$Rh_2(OAc)_4$-catalyzed reaction of 1,3-dioxanes with methyl diazoacetate

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The reactions of methyl diazoacetate with 1,3-dioxanes in the presence of $Rh_2(OAc)_4$ afford 1,4-dioxepanes in up to 46% yields. The insertion of methoxycarbonylcarbene into the C—O bond occurs only in the case of 2-phenyl-1,3-dioxanes.

Key words: 1,3-dioxanes, 1,4-dioxepanes, methyl diazoacetate, catalysis, $Rh_2(OAc)_4$, 1,2-anionic rearrangement, carbene insertion into the C—O bond.

It is known that the reactions of alkyl diazoacetates with 1,3-dioxolanes in the presence of $BF_3 \cdot OEt_2$, $Rh_2(OAc)_4$, or $CuSO_4$ yield 1,4-dioxanecarboxylates, products of formal insertion of alkoxycarbonylcarbene into the C—O bond.[1—3] Catalytic reactions of diazo esters with 1,3-dioxanes, which are the homologs of 1,3-dioxolane, remain poorly studied, though some examples of Rh-catalyzed intramolecular transformations of 1,3-dioxanyl derivatives of diazo esters and diazo ketones have been reported.[4—6]

The goal of the present work is to study catalytic reactions of some 1,3-dioxanes with methyl diazoacetate and determine the regio- and stereoselectivity of this reaction.

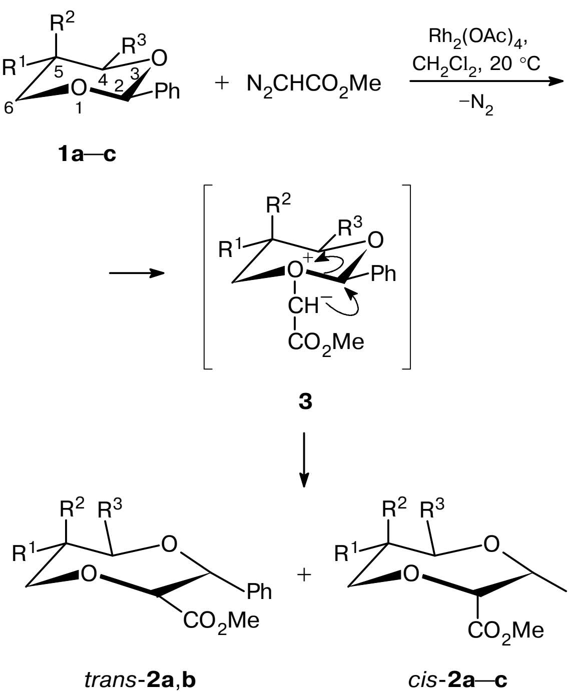
Results and Discussion

The experiments were carried out by adding methyl diazoacetate to a solution of 1,3-dioxane (**1a**—**c**) in CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (0.5 mol %) at 20 °C. The reaction affords 1,4-dioxepanes **2a**—**c** in 20, 40, and 46% yields, respectively (Table 1). The individual *cis*- and *trans*-isomers of 1,4-dioxepanes **2a**—**c** were isolated by column chromatography (Scheme 1). It should be noted that the reaction mixture contained no product in which methoxycarbonylcarbene is inserted between the C(2) and O(3) atoms of dioxane **1b**.

2-Unsubstituted and alkyl-containing 1,3-dioxanes (1,3-dioxane, 1,5-dioxaspiro[5.5]undecane, and 4-methyl-, 2,2,4-trimethyl-, and 2-isopropyl-4-methyl-1,3-dioxanes) did not react with methyl diazoacetate under the chosen conditions.

The stereochemical composition of the reaction products is of great interest. The resulting 1,4-dioxepanes **2a**,**b** are mixtures of two stereoisomers with dominant *cis*-isomer (≥80%, see Table 1). However, dioxane **1c** reacts stereospecifically to give *cis*-6,6-dimethyl-2-methoxycarbonyl-3-phenyl-1,4-dioxepane (**2c**) in 46% yield.

Scheme 1



a: $R^1 = R^2 = R^3 = H$;
b: $R^1 = R^2 = H$, $R^3 = Me$;
c: $R^1 = R^2 = Me$, $R^3 = H$

The possible mechanism of the reaction can include generation of ylide **3** followed by 1,2-anionic rearrangement (the Stevens rearrangement).[1,7] Apparently, the O(1) atom is involved in the formation of ylide **3**; this is confirmed by the selective formation of products of

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Table 1. Characteristics of 1,4-dioxepanes synthesized

Compound	Yield (%)[a]	R_f[b]	Found/Calculated (%) C	Found/Calculated (%) H	Molecular formula	IR, ν/cm^{-1}
2a	20 (8 : 2)	0.37, 0.51	66.10 66.09	6.95 6.83	$C_{13}H_{16}O_4$	704, 728, 812, 1024, 1040, 1112, 1152, 1160, 1204, 1248, 1272, 1368, 1436, 1676, 1744, 2392, 2950, 3200—3480
2b	40 (9 : 1)	0.18, 0.58	67.80 67.18	7.47 7.25	$C_{14}H_{18}O_4$	704, 736, 1024, 1124, 1168, 1204, 1276, 1376, 1436, 1504, 1714, 2952, 3200—3512
2c	46 (10 : 0)	0.08, —	68.25 68.16	6.60 7.63	$C_{15}H_{20}O_4$	704, 1028, 1128, 1168, 1204, 1276, 1360, 1436, 1504, 1744, 2872, 2952, 3200—3512

[a] The ratio between the *cis*- and *trans*-isomers are given in parentheses.

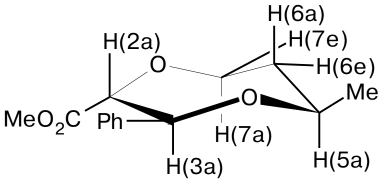
[b] In hexane—EtOAc (1 : 1); the first number relates to the *cis*-isomer, while the second number relates to the *trans*-isomer.

Table 2. Chemical shifts ($CDCl_3$, δ) in the ^{1}H NMR spectra of 1,4-dioxepanes **2a—c**

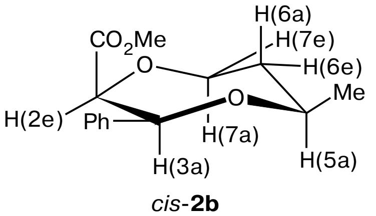
Compound	H(2)	H(3)	H(6e)	H(6a)	H(5a)	H(5e)	H(7a)	H(7e)	OMe	Me	Ph
trans-**2a**	4.04 (d)	4.55 (d)	1.95—2.20 (m, 2 H)		3.72—4.23 (m, 4 H)				3.38 (s)	—	7.15—7.35 (m)
cis-**2a**	4.65 (d)	5.00 (d)	1.80—1.95 (m)	2.2—2.35 (m)	3.50—3.90 (m, 4 H)				3.40 (s)	—	7.20—7.40 (m)
trans-**2b**	4.15 (d)	4.65 (d)	1.90	2.15	4.10	—	3.92	4.25	3.40 (s)	1.20 (d)	7.15—7.35 (m)
cis-**2b**	4.68 (d)	5.00	1.85	2.10	4.08	—	4.05	4.35	3.30 (s)	1.22	7.15—7.35 (m)
cis-**2c**	4.60 (d)	4.95	—	—	3.52—3.92 (m, 4 H)				3.30 (s)	0.70 (s), 1.40 (s)	7.20—7.45 (m)

formal insertion of methoxycarbonylcarbene into O(1)—C(2) bond. Successful reaction of methyl diazoacetate with benzaldehyde derivatives correlates well with the mechanism of 1,2-anionic rearrangement.[7] According to this mechanism, the migrating group in its transition state is a free radical stabilized by conjugation in its substituents, and thus the process occurs more easily.

The stereochemical composition of the reaction products was determined by analyzing the chemical shifts and spin-spin coupling constants in the ^{1}H and ^{13}C NMR spectra (Tables 2—4) and confirmed by the nuclear Overhauser effect (NOE).



trans-**2b**



cis-**2b**

Thus, the ^{1}H NMR spectra of *cis*- and *trans*-isomers of 5-methyl-2-methoxycarbonyl-3-phenyl-1,4-dioxepanes (**2b**) show that the protons of the heterocycle form weakly bound spin-spin systems, *e.g.*, a two-spin system (the H(2) and H(3) protons) with the vicinal constants $^3J_{2,3}$ = 9.2 and 4.8 Hz for the *trans*- and the *cis*-isomer, respectively, and an eight-spin system, in which three α-protons (relative to the O atoms) resonate at δ 3.5—5.0 (see Table 3). NOE measurements also allow a doublet at δ 4.65 to be assigned to the H(3) proton in *trans*-**2b**.

Table 3. Spin-spin coupling constants (Hz) of 1,4-dioxepanes **2a—c***

Coupling	**2b** *trans*	**2b** *cis*
H(2)—H(3)	9.2	4.8
H(5a)—H(6a)	9.3	6.5
H(5a)—H(6e)	4.2	2.0
H(6a)—H(6e)	−12.0	−14.6
H(6e)—H(7a)	6.6	1.8
H(6a)—H(7a)	6.5	5.3
H(6e)—H(7e)	8.4	2.8
H(6a)—H(7e)	8.4	4.9
H(7a)—H(7e)	−13.0	−12.3
Me	6.4	6.2

* H(2)—H(3) coupling constants for *trans*-**2a**, *cis*-**2a**, and *cis*-**2c** are equal to 14.2, 4.6, and 5.8 Hz, respectively.

Table 4. Chemical shifts ($CDCl_3$, δ) in the ^{13}C NMR spectra of 1,4-dioxepanes **2a—c**

Compound	C(2)	C(3)	C(5)	C(6)	C(7)	C=O	OMe	Me	Ph
trans-**2a**	86.5	86.3	68.2	32.3	69.3	169.2	51.8	—	137.4, 128.5, 126.1, 127.7
cis-**2a**	82.4	81.0	66.6	33.3	71.4	169.6	51.7	—	137.4, 128.1, 127.7, 128.0
trans-**2b**	86.5	84.7	76.6	39.9	67.2	170.3	51.8	22.9	138.1, 128.5, 127.1, 128.4
cis-**2b**	82.9	80.1	73.6	40.4	70.6	169.7	51.5	23.1	138.6, 128.0, 127.5, 128.0
cis-**2c**	84.3	83.6	81.9	38.7	68.4	171.4	51.9	24.3, 21.7	138.4, 128.7, 128.3, 128.4

Its irradiation produces an Overhauser effect (2%) on the phenyl protons, which was not observed upon irradiation of the H(2) proton. The arrangement of Me and Ph substituents was determined by recording an XY spectrum in the HH COSY LR regime; this reveals a long-range coupling constant $^4J_{3,5} \approx 0.5—1$ Hz. The Overhauser effect (12%) between the H(3) and H(5) protons spaced at 2.5 Å indicates, according to the molecular mechanics calculations (PCM4), their *cis*-orientation. As in 1,3-dioxanes, the H(6e) and H(6a) protons in *trans*- and *cis*-**2b** are symmetrically separated by three σ-bonds from both O atoms[8] and affected by the lone pairs of the O atoms. Because of this, a signal for the equatorial proton is shifted upfield compared to that of the axial proton. An increased sum of the vicinal constants (~15 Hz) ($^3J_{6a,7a} + {}^3J_{6e,7e}$) suggests that their seven-membered ring has a distorted chair conformation.

Thus, it was found that methyl diazoacetate reacts only with 2-phenyl-1,3-dioxanes in the presence of $Rh_2(OAc)_4$ to give 1,4-dioxepanes.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer in Vaseline oil. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. The reaction mixtures were chromatographed on a Tsvet-500 chromatograph using 120×0.3 cm column with 5%-SE-30 on Chromaton N-W-HMDS (flame ionization detector, helium as carrier gas). Column chromatography was carried out on Chemapol L silica gel (100/160 μm) (Czech and Slovak Federative Republic). The starting 1,3-dioxanes were synthesized according to the known procedure,[9] distilled in a flow of argon, and kept in an inert atmosphere over metallic sodium. The used solvents were purified by the conventional methods.[10] Their physicochemical constants coincide with the literature data.

Reactions of 1,3-dioxanes with methyl diazoacetate (general procedure). Methyl diazoacetate (1.12 g, 11.2 mmol) in 3 mL of CH_2Cl_2 was added with vigorous stirring at 20 °C over 1 h to a solution of 1,3-dioxane (15 mmol) and $Rh_2(OAc)_4$ (0.03 g, 0.056 mmol) in 10 mL of CH_2Cl_2. One hour after, methylene chloride was evaporated, and the residue was dissolved in 10 mL of diethyl ether and passed through a thin layer of Al_2O_3. The solvent was removed, and the residue was chromatographed on silica gel in hexane—AcOEt with a gradient from 5 to 100% of AcOEt. The yields and spectral characteristics of the compounds obtained are presented in Tables 1—4.

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