones) and at 2251 cm^{-1} (characteristic for a C≡N bond linked to a sp^3 hybridized carbon atom).

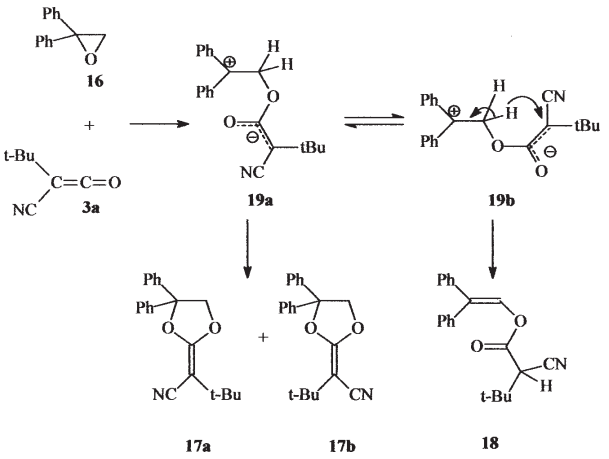
The ^{1}H-NMR spectrum shows three singlets located at δ 1.10, 3.31 and 7.59 ppm, in agreement with a diphenylvinylic ester structure for compound **18**. The presence of the δ 7.59 ppm signal, typical for an unsaturated proton, rules out a cyclic lactone structure.



18

The ^{1}H and ^{13}C NMR data of the compound **18** are presented in tables 3 and 4.

For the formation of ester **18** one can consider a mechanism based on an intramolecular proton transfer in one of the possible conformations of the zwitterionic intermediate **19** involved in the formation of acetals **17**.



16 **3a** **19a** **19b** **17a** **17b** **18**

The presence of the two phenyl groups attached at the carbocationic centre could stabilize the zwitterion allowing the formation of conformer **19b**, having the geometry needed for an internal proton transfer. On the other hand, this intramolecular process would be an 1,4 transfer and such processes are reported only for excited-state intramolecular proton transfers (ESIPT) [9].

Another possibility is an acid catalyzed ring opening of the acetals **17** followed by a proton elimination. The azide precursor of TBCK is a hygroscopic compound, and thus in the reaction medium we always had some traces of water generating *tert*-butylcyanoacetic acid, a proton source that can act as catalyst.

In order to test this second hypothesis we have done a reaction between acetal **17a** and deuterated trifluoroacetic acid (CF_3COOD) at room temperature. The ^{1}H-NMR spectra of the crude reaction product shows the signals at δ 1.11, 3.31 and at 7.59 ppm that are attributed to the diphenylvinylic ester **18**. The ratio of proton signals at δ 3.31 and 7.59 were in agreement with the formation of deuterated ester **20** with 75% yield accompanied by 25% nondeuterated ester **18**.

Due to the elimination of protons, in the reaction mixture we will have both protons and deuterium ions. Because of the proton's higher mobility, the yield of nondeuterated ester **18** is higher than the one expected based on the accumulation of protons.

Compound	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}
17a	75.51	70.06	139.16	125.48	128.57	128.00	166.48	91.62	118.97	30.56	30.05
17b	78.02	70.08	139.16	125.35	128.40	127.99	166.67	88.52	118.99	30.41	29.74

Table 2

^{13}C NMR DATA FOR COMPOUNDS **17a** AND **17b** ($CDCl_3$, δ, ppm)

H^1(*t*-Bu)	H^4	H^6	Ph
1.10	3.31	7.59	7.25÷7.40

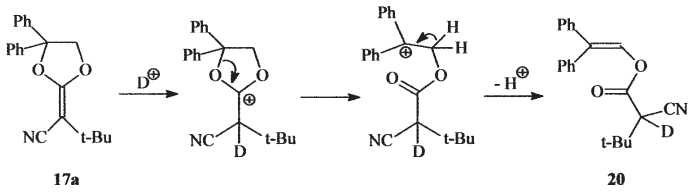
Table 3

^{1}H NMR DATA FOR COMPOUND **18** ($CDCl_3$, δ, ppm)

C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	$C^9/C^{9'}$	$C^{10}/C^{10'}$	$C^{11}/C^{11'}$
27.96	35.75	115.45	49.70	163.00	131.84	138.40	136.17	128.54/ 128.49	130.25/ 128.80	128.38/ 128.27

Table 4

^{13}C NMR DATA FOR COMPOUNDS **18** ($CDCl_3$, δ, ppm)



17a 20

Conclusions

The reactions of TBCK and CCK with styreneoxide take place starting with the electrophylic attack of the ketene's central carbon atom at the oxirane's oxigen atom, followed by the α breaking of the oxiranic ring and formation of the zwitterion **13** and then ring closure to the cyclic acetals **11**. This mechanism is confirmed by the reaction between TBCK and optically active styreneoxide (R(-)), where optical activity loss due to the free rotation around the C-C σ bond adjacent to the aromatic ring was observed.

The reaction products in the addition of TBCK to 1,1-diphenyletyleneoxide were the acetals **17a**, **17b** and the unsaturated vinyl ester **18**, whose structures we attributed using IR, NMR and GC-MS spectrometry data.

In the case of ester formation, the probable mechanisme involves ring opening of the acetals **17a** and **17b** under acid catalysis. The presence of two phenyl groups at the epoxide's carbon atom increases the cationic center stability and thus, facilitates the opening of the acetals and the proton elimination.

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