2,5-BIS(TRIFLUOROMETHYL)-1,3,4-OXADIAZOLE IN CYCLOADDITION REACTIONS*

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The cycloaddition of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole to dienophiles with cyclic and acyclic structures takes place according to a two-step mechanism with the extrusion of nitrogen and results in the formation of derivatives of 7-oxabicyclo[2.2.1]heptanes. A significant influence of the donor properties of the dienophiles, as well as of the spatial factors, on the realization of these processes has been discovered. However, solvation efects do not have a significant effect on the formation of the cycloadducts. The regio- and stereoselectivity of the cycloaddition reactions has been noted.

The reactivity of hydrocarbon 2,5-dialkyl(diaryl)-1,3,4-oxadiazoles has been studied extensively [2-4]; however, [2+4]-cycloaddition reactions involving these compounds are not known, apparently due to their high aromaticity [2]. Nevertheless, it was recently discovered that 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (I) reacts with some alkenes at high temperatures according to a two-step mechanism and that the cycloaddition process is accompanied by the extrusion of nitrogen [1, 5, 6].

In this communication we shall present the results of a study of the reactivity of oxadiazole I with respect to acyclic and alicyclic alkenes.

It was found that oxadiazole I reacts with ethylene only at 180-222°C and that 1,4-bis-(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (II) forms with an 80% yield. Propylene reacts with oxadiazole I under more mild conditions, and at 160-180°C cycloadduct III forms with a high yield. At the same time, the stereo- and regioselectivity of the cycloaddition reaction are low: according to the data from ^{19}F NMR spectroscopy, cycloadduct II is a mixture of five of the six possible regio- and stereoisomers.

The regioisomers with a "head-to-tail" orientation predominate to some extent (1.5:1) in the mixture. The ratio between the endo,endo-, endo,exo-, and exo,exo- isomers is equal to 5.6:8.4:1. The exo,exo-2,6-dimethylated oxadicycloheptane was not discovered in the mixture. The assignment of the isomers in the mixture of III was based on the values of the H-F spin–spin coupling constant [7].

The cycloaddition of oxadiazole I to isobutylene takes place somewhat less readily than does that to propylene, and the yield of cycloadduct IV does not exceed 40%. The reaction is distinguished by its high regioselectivity: the "head-to-tail" isomer, which is apparently more advantageous, predominates, and the formation of the "head-to-head" isomer does not exceed 15%, according to the GLC and ^{19}F NMR data.

It is significant that tetramethylethylene, which has stronger donor properties, but is sterically hindered, does not react with oxadiazole I even under severe conditions.

Unlike alkylethylenes, styrene reacts regio- and stereospecifically with oxadiazole I to form endo,endo-2,5-diphenyl-substituted adduct V, although the yield is low due to the attendant oligomerization processes.

Ethyl vinyl ether reacts with oxadiazole I under very mild conditions. The reaction begins already at 100°C, and at 160°C the yield of cycloadduct VI reaches 90%. At the same time, the solvation effects, whose influence was studied at 100°C, do not have a promoting effect on the formation of cycloadduct VI when the n-donor properties and the polarity of the solvents are varied. The stabilizing influence of additions of triethylamine, which prevents the polymerization of ethyl vinyl ether by binding the acidic impurities, should, however, be noted.

*For a preliminary report, see [1].

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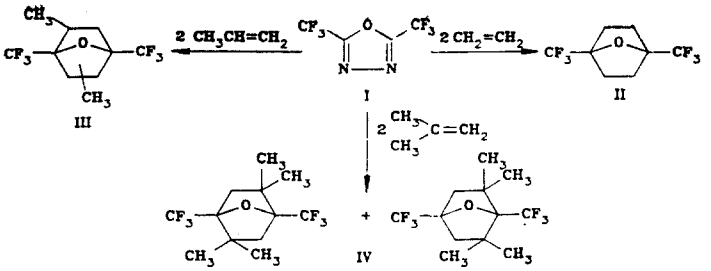
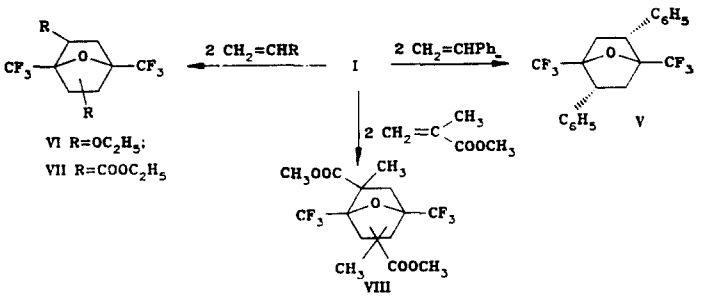


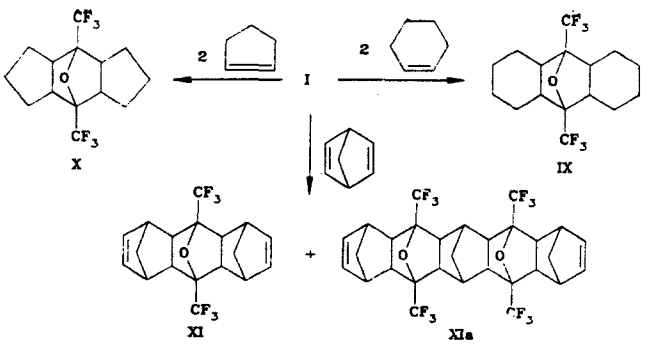
The reaction of oxadiazole I with ethyl acrylate, which takes place under somewhat more severe conditions than does the reaction with ethyl vinyl ether, results in the formation of cycloadduct VII with a satisfactory yield.

According to the NMR data, compounds VI and VII apparently exist in the form of a mixture of two isomers, but it was not possible to unequivocally determine their structures. It is noteworthy that methyl methacrylate forms cycloadducts VIII with a very low yield even under more severe conditions.



It should be noted that the attempts to involve dienophiles of the electron-acceptor type (maleic anhydride, esters of maleic acid and fumaric acid, and polyfluoroalkenes) in cycloaddition reactions did not yield positive results. Alkynes, viz., acetylene, phenylacetylene, an ester of acetylenedicarboxylic acid, and perfluoro-2-butyne, do not participate in these reactions even at 220°C.

The activity of acyclic alkenes in cycloaddition reactions with oxadiazole I increases significantly in parallel with the increase in the degree to which their multiple bonds are stressed. For example, cyclohexene forms cycloadducts IX with very low yields and poor reproducibility under severe conditions. Cyclopentene reacts with I more effectively under comparable conditions: according to the PMR spectrum, the cycloadduct formed as a result, i.e., product X, has an exo,endo-configuration. Norbornadiene reacts even more readily with I, and a product of repeated addition is detected along with the cycloadduct.



According to the ^{19}F NMR and PMR spectra, cycloadduct XI exists in a single highly advantageous configuration, which could not be established in view of the possibility of the large number of stereoisomers.

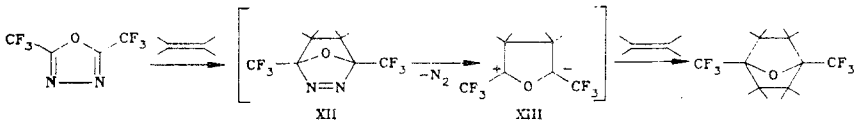
Thus, the conversions described take place as two-step processes, which include [2+4]-cycloaddition in the first step. Intermediate oxadiazabicycloheptenes XII were not detected in any of the cases. This fact is consistent with the data on the thermal instability of 1,3,4-oxadiazolines, which are inclined to extrude nitrogen and to form carbonyl ylids with

TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formula	bp, °C (hPa)	mp, °C	n_D^{20}	Compound	Empirical formula	mp, °C
II	$C_8H_8F_6O$	143	24	1.3512 (25)	VIII*	$C_{14}H_{16}F_6O_5$	—
III	$C_{10}H_{12}F_6O$	56 (18)	—	1.3733	IX	$C_{16}H_{20}F_6O$	101
IV	$C_{12}H_{16}F_6O$	72 (20)	—	1.3900	X	$C_{14}H_{12}F_6O$	93
V	$C_{20}H_{16}F_6O$	—	235	—	XI	$C_{18}H_{16}F_6O$	140
VI	$C_{12}H_{16}F_6O_3$	86 (13)	—	1.3868	XIa	$C_{20}H_{14}F_{12}O_2$	199 (dec.)
VII	$C_{14}H_{18}F_6O_5$	145 (30)		1.4050			

*bp 125°C (22 hPa); n_D^{20} 1.4010.

their subsequent [2+3]-cycloaddition already under mild conditions [8]. Apparently, oxadiazabicycloheptenes XII also eliminate nitrogen in a similar manner, and the formation of intermediate carbonyl ylids XIII has not been ruled out. Thus, the second step may be regarded as the [2+3]-cycloaddition of carbonyl ylids XIII.



XII XIII

The data obtained allow us to regard the cycloaddition of oxadiazole I as an LUMO-controlled process, as is evidenced by the comparatively mild conditions for addition to donor dienophiles and the absence of reaction with dienophiles of the acceptor type.

Another feature of the cycloaddition of oxadiazole I is its high sensitivity to spatial effects, which is manifested by its regio- and stereoselectivity, and, in some cases, by its complete reigio- and stereospecificity, as well as by its significant dependence on the spatial hindrances appearing when the transition state is formed. The latter is characteristic of a long list of [2+3]-cycloaddition reactions [9] and may attest to the control of the two-step process not only in the step of [2+4]-cycloaddition, but also in the step of [2+3]-cycloaddition.

EXPERIMENTAL

The ^{19}F and ^1H NMR spectra of compounds II, VIII, and IX-XI were recorded on a Perkin-Elmer R-20 spectrometer [56.45 (^{19}F) and 60 MHz (^1H)], and the spectra of compounds III-VII were recorded on a Bruker WP-200 SY spectrometer [200.13 (^1H) and 188.31 MHz (^{19}F)] in $CDCl_3$: the chemical shifts are given relative to TMS (an internal reference) in the case of ^1H nuclei and relative to trifluoroacetic acid (an external reference) in the case of the ^{19}F. The IR spectra were recorded on a Perkin-Elmer R-255 instrument in thin layers and in KBr tablets.

The characteristics of the compounds synthesized are presented in Tables 1 and 2. The data from the elemental analyses of the compounds for C, H, and F correspond to the calculated values.

Interaction of Oxadiazole I with Ethylene. A mixture of 5.0 g (24 mmole) of oxadiazole I and 2.1 g (75 mmole) of ethylene was heated in a closed vessel for 20 h at 220°C. The mixture was distilled, and 4.5 g (79%) of 1,4-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]heptane (II) were obtained.

Reaction of Oxadiazole I with Propylene. A mixture of 3.0 g (14 mmole) of oxadiazole I and 2.0 g (47 mmole) of propylene was heated in a closed vessel for 25 h at 180°C. The mixture was vacuum-distilled, and 3.0 g (78%) of 2,5(6)-dimethyl-1,4-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]heptane (III) were obtained.

Reaction of Oxadiazole I with Isobutylene. A mixture of 5.0 g (24 mmole) of oxadiazole I and 4.0 g (75 mmole) of isobutylene was heated in a closed vessel for 30 h at 190°C. The mixture was vacuum-distilled, and 2.5 g (36%) of 2,2,5,5(6,6)-tetramethyl-1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (IV) were obtained. The 2,2,6,6-tetramethylated isomer of IV is indistinguishable in the spectrum due to its low concentration.

Reaction of Oxadiazole I with Styrene. A mixture of 3.0 g (14 mmole) of oxadiazole I and 3.0 g (29 mmole) of styrene was heated in a closed vessel over the course of 5 h at 160°C.

TABLE 2. Spectroscopic Characteristics of Compounds II-X

Compound	IR spectrum, cm^{-1} (CH)	^{19}F NMR spectrum, ppm (J, Hz)(CF_3)	PMR spectrum, ppm (J, Hz)
II	2870...3000	0,0 s	2,1 (s, br, CH_2)
2,6-endo,exo-III	2870...3010	−0,2 s; −7,4 q (J=2,2)	1,0 (m, CH_3); 1,2 (m, CH_3); 1,6 (m, CH); 2,4 (m, CH)
2,6-endo, endo-III		−0,5 s; −10,9 sept (J=2,6)	
2,5-exo,exo-III		−1,4 s	
2,5-exo-endo-III		−1,9 s; −5,4 q (J=2,2)	
2,5-endo,endo-III		−5,8 q (J=2,2)	
2,2,6,6-IV		1,0 s; −16,2 sept (J=3,5)	—*
2,2,5,5-IV	2880...3020	−6,7 q (J=2,2)	1,1 (q, J=2,2, endo-CH_3); 1,2 (s, exoCH_3); 1,8 (d, J_{HH}=14,0, CH); 2,0 (d, J_{HH}=14,0, CH)
V		−6,9 s	2,4 (d d, $J_{endo\text{-}HH}$=13,5, $J_{exo\text{-}HH}$=3,8, 3,6-H_{endo}); 2,8 (d d, $J_{gem\text{-}HH}$=13,5, $J_{vic\text{-}HH}$=9,0, 3,6-H_{exo}); 3,8 (d d, $J_{vic\text{-}HH}$=3,8; $J_{vic\text{-}HH}$=9,0, 2,5-H_{exo}); 7,3 (m, Ph)
VI	2840...3000	0,0 s; −2,2 s; −5,7 s; 7,5 s	1,1 (m, CH_3); 3,4 (m, CH_2); 1,3 (d d, J=3,5, J=13,0, CH); 1,4 (d.d, J=2,7, J=12,5, CH); 1,7 (d.d, J=12,5, CH); 2,0 (m, J=12,5, CH); 2,3 (m, CH); 2,8 (d.d, J=13,0, J=6,0, CH); 3,9 (d d, J=7,0, J=2,8, CH); 4,0 (d d, J=10,0, J=2,5, CH); 4,1 (d.d, J=10,0, J=2,5, CH); 4,4 (d.d, J=7,0, J=3,0, CH)
VII	1730,** 2900...3020	−0,5 s; −2,2 s; −3,7 s, −5,6 s	1,2 (m, CH_3); 4,1 (m, CH_2); 2,1...2,4 (m, CH); 2,5...2,8 (m, CH); 3,1...3,4 (m, CH)
Heptane VIII	1750,** 2850...3050	−8,0 q (J=2,4); −7,6 q (J=2,3); −4,5 s; −2,6 s	
IX	2840...2970	−7,6 s	
X	2840...2960	−9,4 s, br	1,7 (m, CH_2); 2,6 (m, endo CH); 3,1 (m, exo CH)
Diene VIII		−9,6 s	1,3 (m, CH_2); 2,1 (s, br, CH); 3,1 (m, CH); 6,1 (m, CH=CH)

*The 2,2,6,6,-tetramethylated isomer of IV is indistinguishable in the spectrum due to its low concentration.

**C=O.

The volatile components were vacuum-distilled, the residue was reprecipitated from ether by methanol, and the precipitate was filtered out and then subjected to fractional sublimation in a vacuum (20 hPa). This gave 0.6 g (11%) of endo,endo-2,5-diphenyl-1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (V).

Reaction of Oxadiazole I with Ethyl Vinyl Ether. A mixture of 5.0 g (24 mmole) of oxadiazole I and 5.0 g (69 mmole) of ethyl vinyl ether was heated in a closed vessel over the course of 10 h at 150-160°C. The mixture was vacuum-distilled, and 6.6 g (84%) of 2,5(6)-diethoxy-1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (VI) were obtained.

Reaction of Oxadiazole I with Ethyl Acrylate. A mixture of 3.0 g (14 mmole) of oxadiazole I and 3.0 g (30 mmole) of ethyl acrylate was heated in a closed vessel for 10 h at 170°C. The mixture was distilled, and 3.3 g (60%) of 2,5(6)-bis(ethoxycarbonyl)-1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (VII) were obtained.

Reaction of Oxadiazole I with Methyl Methacrylate. A mixture of 3.6 g (14 mmole) of oxadiazole I and 3.0 g (30 mmole) of methyl methacrylate was heated in a closed vessel for 40 h at 200°C. The mixture was distilled, and 0.3 g (5%) of 2,5(6)-dimethyl-2,5(6)-bis(methylcarbonyl)-1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptane (VIII) was obtained.

Reaction of Oxadiazole I with Cyclohexene. A mixture of 3.0 g (14 mmole) of oxadiazole I and 3.0 g (37 mmole) of cyclohexene was heated in a closed vessel for 10 h at 180-190°C for 10 h. The crystals precipitated when the system was cooled to −78°C were washed with a small quantity of cold methanol and recrystallized from a mimimal quantity of methanol. This gave 0.2 g (4%) of 1,8-bis(trifluoromethyl)-15-oxatetracyclo[6,6.1.$0^{2,7}$.$0^{9,14}$]pentadecane (IX).

Reaction of Oxadiazole I with Cyclopentene. A mixture of 2.0 g (10 mmole) of oxadiazole I and 1.7 g (25 mmole) of cyclopentene was heated for 6 h at 200°C. The crystals formed were recrystallized from ethanol. This gave 1.0 g (34%) of 1,7-bis(trifluoromethyl)-13-oxatetracyclo[5.5.1.$0^{2,6}$.$0^{8,12}$]tridecane (X).

Reaction of Oxadiazole I with Norbornadiene. A mixture of 1.5 g (7 mmole) of oxadiazole I and 1.3 g (14 mmole) of norbornadiene was heated in a closed vessel over the course of 4 h at 160-170°C. The crystals formed were sublimed at a reduced pressure (20 hPa), and the sublimed product was reprecipitated from chloroform by methanol. This gave 0.5 g (20%) of 1,8-bis(trifluoromethyl)-15-oxahexacyclo[6.6.1.$1^{3,6}$.$1^{10,13}$.$0^{2,7}$.$0^{9,14}$]-heptadeca-4,11-diene (VIII). The unsublimed residue was recrystallized twice from a toluene-methanol mixture, and 0.4 g (23%) of adduct XIa was obtained. Product XIa is practically insoluble in organic solvents at 20°C, precluding its investigation by NMR.

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