

Reaction of Ketenes with Three Membered Heterocyclic Rings

V. Addition of *tert*-butylcyanoketene to 1-methyl-1-phenylethyleneoxide

MONA IRINA DOANA^{1*}, MARIANA-GABRIELA DANILA¹, CONSTANTIN DRAGHICI², PETRU IVAN FILIP¹

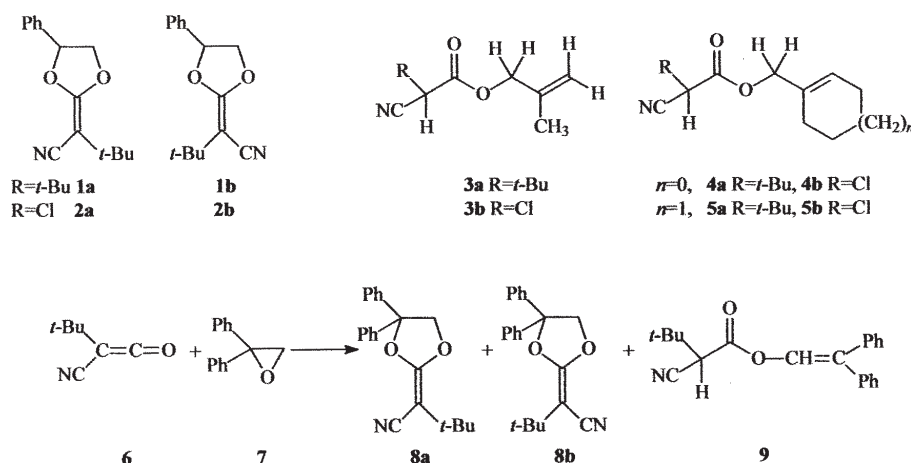
¹Romanian Academy, "Costin D. Nenitzescu" Organic Chemistry Center, 202B Spl. Independenței, 060023, Bucharest, Romania

²Army Center for Medical Research, 24-28 Cobalcescu Str., 010195, Bucharest, Romania

The reaction of *tert*-butylcyanoketene with 1-methyl-1-phenylethyleneoxide is presented. The reaction products are two isomeric acetals and an unsaturated ester. Their structures were assigned on the basis of IR, ¹H and ¹³C NMR and MS data.

Keywords: cyanoketenes, TBCK, oxiranes

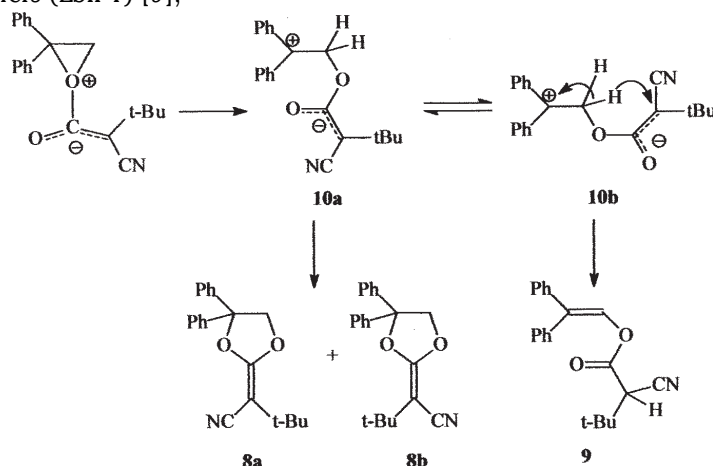
In our previous works [1-3] we have shown that the reaction of stable cyanoketenes (TBCK and CCK) with monosubstituted aromatic epoxides (styreneoxide) [1] leads to cyclic acetals (**1a,b** and **2a,b**), while in the reaction with asymmetric dialkylepoxides (isobutyleneoxide [2] and spiranic epoxides [3]) unsaturated esters are obtained (**3a,b**, respectively **4a,b** and **5a,b**). The reaction between *tert*-butylcyanoketene (TBCK) **6** and an asymmetric disubstituted aromatic epoxide 1,1-diphenylethyleneoxide **7** [4] lead to a mixture of two isomeric acetals (**8a, 8b**) and an unsaturated ester (**9**).



While the formation of acetals and lactones, when reacting epoxides with ketenes, has been described in the literature [5,8], the addition of TBCK **6** to asymmetric dialkylepoxides leading to unsaturated esters [2, 3] follows a new route, previously not described in the literature, involving an "ene"-like reaction pathway. The studies performed till now could not discriminate between a concerted mechanism and an ionic one in which an intramolecular proton transfer is involved [2, 3].

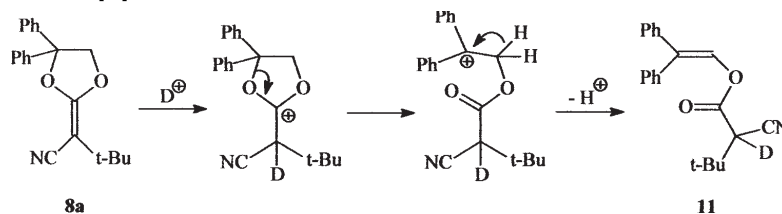
For the formation of ester **9** besides acetals **8a,b**, in the reaction between TBCK **6** and 1,1-diphenylethyleneoxide **7** [4], we took into consideration two different mechanistic routes:

- formation of ester **9** involving an intramolecular proton transfer in one of the possible zwitterionic intermediate **10** [4]. This route was ruled out because this type of 1,4 processes have been reported only for excited-state intramolecular proton transfers (ESIPT) [9];



* Tel.: 021 316 79 00

- the acid catalysed ring opening of the acetals **8a,b** in the presence of *tert*-butylcyanoacetic acid (generated in the reaction medium as a result of the reaction between TBCK **6** and water traces), followed by a proton elimination. This latter mechanism is supported by the formation of deuterated unsaturated ester **11** in the reaction between acetal **8a** and deuterated trifluoroacetic acid [4].



In order to clarify the mechanism of this reaction, we studied the addition of TBCK to an asymmetric epoxide substituted with one alkyl and one aryl group: 1-methyl-1-phenylethyleneoxide. This could also show if there is a competition between the classic formation of acetals and the "ene" route.

Experimental part

All infrared spectra were recorded with a Bruker Vertex 70 (FTIR) instrument, equipped with diamond crystal ATR. The NMR data were recorded using a Gemini 300 Varian instrument. 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.

The reaction of *in situ* generated TBCK with 1-methyl-1-phenylethyleneoxide

A solution of 2.05 g (6.8 mmol) 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone and 1.73 g (13 mmol) 1-methyl-1-phenylethyleneoxide in 40 mL dry benzene was refluxed for 1.5 h until the complete decomposition of the azide and consumption of the ketene, confirmed by the disappearance of the specific absorption bands from the IR spectra (the bands from 2110 cm^{-1} (N_3), 2250 cm^{-1} ($\text{C}\equiv\text{N}$) and 2130 cm^{-1} ($\text{C}=\text{C}=\text{O}$)). After solvent removal under vacuum we obtained 3.60 g of an orange liquid that was analysed by IR, NMR and GC-MS spectroscopy.

The IR spectra of the crude reaction product showed a very strong band at 1642 cm^{-1} , a weak band at 1742 cm^{-1} and a strong band at 2198 cm^{-1} .

GC-MS analysis of the crude reaction product showed the formation of three 1:1 ketene-epoxide adducts, two of them having an almost identical fragmentation pattern.

The ^1H -NMR spectra of the crude reaction product showed, besides the multiplet for the aromatic protons (δ 7.30-7.50 ppm), three series of signals with different intensities:

- two singlet signals in a region specific for the methyl protons of *tert*-butyl groups, located at δ 1.21 ppm (weak signal) and at δ 1.28 ppm (strong signal);

- two singlet signals characteristic for the methyl protons, located at δ 1.79 ppm (weak signal) and at δ 1.80 ppm (strong signal);

- two series of doublet signals of different intensities centered at δ 4.33 and at 4.41 ppm, with a coupling constant $J = 8.2\text{ Hz}$ in the case of the stronger signals and at δ 4.44 and at 4.51 ppm with a coupling constant $J = 8.0\text{ Hz}$ in the case of the weaker signals.

The ^1H -NMR spectra also show other very low intensity signals δ 1.07, 3.27, 5.09, 5.43 and at 5.58 ppm belonging to the third adduct.

After solvent evaporation, one of the adducts crystallized on cooling. By washing the crystals with methanol we obtained a colorless crystalline compound with m.p. = $104\text{--}107^\circ\text{C}$. The IR, NMR and GC-MS analysis indicated that the

compound is 1-cyano-1-*tert*-butyl-2-(4-methyl-4-phenyl-2,5-dioxo-cyclopentylidene)-ethylene (compound **15a**, obtained in greater amount).

Using NMR and GC-MS spectroscopy we also identified and characterized compound **15b** (obtained in smaller amount) as 1-cyano-1-*tert*-butyl-2-(3-methyl-3-phenyl-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 was identified using IR, NMR and GC-MS analysis as 2-phenyl-1-propenyl-*tert*-butylcyanoacetate **16**.

15a: IR (solid in ATR, cm^{-1}): 1642 vs., 2198 s. - **^1H -NMR** (CDCl_3 , δ ppm, J Hz): 1.28 (s, 9H, H^{12}); 1.80 (s, 3H, H^7); 4.33 (d, $J=8.2$, 1H, H^{1A}); 4.41 (d, $J=8.2$, 1H, H^{1B}); 7.30-7.50 (m, 5H, H-arom.). - **^{13}C -NMR** (CDCl_3 , δ ppm): 25.96 (C^7); 30.34 (C^{12}); 30.84 (C^{11}); 67.59 (C^2); 76.67 (C^1); 88.76 (C^9); 119.54 (C^{10}); 124.29 (C^4); 128.76 (C^6); 129.10 (C^5); 140.44 (C^3); 167.16 (C^8). - **MS** (m/z , (relative abundance, %)): 39 (18.25); 41 (15.12); 43 (7.79); 50 (5.81); 51 (14.30); 52 (9.46); 53 (32.14); 57 (26.80); 63 (6.31); 65 (8.14); 68 (6.38); 77 (36.59); 78 (19.36); 79 (9.30); 80 (6.17); 91 (32.69); 102 (6.10); 103 (24.87); 105 (B.P. 100); 106 (28.21); 108 (91.65); 109 (4.96); 115 (29.85); 117 (60.93); 118 (15.62); 124 (14.92); 134 (13.36); 242 (10.81); 257 (M.P. 7.68).

15b: IR (solid in ATR, cm^{-1}): 1642 vs., 2198 s. - **^1H -NMR** (CDCl_3 , δ ppm, J Hz): 1.21 (s, 9H, H^{12}); 1.79 (s, 3H, H^7); 4.44 (d, $J=8.0$, 1H, H^{1A}); 4.51 (d, $J=8.0$, 1H, H^{1B}); 7.30-7.50 (m, 5H, H-arom.). - **^{13}C -NMR** (CDCl_3 , δ ppm): 26.10 (C^7); 30.16 (C^{12}); 30.84 (C^{11}); 70.00 (C^2); 79.03 (C^1); 85.95 (C^9); 119.54 (C^{10}); 126.20 (C^4); 128.56 (C^6); 129.03 (C^5); 140.83 (C^3); 167.37 (C^8). - **MS** (m/z , (relative abundance, %)): 39 (18.02); 41 (16.72); 43 (14.20); 50 (5.77); 51 (14.57); 52 (9.33); 53 (36.77); 57 (28.69); 63 (5.14); 65 (9.36); 68 (7.09); 77 (36.56); 78 (18.58); 79 (9.02); 80 (6.29); 91 (32.30); 102 (5.91); 103 (22.55); 105 (B.P. 100); 106 (28.92); 108 (94.52); 109 (5.27); 115 (28.06); 117 (59.18); 118 (14.87); 124 (15.46); 134 (12.32); 242 (12.12); 257 (M.P. 8.46).

16: IR (solid in ATR, cm^{-1}): 1742 vs., 2250 w. - **^1H -NMR** (CDCl_3 , δ ppm, J Hz): 1.07 (s, 9H, H^1); 3.27 (s, 1H, H^4); 5.07 (m, $J=13.0$, 1H, H^{6A}); 5.12 (m, $J=13.0$, 1H, H^{6B}); 5.43 (m, $J=1.2$, 1H, H^{8B}); 5.58 (bs, 1H, H^{8A}); 7.30-7.45 (m, 5H, H-arom.). - **^{13}C -NMR** (CDCl_3 , δ ppm): 27.94 (C^1); 35.36 (C^2); 49.78 (C^4); 67.79 (C^6); 116.11 (C^3); 117.00 (C^8); 126.44 (C^{10}); 128.61 (C^{12}); 128.91 (C^{11}); 137.99 (C^7); 142.14 (C^9); 165.45 (C^5). - **MS** (m/z , (relative abundance, %)): 39 (4.91); 41 (8.61); 51 (4.39); 57 (27.94); 77 (10.24); 91 (18.92); 103 (12.29); 105 (13.15); 115 (45.62); 116 (12.62); 117 (43.31); 118 (4.62); 134 (B.P. 100); 156 (4.33); 183 (4.13); 198 (12.99); 257 (M.P. 26.39).

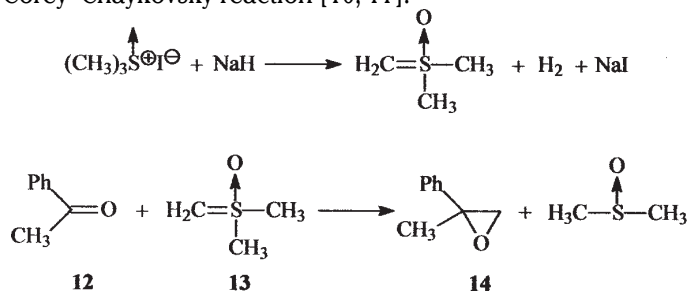
The reaction of 1-cyano-1-*tert*-butyl-2-(4-methyl-4-phenyl-2,5-dioxo-cyclopentylidene)-ethylene with trifluoroacetic acid (CF_3COOH)

To a solution of 30 mg (0.094 mmol) 1-cyano-1-*tert*-butyl-2-(4-methyl-4-phenyl-2,5-dioxo-cyclopentylidene)-ethylene (**15a**) in 0.7 mL CDCl_3 we added 0.02 mL (0.0299

mg, 0.00026 mmoles) CF_3COOH . The reaction was allowed to take place at room temperature for 4.5 h. $^1\text{H-NMR}$ analysis showed the formation of 2-phenyl-1-propenyl-*tert*-butyl-cyanoacetate (**16**).

Results and discussions

1-methyl-1-phenylethyleneoxide **14** was obtained from methyl-phenylketone **12** and dimethyloxosulfonium methylide **13**, using the Johnson–Corey–Chaykovsky reaction [10, 11].



The reaction between TBCK **6** and 1-methyl-1-phenylethyleneoxide [**14**] was performed by generating the ketenes *in situ*, using benzene as a solvent (Moore [12]), in the presence of the epoxide, at reflux (approx. 1.5 h) until the consumption of the ketene. The ratio between ketene and epoxide was 1/1. After solvent removal the crude reaction product was analyzed by IR, NMR and GC-MS spectrometry.

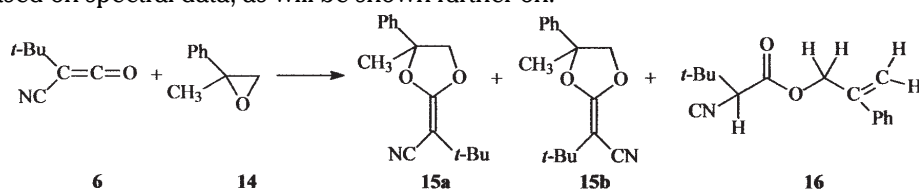
The IR spectra of crude reaction product showed three absorption bands at 1642 cm^{-1} (characteristic for exocyclic $\text{C}=\text{C}$ bonds), at 1742 cm^{-1} (characteristic for esters or lactones $\text{C}=\text{O}$ bonds), and at 2198 cm^{-1} (characteristic for a $\text{C}\equiv\text{N}$ bond close to a double bond).

The chromatogram of crude reaction product obtained by GC-MS showed three peaks corresponding to the 1:1 ketene-epoxide adducts ($m/z=257$), two of them having identical fragmentation pattern.

After solvent removal and cooling a colorless crystalline compound has been isolated. According to GC-MS data, this is the major compound of the pair with identical fragmentation pattern.

Based on IR, GC-MS and NMR data, structure **15a** has been attributed to this compound and **15b** to its geometric isomer.

For the adduct with a different fragmentation pattern, a 2-phenyl-1-propenyl-*tert*-butyl-cyanoacetate structure **16** has been assigned based on spectral data, as will be shown further on.



The proposed MS fragmentation scheme for the two isomeric acetals **15a,b** is shown in figure 1.

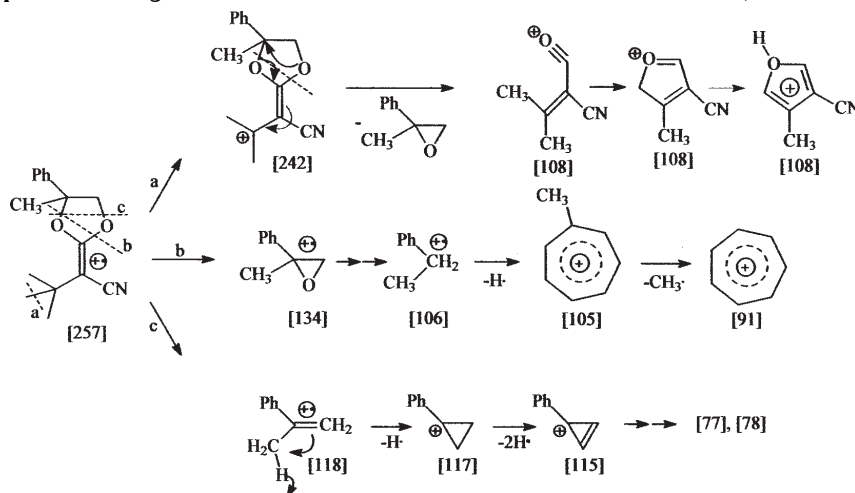


Fig. 1. MS fragmentation routes of the acetals **15a** and **15b**

The main fragmentation route (a) involves the elimination of a methyl radical from the primary radical cation, leading to the formation of a heterocyclic cation ($m/z=242$), from which a cation with $m/z=108$ is obtained, by the removal of a neutral 1-methyl-1-phenylethyleneoxide fragment.

The two others fragmentation paths (b and c), involving the elimination of a neutral fragment from the primary radical cation leading to the formation of the radical-cations corresponding to 1-methyl-1-phenylethyleneoxide and α -

methylstyrene, are confirmed by the presence in mass spectra of the acetals of the characteristics peaks present in the spectra of the two mentioned compounds (fig. 2).

The MS fragmentation patterns proposed for the unsaturated ester **16** is shown in figure 3. The main fragmentation route (b) involves the removal of a neutral *tert*-butylcyano ketene fragment from the primary radical-cation with the formation of the radical-cation corresponding to 2-phenylprop-2-en-1-ol ($m/z = 134$) (fig. 4).

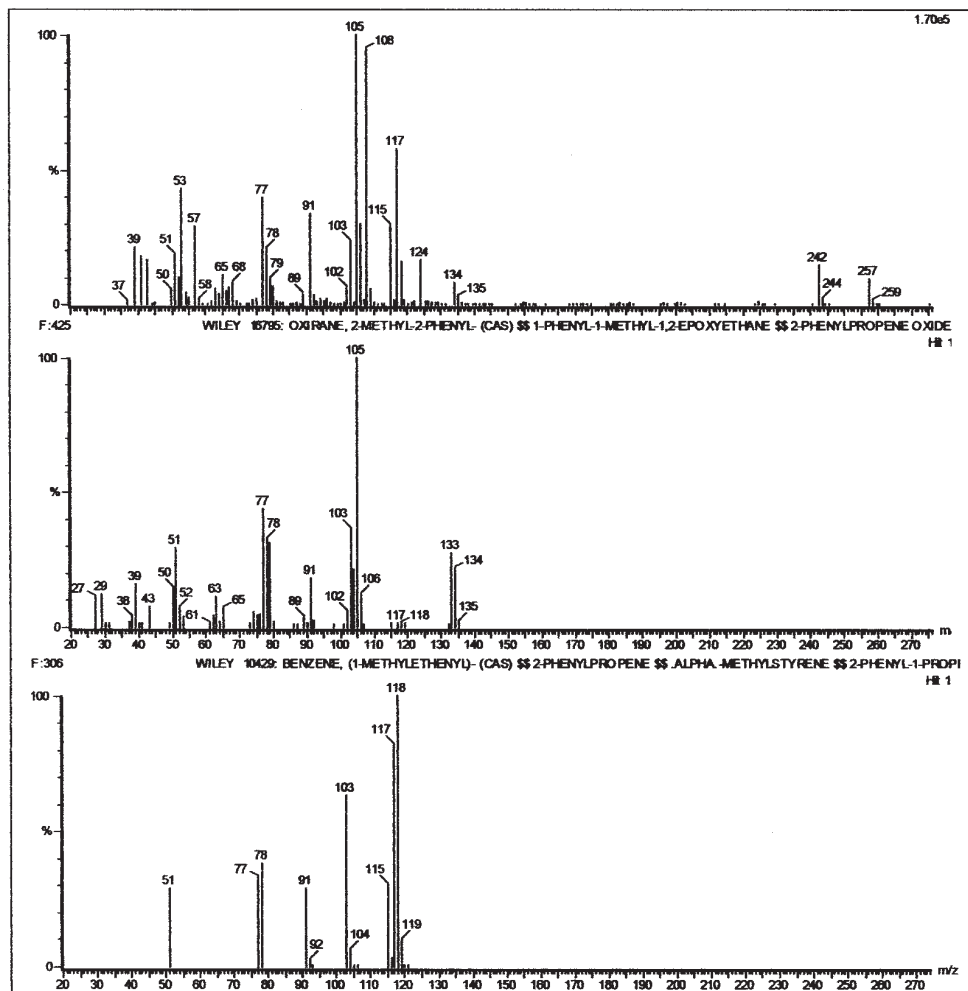


Fig. 2. The mass spectra of acetals **15a,b** relative to the mass spectra of 1-methyl-1-phenylethyleneoxide and α -methylstyrene

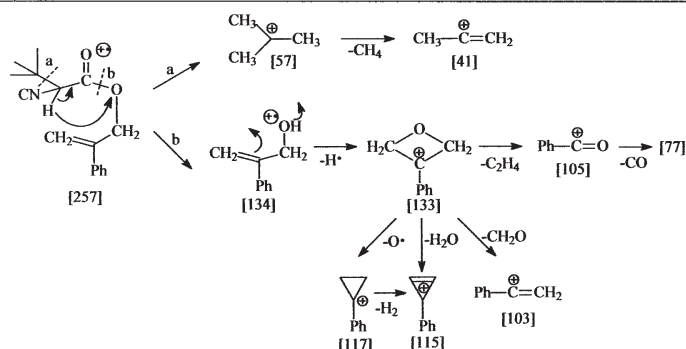


Fig. 3. MS fragmentation routes of the unsaturated ester **16**

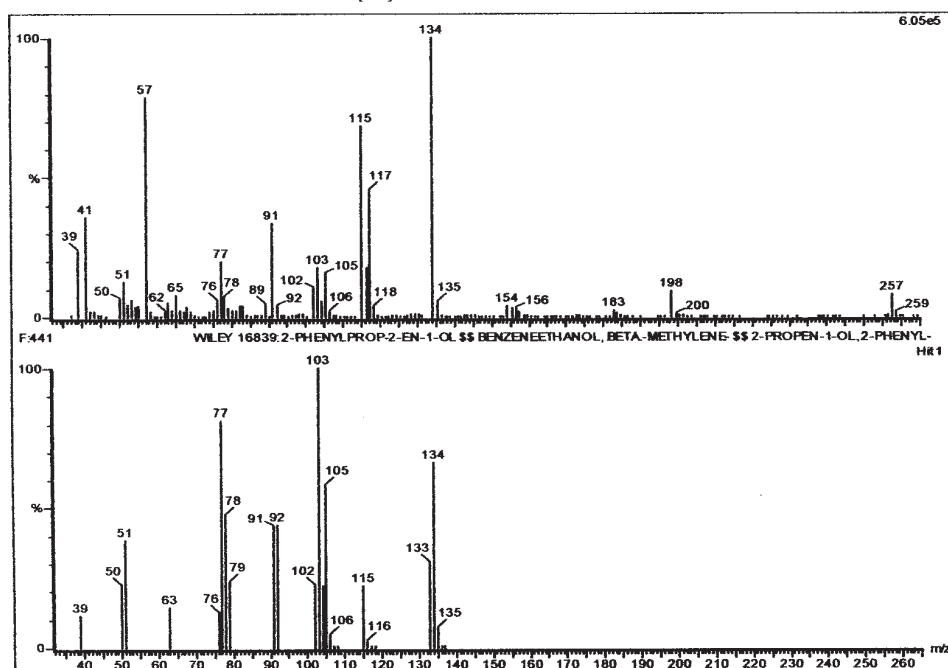


Fig. 4. The mass spectra of unsaturated ester **16** relative to the mass spectra of 2-phenylprop-2-en-1-ol

The ^1H -NMR spectrum of the crude reaction product shows four main groups of signals:

- two singlet signals in a region specific for the methyl protons of *tert*-butyl groups, located at δ 1.21 ppm (weak signal) and at δ 1.28 ppm (strong signal);

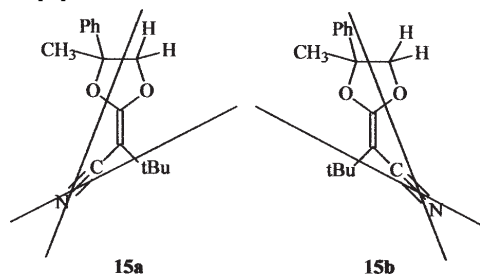
- two singlet signals characteristic for the methyl protons, located at δ 1.79 ppm (weak signal) and at δ 1.80 ppm (strong signal);

- two series of doublet signals of different intensities centered at δ 4.33 and at 4.41 ppm, with a coupling constant $J = 8.2$ Hz in the case of the stronger signals and at δ 4.44 and at 4.51 ppm with a coupling constant $J = 8.0$ Hz in the case of the weaker signals;

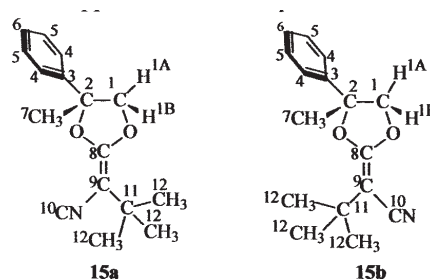
- a multiplet specific for the aromatic protons at δ 7.30-7.50 ppm.

The different intensities of the two series of signals shows the formation in different proportions of two isomeric adducts, namely the acetals **15a** and **15b**.

These data confirm the acetal structure for the two compounds and their isomery, but do not allow the correct assignment of the signals from the NMR spectra to the two geometric isomers. The difference in chemical shift ($\Delta\delta=0.1$ ppm) of the CH_2 protons in the two isomers can be explained by the magnetic anisotropy induced by the cyano group. Thus, 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 [1].



According to these data, the isomer with the *tert*-butyl protons at δ 1.28 ppm, the methyl protons at δ 1.80 ppm and the AB signals centered at δ 4.33 and at 4.41 ppm is the **15a** compound, while the one with the *tert*-butyl protons at δ 1.21 ppm, the methyl protons at δ 1.79 ppm and the AB signals centered at δ 4.44 and at 4.51 ppm is the **15b** compound.

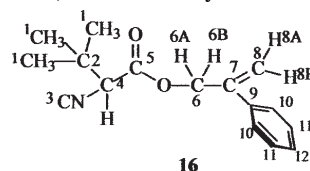


In table 1 and 2 are presented the ^1H - and ^{13}C -NMR data of the acetals **15a** and **15b**.

Using column chromatography (silicagel, petroleum ether/diethyl ether, 19/1), from the crude reaction product we have separated a fraction identified, based on IR, NMR and GC-MS analysis, as the unsaturated phenylallylic ester **16**.

The IR spectra presents two absorption bands at 1742 cm^{-1} (specific for $\text{C}=\text{O}$ bonds in esters or lactones) and at 2250 cm^{-1} (typical for a $\text{C}\equiv\text{N}$ bond linked to a sp^3 hybridized carbon atom).

The ^1H -NMR spectrum shows, besides the aromatic protons located at δ 7.30-7.45 ppm, five singlets at δ 1.07 (3H), 3.27 (1H), 5.09 (2H), 5.43 (1H) and at 5.58 (1H) ppm. The presence of the δ 5.43 and at 5.58 ppm signals, typical for vinylic protons, rules out a cyclic lactone structure.



The ^1H - and ^{13}C -NMR data of the compound **16** are presented in tables 3 and 4.

For the formation of ester **16** we can consider three different mechanistic pathway: the concerted addition of the ketene $\text{C}=\text{O}$ or $\text{C}=\text{C}$ double bond on the oxirane ring, the stepwise one ionic process via a zwitterionic intermediate and the acid catalyzed ring opening of the acetals.

In the case of the concerted addition to the $\text{C}=\text{O}$ double bond, the formed enol **17** undergoes tautomerization to ester **16**, which could be obtained by the concerted addition to the $\text{C}=\text{C}$ double bond.

Table 1

^1H -NMR DATA FOR COMPOUNDS **15a** AND **15b** (CDCl_3 , δ ppm, J Hz)

Compound	H^7	H^{1A}	H^{1B}	H^{12}	Ph	$J_{1A,1B}$
15a	1.80	4.33	4.41	1.28	7.30-7.50	8.2
15b	1.79	4.44	4.51	1.21	7.30-7.50	8.0

Table 2

^{13}C -NMR DATA FOR COMPOUNDS **15a** AND **15b** (CDCl_3 , δ ppm)

Compound	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
15a	76.67	67.59	140.44	124.29	129.10	128.76	25.96	167.16	88.76	119.54	30.84	30.34
15b	79.03	70.00	140.83	126.20	129.03	128.56	26.10	167.37	85.95	119.54	30.84	30.16

Table 3

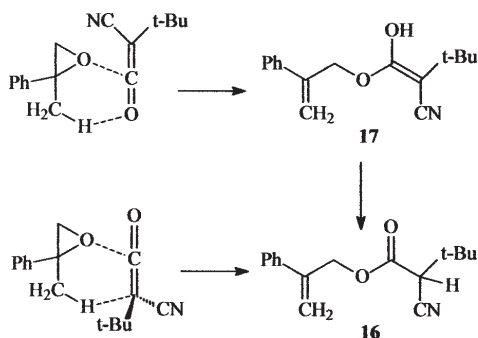
^1H -NMR DATA FOR COMPOUND **16** (CDCl_3 , δ ppm, J Hz)

H^1	H^4	H^{6A}	H^{6B}	H^{8A}	H^{8B}	Ph	$J_{6A,6B}$	$J_{8A,8B}$
1.07	3.27	5.07	5.12	5.58	5.43	7.30-7.45	13.0	1.2

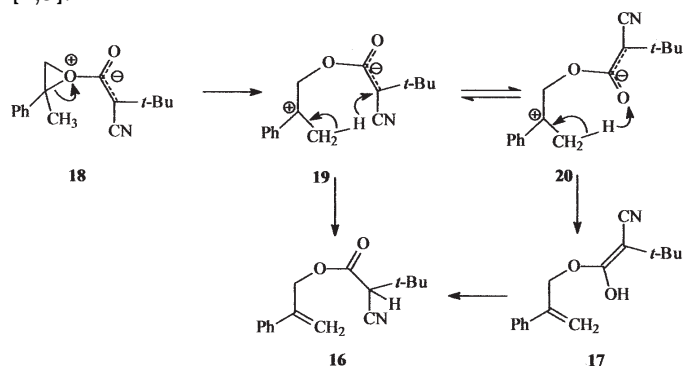
Table 4

^{13}C -NMR DATA FOR COMPOUND **16** (CDCl_3 , δ ppm)

C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
27.94	35.36	116.11	49.78	165.45	67.79	137.99	117.00	142.14	126.44	128.91	128.61



If the mechanism is ionic, the electrophilic attack of the ketene central carbon atom to the oxirane's oxygen atom give the zwitterionic intermediate **18**. In this zwitterion, the oxirane ring opening lead to the formation of intermediate **19**, in equilibrium with **20**, with the positive charge located at a tertiary carbon atom. By transferring a proton from the methyl groups linked to the carbocationic centre to the non-central carbon atom or the oxygen from the original ketene, ester **16** or enole **17** will be generated [2,3].

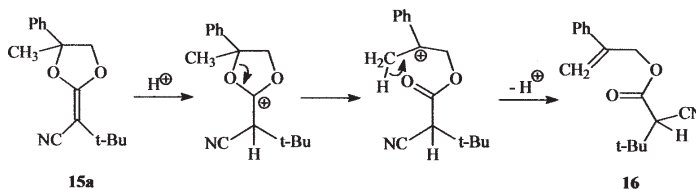


The reaction of TBCK **6** with optically active styreneoxide (R(-)) shows clearly the loss of optical activity due to the free rotation around the C-C σ bond adjacent to the aromatic ring [4]. The oxirane ring opening is favoured by the stabilisation of the cationic centre by the vicinity of the phenil group. Probably the presence of phenyl group in **14** promotes a similar mechanism leading to intermediates **19** and **20**. In the case of such a mechanism a hydrogen transfer over six centers in the next step seems hard to accept.

The third plausible alternative is the formation of the ester by acid-catalyzed ring opening of acetals [4].

To check if ester **16** can be formed in acid catalysis, by ring opening of the acetals **15a,b** followed by a proton elimination, we have performed a reaction between acetal **15a** and CF₃COOH at room temperature. The ¹H-NMR

spectra of the crude reaction product show δ 1.07, 3.29, 5.09, 5.43 and at 5.58 ppm signals that are attributed to the phenylallylic ester **16**.



Conclusions

The reaction products in the reaction between TBCK **6** and 1-methyl-1-phenylethyleneoxide **14** were the isomeric acetals **15a,b** and the unsaturated phenylallylic ester **16**, whose structures were assigned on the basis of IR, ¹H- and ¹³C-NMR and GC-MS data.

Apparently the "ene" route does not seem to be a competitive pathway to the formation of esters but rather a side process occuring by acid catalysed rearrangement of the initially formed acetals **15a,b**.

References

- DĂNILĂ, M-G., DOANĂ, M. I. and FILIP, P., Rev. Roum. Chim., **47**, no. 3-4, 2002, p. 79
- DĂNILĂ, M-G., GOTTLIEB, H., BARTOȘ, A. and FILIP, P., Rev. Chim.(Bucharest), **39**,no. 10, 1994, p. 1223
- DOANĂ, M. I., DĂNILĂ, M-G, SEZONOV, P. and FILIP, P., Rev. Chim. (Bucharest), Reaction of ketenes with three membered heterocyclic rings. III. Cyanoketenes reaction with spiranic epoxides, **66**, no. 6, 2015, p. 792
- DOANĂ, M. I., DĂNILĂ, M-G, DRĂGHICI, C. and FILIP, P., Rev. Chim. (Bucharest), Reaction of ketenes with three membered heterocyclic rings. IV. Addition of tert-butylcyanoketene to optically active styreneoxide and 1,1-diphenylethyleneoxide, **66**,no. 7, 2015, p. 942
- GULBINS, K., HAMANN, K., Chem. Berichte, **94**, 1961, p. 3287
- SHIBATA, I., BABA, A., MATSUDA, H., Bull. Chem. Soc. Jpn., **59**, no. 12, 1986,, p. 4000
- ODA, R., MUNIEMIYA, S., OKANO, M., J. Org. Chem., **26**, no. 5, 1961, p. 1341
- FUJIWARA, M., IMADA, M., BABA, A., MATSUDA, H., J. Org. Chem., **53**, 1988,p. 5974
- YU, W-S., CHUNG, C-C., CHENG, Y-M., WU, P-C., SONG, Y-H., CHI, Y., CHOU, P-T., J. Am. Chem. Soc., **125**, no. 36, 2003, p.10800; AMEER-BEG, S., ORMSON, S. M., BROWN, R. G., NIBBERING, E. T. J., FOGGI, P., NEUWAHL, F. V. R., J. Phys. Chem. A, **105**, no. 15, 2001, p. 3709
- JOHNSON, A.W., LaCOUNT, R. B., J. Am. Chem. Soc., **83**, no. 2, 1961, p. 417
- COREY, E. J., CHAYKOVSKY, M., J. Am. Chem. Soc., **87**, no. 6, 1965, p. 1345
- WEYLER, W. Jr., DUNCAN, W. G., LIEWEN, M. B. and MOORE, H. W., Org. Synth., **55**, 1976, p. 32

Manuscript received: 29.06.2015