HETEROCYCLES, Vol. 73, 2007, pp. 433 - 449. © The Japan Institute of Heterocyclic Chemistry
Received, 7th June, 2007, Accepted, 10th August, 2007, Published online, 14th August, 2007. COM-07-S(U)13

SPIROCYCLIC AND FUSED DERIVATIVES OF MALEIMIDE BASED ON INTRA- AND INTERMOLECULAR REACTIONS OF CARBONYL YLIDES FROM DIAZOCARBONYL COMPOUNDS

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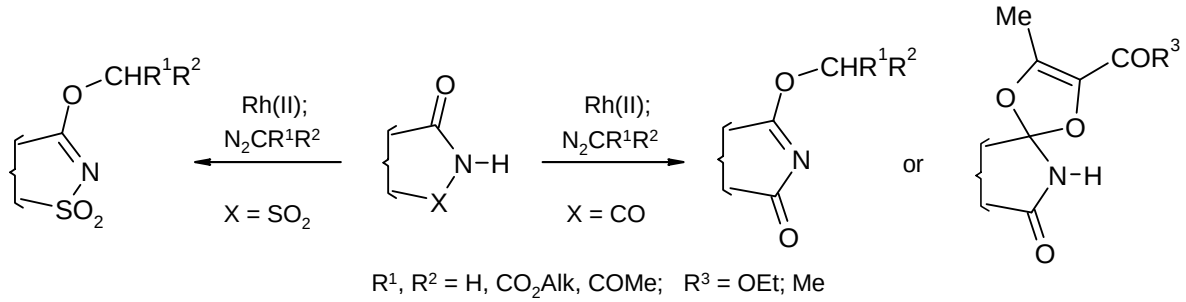
Abstract – The reaction of maleimide with Rh(II)-ketocarbenoids, derived from acyclic diazocarbonyl compounds, proceeds chemoselectively at the oxygen atom of the imidic C=O group to give carbonyl ylides as reactive intermediates. The carbonyl ylide generated from maleimide and ethyl diazoacetate reacts intermolecularly with the double bond of another molecule of maleimide to yield tricyclic spiroadducts *via* [3+2]-cycloaddition. Intramolecular stabilization is characteristic for carbonyl ylides with two bulky electron-withdrawing groups at the carbanionic center and occurs in two different ways, depending on the structure of the substituents: carbonyl ylides from diazomalonate, which possess two alkoxycarbonyl groups at the carbanionic C-atom, experience a 1,3-dipolar electrocyclization with formation of an oxirane, while carbonyl ylides with at least one α-acyl group, derived from diazoacetoacetate or diazoacetylacetone, undergo an intramolecular 1,5-dipolar electrocyclization to produce 1,3-dioxole derivatives of maleimide.

INTRODUCTION

Recent investigations in catalytic reactions of diazocarbonyl compounds with $Rh_2(OAc)_4$ in the presence of saccharines (sulfonimides) showed that, in spite of a few possible alternatives, the initial attack of the Rh(II)-carbenoid occurs basically at the carbonyl O-atom of the sulfonimide with formation of the respective carbonyl-ylides as intermediates.[1] The subsequent stabilization of these highly reactive species proceeds exclusively *via* [1,4]-hydrogen shift, and corresponding *O*-alkylimidates are the sole products of this reaction with saccharines, independent of the nature of substituents on the carbanionic center of the carbonyl ylide (*Scheme 1*; X = SO_2).



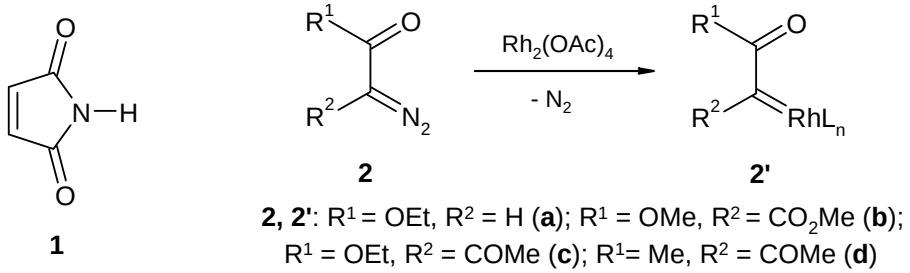
Scheme 1. Reactivity of dicarbox- and sulfonimides with Rh(II)-oxocarbenoids

In the case of dicarboximides (phthalimide, succinimide), the attack of the intermediate rhodium carbenoid under the same reaction conditions occurs also at the O-atom of the C=O group, but in this case, the type of stabilization of the intermediate carbonyl ylide depends on the nature of the substituents at the carbanionic center of the ylide.[2] The formation of *O*-alkylimidates, similar to sulphonimides, is observed only with diazoesters (diazoacetates and diazomalonates), whereas carbonyl ylides, which possess at least one α-acyl group, undergo a 1,5-dipolar electrocyclization with formation of 1,3-dioxoles as the main products (*Scheme 1*; X = CO).

In the present paper, we report the results of the catalytic decomposition of acyclic diazocarbonyl compounds with $Rh_2(OAc)_4$ in the presence of maleimide.[3] The investigation of the reactions with maleimide comprised a increased challenge, since this imide, besides the imidic NH and C=O groups, possesses another potential center for the interaction with the electrophilic oxocarbenoid, *i.e.*, the C,C-double bond of the heterocycle. One might expect that in this case, apart from the reaction with carbenoids, this double bond can also take part in a [3+2]-cycloaddition with the initial diazocarbonyl compounds, as widely exemplified in the chemistry of aliphatic diazo compounds.[4] This assumption was justified only for the reaction of maleimide with diazoacetic ester.

RESULTS AND DISCUSSION

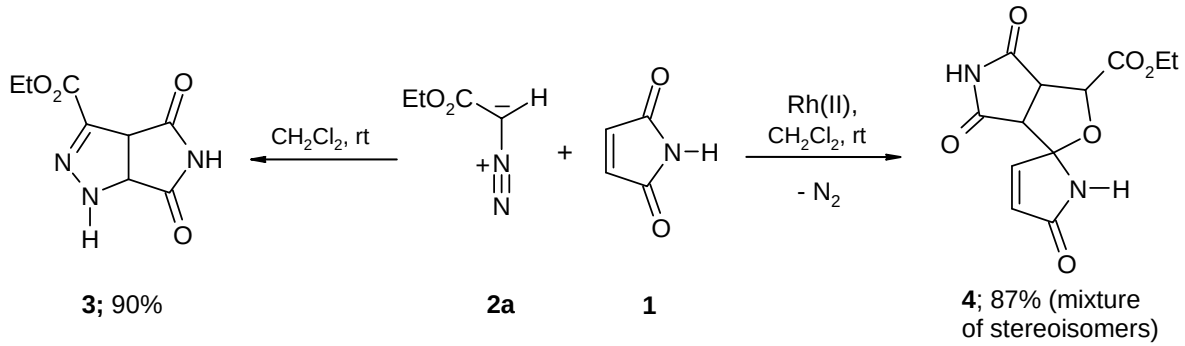
For a clear comparison, the same series of diazo compounds (**2**), which have been used previously in the reactions with other dicarbox- and sulfonimides, was used for the generation of Rh(II)-oxocarbenoids (**2'**) in catalytic reactions with maleimide (**1**), namely: ethyl diazoacetate (**2a**), dimethyl diazomalonate (**2b**), ethyl diazoacetoacetate (**2c**), and diazoacetylacetone (**2d**) (*Scheme 2*). These diazocarbonyl compounds represent different classes of aliphatic diazo compounds – *i.e.*, diazoesters, diazoketoesters, and diazodiketones, which usually demonstrate rather different reactivities.[2,5,6]



Scheme 2. Starting compounds **1**, **2**, and corresponding Rh(II)-oxocarbenoids (**2'**)

Catalytic reactions of diazocarbonyl compounds (**2a**–**d**) were carried out at room temperature either by adding 1–2% (mole) $Rh_2(OAc)_4$ as the catalyst to the solution of maleimide (**1**) and diazo compounds (**2b**–**d**) in dry dichloromethane, or by addition of diazoester (**2a**) to a mixture of **1** and 1–2% (mole) $Rh_2(OAc)_4$ in dichloromethane. Upon completion of diazo compound decomposition (as indicated by TLC), in most cases the reaction mixture was passed through a plug of silica gel to remove the catalyst, and isolated compounds were characterized by using ^{1}H- and ^{13}C-NMR spectroscopy, mass-spectrometry, and in one case by X-ray crystal structure determination. Since it was known that Rh-catalyzed processes and their products in similar reactions with other imides are very sensitive to traces of moisture and acids,[1,2] the reagents were subject to careful purification by sublimation of maleimide (**1**) *in vacuo* and by distillation of diazo compounds (**2a**–**d**) at reduced pressure. Accordingly, the workup procedure was performed, where possible, under the exclusion of moisture.

As it was already mentioned above, in the absence of rhodium catalyst, ethyl diazoacetate (**2a**) smoothly reacted with the C,C-double bond of maleimide (**1**) leading to the [3+2]-cycloaddition product (**3**). In spite of a considerable number of publications devoted to cycloaddition reactions of aliphatic diazo compounds with unsaturated compounds,[4] no data were available on the reaction of diazoacetates and **1**.



3; 90% **2a** **1** **4**; 87% (mixture of stereoisomers)

Scheme 3. Reactions of diazoacetate (**2a**) with maleimide (**1**) in the absence and presence of $Rh_2(OAc)_4$

The structure of Δ^2-pyrazoline (**3**) (*Scheme 3*) is in complete agreement with the data of the ^{1}H- and ^{13}C-NMR spectra, mass-spectrometry, and elemental analysis obtained for this compound. In the ^{1}H-NMR spectrum four groups of signals are observed in a 1:1:1:1 ratio (in addition to the signals of the ethyl group). The intensity of two low field signals rapidly diminishes on adding a small amount of D_2O + K_2CO_3 to the sample in the NMR tube, which allows to assign these signals to two different NH groups. Furthermore, owing to the H-D exchange, the additional splitting of the doublet at 4.84 ppm (~ 2.0 Hz) disappears, pointing to the presence of the NH–CH pattern in the structure of (**3**).

It is evident the Δ^2-pyrazoline (**3**) results from the initially formed Δ^1-pyrazoline *via* spontaneous isomerization, which was repeatedly described in cycloadducts of diazo compounds and in the chemistry of pyrazolines.[7]

With the aim of avoiding the above cycloaddition reaction with maleimide (**1**), the catalytic decomposition of ethyl diazoacetate (**2a**) was performed by slow addition of its solution to a vigorously stirred mixture of **1** and $Rh_2(OAc)_4$ to prevent high concentration of the free diazo compound in the reaction mixture. When performing the reaction in this way, the formation of the cycloadduct (**3**) was completely suppressed.

In the catalytic decomposition of ethyl diazoacetate (**2a**) with $Rh_2(OAc)_4$ in the presence of (**1**), a mixture of three stereoisomeric compounds (**4**) is formed with a total yield up to 85–87%, along with a small amount of diethyl fumarate and maleate (*Scheme 3*). In an experiment with 10-fold excess of **1**, the ^{1}H-NMR spectrum of the crude reaction mixture showed three well-defined sets of signals related to the H–C=C–H pattern of the molecule, and six distinct NH signals are observed with the relative ratio of 2.3/1.9/1.0, indicating the presence of three isomeric compounds (**4**). When a 2-fold excess of **1** was used pure stereoisomer (**4a**) was managed to isolate after chromatography of the reaction mixture and crystallization of the main fraction from dichloromethane.[3] It was fully characterized by the detailed NMR studies and other methods.

On the basis of these data it is evident that during formation of **4a** one C=O group and one C,C-double

bond of the two involved molecules of imide (**1**) were transformed into other structural elements of the final product. Since with all previously studied imides the reaction of oxocarbenoids proceeded through intermediate formation of carbonyl ylides,[1-3] it was reasonable to assume that in the present case maleimide (**1**) and (ethoxycarbonyl)carbene (**2a'**) initially formed also a carbonyl ylide, which interacted with the C,C-double bond of another molecule **1** to yield the final product.

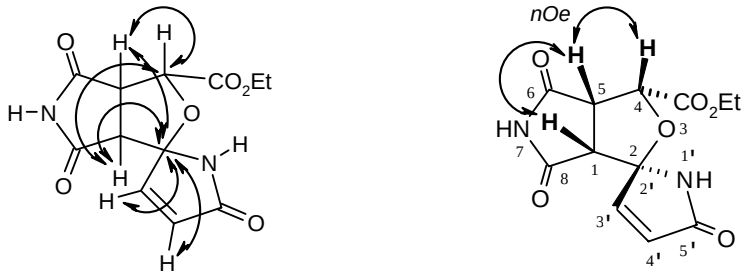
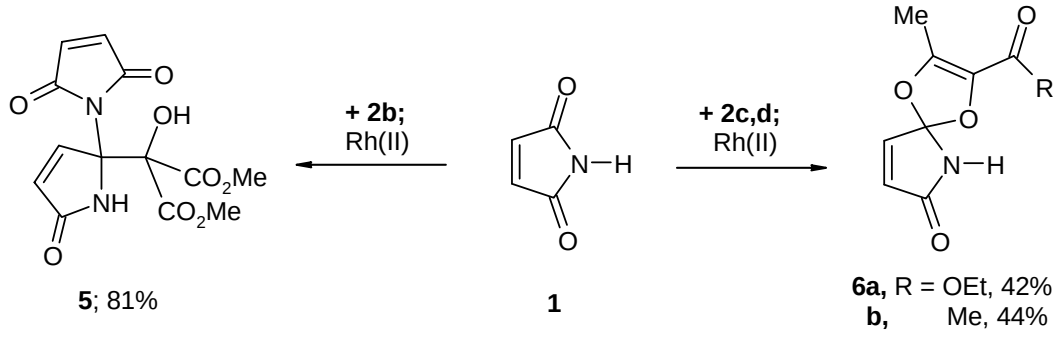


Figure 1. Structure of the major cycloaddition product (**4a**) as revealed from HMBC and NOESY experiments

One of the alternative structures and the most characteristic ^{1}H-^{13}C interactions from the NMR spectrum of adduct (**4a**) are shown in *Figure 1*. It can be pointed out that the most adequate correlation of the major parameters in the ^{1}H- and ^{13}C-NMR spectra (APT, COSY, HMQC, HMBC) is observed with the structure of ethyl 5',6,8-trioxo-2',5'-dihydro- 1'*H*-3-oxa-7-azabicyclo[3.3.0]octane-2-spiro-2'-pyrrole-4-carboxylate (**4a**) (*Figure 1*). The relative configuration of the chiral centers in the molecule of this compound was established on the basis of the nuclear Overhauser effects in the ^{1}H-NMR spectrum and the magnitude of spin-spin coupling constants between HC(1), HC(5), and HC(4) with the chemical shifts of 3.73, 3.85 and 4.81 ppm, respectively.

In the catalytic decomposition of dimethyl diazomalonate (**2b**) with maleimide (**1**), the sole product (**5**) was isolated in 81% yield. Its molecular mass and composition is consistent with the structure of a 2:1 adduct of **1** and di(methoxycarbonyl)carbene, as it was observed in the case of ethyl diazoacetate (**2a**).



Scheme 4. Reactions of dimethyl diazomalonate (**2b**) and diazo compounds (**2c**,**d**) with maleimide (**1**)

However it was elucidated during spectroscopic studies that compound (**5**) has a widely different

structure than adducts (**4**), obtained from ethyl diazoacetate (**2a**). Finally, the structure of the dimethyl 2-hydroxy-2-(dihydropyrrolyl)malonate (**5**) (*Scheme 4*) was unambiguously established by an X-Ray crystal structure determination (*Figure 2*).

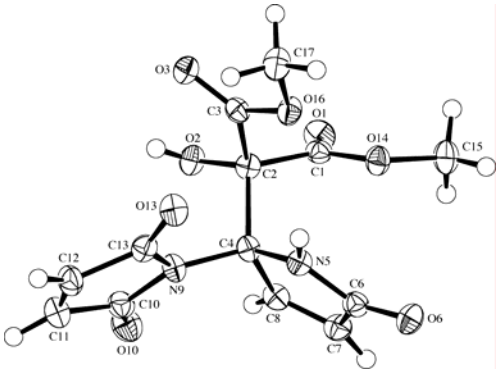
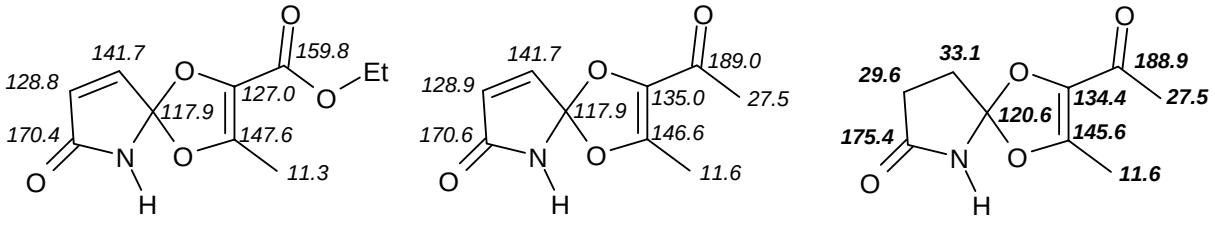


Figure 2. ORTEP plot[8] of the molecular structure of **5** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability)

It should also be mentioned that the corresponding *O*-alkylimidate, of which analogues are usually the main products in similar catalytic reactions of **2b** with dicarbox- and sulfonimides,[1,2] is not formed in this reaction at all. This conclusion is based on the absence of the characteristic **H**–C signal at ca. 5.9-6.1 ppm of *O*-alkylimidates in the ^{1}H-NMR spectra of the crude reaction mixture.

The catalytic decomposition of diazoacetoacetic ester (**2c**) and diazoacetylacetone (**2d**) in the presence of maleimide (**1**), just as with other dicarboximides,[2] leads to spiro-dioxoles (**6a**,**b**) in moderate yields (42–44%; *Scheme 4*). The structure of these adducts was confirmed by comparison of the chemical shifts of the C-atoms of the dioxole pattern in **6a**,**b** with those of spiroadduct (**6c**) (*Figure 3*), whose structure was established previously using X-Ray analysis.[2b]



6a **6b** **6c** [2b]

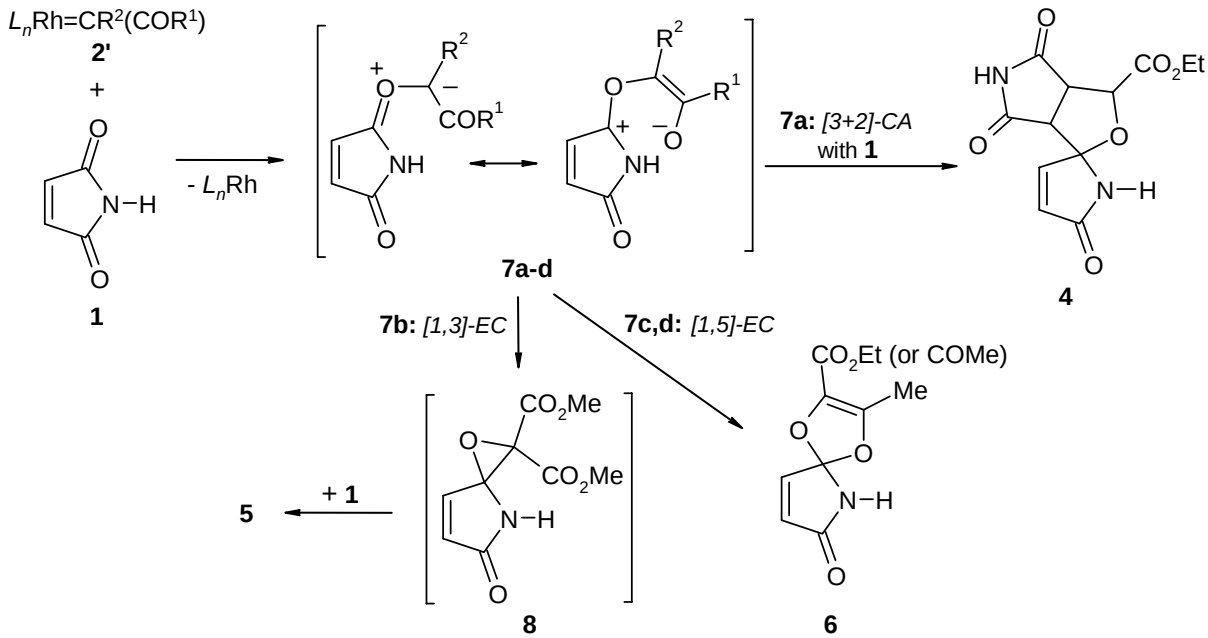
Figure 3. Assignment of the spiro-1,3-dioxolane structure of **6a**,**b** on the basis of ^{13}C-NMR data

As one can see from ^{13}C-NMR data (*Figure 3*), compounds (**6a**,**b**) and the previously described **6c** show a very good correlation of the chemical shifts for C-atoms under consideration. In addition to the other spectroscopic data, this provides a strong argument in support of the spirocyclic structures (**6a**,**b**).

Spiro-adducts (**6**) are very sensitive to moisture and are easily hydrolyzed on air or during chromatography of the reaction mixture on silica gel, yielding the corresponding 2-hydroxy-1,3-dicarbonyl compounds and maleimide (**1**). It is likely that the rather low yields of spiro-adducts (**6a**,**b**) are the result of their easy hydrolysis, which is also characteristic of the analogous derivatives of succinimide and phthalimide.[2]

REACTION PATHWAYS

The obtained results clearly evidence that, like with other dicarbox- and sulfonamides,[1-3] the initial attack of Rh(II)-ketocarbenoids (**2'**) occurs mainly at the O-atom of the C=O group of maleimide (**1**), leading to the highly reactive carbonyl ylides as intermediates,[9,10] while no interaction of carbenoids (**2'**) with the N-atom of **1** and generation of cycloammonium ylides occurs.[3]



7a-d: R^1, R^2 = OEt, H (**a**); OMe, CO_2Me (**b**); Me, CO_2Et (**c**); Me, COMe (**d**)

Scheme 5. Pathways of stabilization of carbonyl ylides (**7a**–**d**)

However, contrary to the other imides, it was established that further stabilization of maleimide carbonyl ylides (**7**) can proceed not only *via intramolecular* but also via *intermolecular* processes (*Scheme 5*). The

intermolecular pathway is characteristic for carbonyl ylide (**7a**). As the result of a [3+2]-cycloaddition reaction of the initially formed **7a** with the C,C-double bond of the abundant **1**, stereoisomeric tricyclic spiro-adducts (**4**) are formed in good yield. This is in fact the first example of an *intermolecular* cycloaddition with an imidic carbonyl ylide that is also generated by an *intermolecular* process. Previous attempts to trap such imidic carbonyl ylides by using for example DMAD failed.[1,2] This fact was assigned to the sterical difficulties for the approach of the dipolarophile to the carbonyl ylide, *i.e.*, the difficult overlap of the corresponding orbitals.[1a] On the other hand, imidic carbonyl ylides, which bear both substituents in the plane of the $C{=}O^{+}{-}C^{-}$ fragment of the ylide, gave such cycloaddition products easily and with high yields.[1a,11]

The application of a similar scheme[1a] for the interpretation of the results with maleimide (**1**) shows that, irrespective of its conformation (*Z,E* or *E,E*), carbonyl ylide (**7a**) also may not exhibit a high sterical barrier for the approach of the dipolarophile, since both substituents at the carbanionic C-atom (H and CO_2Et) can be located essentially in the plane of the $C{=}O^{+}{-}C^{-}$ fragment of this intermediate (*Figure 4*). Thus, carbonyl ylide (**7a**) is able to react with a dipolarophile easily, as we actually observed in the reaction with the maleimide C,C-double bond and formation of tricyclic adducts **(4**).

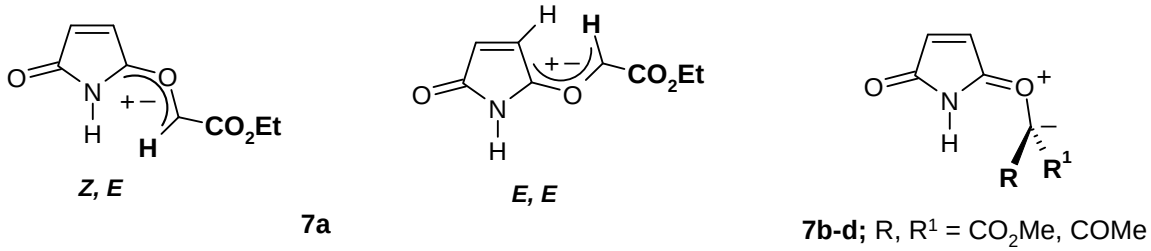
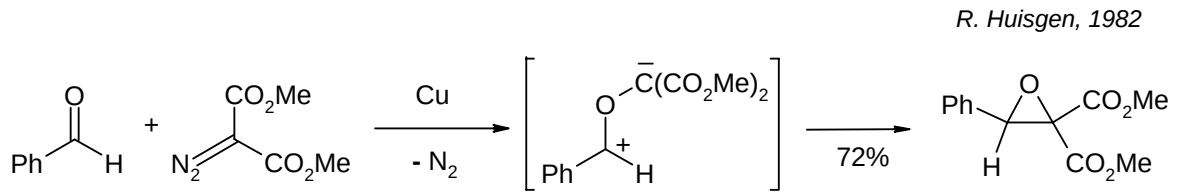


Figure 4. Proposed conformations of the imidic carbonyl ylides (**7a**–**d**)

On the other hand, it is evident that both bulky substituents at the carbanionic centre of carbonyl ylides (**7b**–**d**, R, R^1 = CO_2Me or COMe) must be oriented in an orthogonal plane on steric reasons, thereby inhibiting the approach of a dipolarophile to the relevant orbitals of the carbonyl ylide (*Figure 4*). Therefore, **7b**–**d**, like their analogues in the series of dicarbox- and sulfonimides,[1,2] do not reveal a tendency for intermolecular cycloaddition any more,[12] and this observation can be considered as an additional argument in support of the assumption on the sterical control of this cycloaddition process.

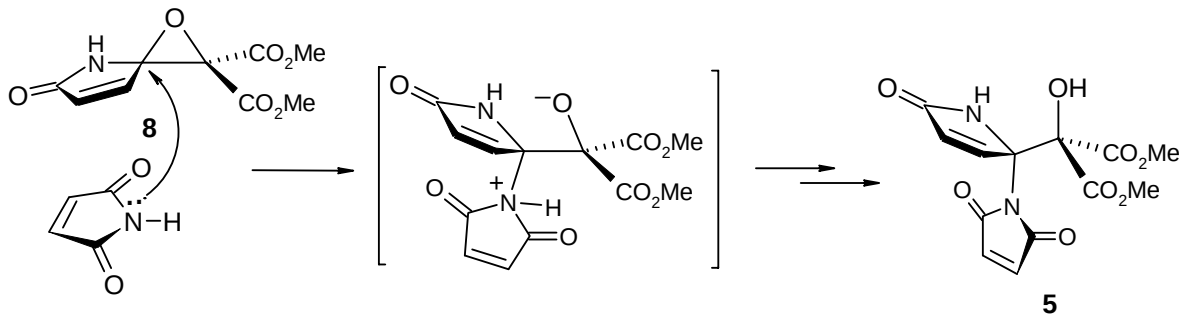
Instead, the *intramolecular* processes are more typical for carbonyl ylides (**7b**–**d**) (*Scheme 5*). Stabilization of ylide (**7b**), generated from diazomalonate (**2b**) and **1**, apparently proceeds *via* [1,3]-dipolar electrocyclization and intermediate formation of oxirane (**8**), followed by the reaction of the latter with a second molecule of **1** to produce hydroxymalonate (**5**) **(***Scheme 5*). An analogues product has been isolated in the Rh(II)-catalyzed reaction of **2b** with phthalimide, albeit it was only a minor product (13%).

The assumed occurance of oxirane (**8**) in this process is supported by a few literature analogies. Carbonyl ylides and oxiranes are valence isomers, which readily interconvert, and rather stable oxiranes are often used in thermal and photochemical reactions as the precursors of highly reactive carbonyl ylides.[10c,13] Another argument in favor of this speculation are the experimental results by *De March* and *Huisgen*,[14] who obtained a similar oxirane with high yield in the catalytic decomposition of diazomalonate (**2b**) in the presence of benzaldehyde, followed by intramolecular [1,3]-dipolar electrocyclization of the initially formed carbonyl ylide (*Scheme 6*).



Scheme 6. Formation of an oxirane from benzaldehyde and dimethyl diazomalonate[14]

Thus, it is very likely that in the catalytic decomposition of dimethyl diazomalonate (**2b**) with maleimide (**1**) a similar pathway leads to the intermediate carbonyl ylide (**7b**) and its stabilization *via* the formation of oxirane (**8**). The mechanism of the next step, *i.e.*, the formation of the hydroxymalonate **(5**), may include the direct reaction of **8** with another molecule of **1** (*Scheme 7*), which can proceed under acid catalysis *via* protonation of the oxirane oxygen atom, followed by ring opening due to the nucleophilic attack by the second molecule of **1** on the protonated oxirane.[2a] A reaction mechanism *via* initial ring opening of the oxirane as a result of the aminal structure of **8**, leading to the iminium-olate intermediate is also conceivable.[2b]



Scheme 7. Nucleophilic ring-opening of the oxirane (**8**)

The regioselectivity of the second step in this reaction depends on the nature of the oxirane substituents. It is known that electron-withdrawing groups on the oxirane ring hinder the nucleophilic attack at the C-atom they are attached to, but this attack easily occurs on the C-atom, which bears substituents, which are able to stabilize a positive charge during of the process.[13] In accordance with this expectation, the preferred nucleophilic attack in **8** should occur at the spiro C-atom, because it bears two substituents (C,C-double bond and NH group), which both stabilize the positive charge in contrast to the two alkoxycarbonyl groups, attached to the other C-atom of the oxirane ring. Hence, in the reaction under consideration one should expect the formation of the observed regioisomer (**5**).

It is worth mentioning that neither with **7a** nor with **7b** *O*-alkylimidates were formed.

Carbonyl-ylides (**7c**,**d**) with at least one α-acyl group experience an *intramolecular* 1,5-dipolar electrocyclization leading to spiro-1,3-dioxole derivatives (**6c**,**d**) (*Scheme 5*). The analogous stabilization of imidic carbonyl-ylides was observed previously in catalytic reactions of the same diazo compounds (**2c**) and (**2d**) with phthalimide or succinimide,[2] as well as in a series of thiocarbonyl ylides.[15]

A few examples, in which 1,3-dioxoles of type **(6**) were formed during the photochemical or catalytic decomposition of diazocarbonyl compounds in the presence of simple aldehydes or ketones, are also known.[6,16] Initially, it was suggested that dioxoles in these processes originate from a 1,3-cycloaddition reaction of the metal carbene complex or oxocarbene (in its 1,3-dipolar form) with the C=O-bond of the carbonyl substrate.[16] However, the currently accepted mechanism of the formation of 1,3-dioxoles from diazocarbonyl compounds and C=O-containing substrates implies the intermediate appearance of corresponding carbonyl ylides.[6,14,17]

The results of our studies in addition clearly demonstrate that intramolecular 1,5-dipolar electrocyclization of the imidic carbonyl ylides to give 1,3-dioxoles is feasible only with diazocarbonyl compounds/oxocarbenoids bearing an α-acyl group adjacent to the diazo functionality (or carbenoid C-atom). Basically, the stabilization of ylides (**7c**,**d**) *via* [1,3]-electrocyclization is also plausible, but the products of this pathway were never observed in our experiments with imides. [1-3]

CONCLUSIONS

In summary, the initial interaction of maleimide with Rh(II)-oxocarbenoids, which are generated from acyclic diazocarbonyl compounds, proceeds in the same manner as with other dicarbox- and sulfonimides, *i.e.*, chemoselectively at the O-atom of the imidic C=O group, leading to the formation of highly reactive carbonyl-ylides as intermediates. However, unlike other imides, further stabilization of carbonyl ylides of maleimide takes place not only in an *intramolecular* manner but also by *intermolecular* processes.

An *intermolecular* [3+2]-cycloaddition of the carbonyl-ylide generated from ethyl diazoacetate and maleimide occurs with the C,C-double bond of another molecule of maleimide. This is the first example of an intermolecular reaction of this type in the series of the imidic carbonyl ylides. *Intramolecular* stabilization of maleimide carbonyl ylides proceeds in two different ways, which are governed by the structure of the initial diazocarbonyl compound. Carbonyl ylides derived from diazomalonate undergo 1,3-dipolar electrocyclization to produce oxiranes, followed by nucleophilic oxirane ring opening with the formation of hydroxy pyrrolylmalonates as the final reaction products. Carbonyl-ylides with at least one α-acyl group in the carbenoid fragment of the molecule undergo 1,5-dipolar electrocyclizations to yield 1,3-dioxole derivatives of maleimide.

Thus, reactions of Rh(II)-oxocarbenoids with maleimide can serve as a new synthetic approach to the labile and otherwise not readily accessible spirocyclic 5-acyl-1,3-dioxoles and fused tricyclic derivatives of maleimide, and the carbonyl units of the new compounds provide additional opportunities for versatile structural modifications of these nitrogen-containing heterocycles.

EXPERIMENTAL

General remarks. ^{1}H- and ^{13}C-NMR spectra were measured on *Bruker AV-300*, *Bruker ARX-300*, and *Bruker Digital Avance 600* spectrometers, with working frequencies of 300 and 600 MHz for ^{1}H-NMR, and 75.45 and 150.92 MHz for ^{13}C-NMR spectra, respectively, in $CDCl_3$, aceton-d_6, or DMSO-d_6 solutions; internal standard Me_4Si (δ, ppm), *J* values are given in Hz. IR spectra were obtained using a *Perkin Elmer Spectrum One CSI Beam Splitter* or an *ATI Mattson 'Genesis Series FTIR'* instrument. Mass spectra were determined on a *Finnigan TSQ-700*, a *Bruker Autoflex I MALDI-TOF*, or a *Bruker Esquirel LC/MS* spectrometer. Microanalyses were performed on a *Heraeus CHNS Rapid Analyser*. Melting points were determined on a *Büchi B-540* melting point apparatus and are uncorrected.

All reactions were carried out in carefully dried and distilled solvents. Rhodium acetate ($Rh_2(OAc)_4$) and maleimide (**1**) were commercially available (*Fluka*). Diazodicarbonyl compounds **2b**–**d** were prepared from the corresponding 1,3-dicarbonyl compounds and arenesulfonyl azides by diazotransfer reaction[4,5] followed by distillation *in vacuo*. Commercially available ethyl diazoacetate (**2a**, *Fluka*) was distilled before its use, b.p. 58–60 °C/1 mm Hg. All reactions were monitored by thin-layer chromatography (TLC) on *Merck Silica gel 60 F_{254}* or on *Silufol UV/VIS 254* plates using UV light and I_2 as the visualizing agents. *Merck Silica gel 60* (0.040–0.063 mm) was used for column chromatography.

Ethyl 6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylate (**3**). A mixture of ethyl diazoacetate (**2a**, 1.14 g, 0.01 mol) and maleimide (**1**, 1.0 g, 0.01 mol) in CH_2Cl_2 (10 mL) was stirred at rt until

completion of the reaction (control by TLC). Then, CH_2Cl_2 was removed *in vacuo* and product (**3**) was crystallized from EtOH/H_2O (2:1). Yield: 1.9 g (90%). Colorless crystals; mp 164–165 °C (EtOH/H_2O); R_f = 0.30 (CH_2Cl_2/AcOEt, 5:1). ^{1}H-NMR (DMSO-d_6): 1.20 (t, $J_{H,H}$ = 7.04 Hz, 3H, C*H*$_3$CH$_2$O), 4.15 (q, $J_{H,H}$ = 7.04 Hz, 2H, CH$_3$C*H*$_2$O), 4.42 (d, $J_{H,H}$ = 11.1 Hz, 1H, HC(5)), 4.84 (dd, $J_{H,H}$ = 11.1 Hz, 2.0 Hz, 1H, HC(1)), 9.48 (d, $J_{H,H}$ = 2.0 Hz, 1H, NH), 11.52 (s, 1H, CONHCO). ^{13}C-NMR (DMSO-d_6): 14.2 (*C*H$_3$CH$_2$O), 52.71 (C(5)), 60.3 (CH$_3$*C*H$_2$O), 66.3 (C(1)), 133.8 (C(4)), 161.1 (*C*O$_2$Et), 174.6 (*C*ONH), 176.1 (*C*ONH). IR (KBr): 1779 (68), 1739 (95), 1708 (95), 1340 (84), 1213 (91), 1116 (72). EI-MS (70 eV): *m/z* 211 (100, $M^{+\cdot}$), 141 (12). Anal. Calcd for $C_8H_9N_3O_4$: C, 45.49; H, 4.26; N, 19.91. Found: C, 45.50; H, 4.29; N, 19.90.

*Ethyl 5',6,8-trioxo-2',5'-dihydro-1'*H*-3-oxa-7-azabicyclo[3.3.0]octane-2-spiro-2'-pyrrole-4-carboxylates* **(4)**. A solution of ethyl diazoacetate (**2a**, 0.5 g, 4.3 mmol) in CH_2Cl_2 (25 mL) was added within 3 h to a solution of **1** (4.17 g, 43.0 mmol) and $Rh_2(OAc)_4$ (15 mg, 0.034 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred for an additional 30 min, then the solvent was removed *in vacuo* and the residue was passed through a plug of silica gel using first CH_2Cl_2 as eluent to remove excess of **1**, and then a mixture of CH_2Cl_2/AcOEt (3:1) to get a crude mixture of isomers (**4**). A pure mixture of these isomers (0.625 g, 51%) was obtained after purification on preparative TLC plates using CH_2Cl_2/AcOEt (4:7) as the eluent.
^{1}H-NMR of the mixture (DMSO-d_6): 1.17–1.26 (3t, 9H, 3 C*H*$_3$CH$_2$), 3.42 (d, $J_{H,H}$ = 8.25 Hz, 1H), 3.55 (d, $J_{H,H}$ = 7.90 Hz, 1H), 3.73 (m, 4H), 4.10–4.23 (m, 6H), 4.73 (d, $J_{H,H}$ = 7.74 Hz, 1H), 4.83 (d, $J_{H,H}$ = 6.63 Hz, 1H), 4.84 (d, $J_{H,H}$ = 4.47 Hz, 1H, (**4a**)), 6.07 (dd, $J_{H,H}$ = 5.62 Hz, $J_{H,H}$ = 1.24 Hz, 1H, (**4a**)), 6.09 (dd, $J_{H,H}$ = 5.64 Hz, $J_{H,H}$ = 1.26 Hz, 1H), 6.23 (dd, $J_{H,H}$ = 5.80 Hz, $J_{H,H}$ = 1.24 Hz, 1H), 6.96 (dd, $J_{H,H}$ = 5.79 Hz, $J_{H,H}$ = 1.26 Hz, 1H), 7.14 (dd, $J_{H,H}$ = 5.67 Hz, $J_{H,H}$ = 1.50 Hz, 1H, (**4a**)), 7.46 (dd, $J_{H,H}$ = 5.71 Hz, $J_{H,H}$ = 1.54 Hz, 1H), 8.69 (s, 1H, NH), 8.95 (s, 1H, NH, (**4a**)), 9.03 (s, 1H, NH), 11.37 (s, 1H, NH, (**4a**)), 11.46 (s, 1H, NH), 11.64 (s, 1H, NH).
Repetition of the experiment with **2a** (0.5 g, 4.3 mmol) and **1** (0.83 g, 8.6 mmol) also gave a mixture of isomers, from which stereoisomer (**4a**) was isolated in a pure form after filtration of the crude reaction mixture through a small plug of silica gel followed by crystallization from dichloromethane.

Dimethyl 2-hydroxy-2-(2,5,5'-trioxo-2,2',5,5'-tetrahydro[1,2']bipyrrol-2'-yl)malonate (**5**). To a stirred mixture of maleimide (**1**, 2.0 g, 0.02 mol) and dimethyl diazomalonate (**2b**, 1.58 g, 0.01 mol) in CH_2Cl_2 (15 mL), $Rh_2(OAc)_4$ (8 mg, 0.018 mmol) was added at rt. After complete decomposition of **2b** (ca. 10 h, TLC), the solvent was removed *in vacuo* to reach a volume of 4–5 mL, and the precipitated product was filtered, thoroughly washed with CH_2Cl_2, and dried *in vacuo*. Analytical data were collected without further purification of the compound. Yield of **5**: 2.62 g (81%). Colorless crystals; mp 195–196 °C

(CH_2Cl_2); R_f = 0.30 (CH_2Cl_2/AcOEt, 5:1). ^{1}H-NMR (DMSO-d_6): 3.61 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 6.29 (d, $J_{H,H}$ = 5.8 Hz, 1H, HC(4')), 6.97 (s, 2H, CH=CH), 7.26 (s, 1H, OH), 7.89 (d, $J_{H,H}$ = 5.8 Hz, 1H, HC(3')), 8.02 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): 53.7, 53.8 (2 CH_3O), 80.5 (C(2')), 81.3 C(2)), 128.7 (C(4')), 135.4 (C(3), C(4)), 145.9 (C(3')), 167.3, 167.7 (2 CO_2), 171.1 (C(2), C(5)), 171.7 (C(5')). IR (KBr): 1751 (90), 1720 (84), 1695 (85), 1438 (44), 1349 (67), 1297 (66), 1228 (58), 1159 (60). EI-MS (70 eV): *m/z* 324 (32, $M^{+\cdot}$), 306 (54), 275 (41), 215 (7), 177 (100), 149 (8), 122 (10), 80 (39), 59 (58). Anal. Calcd for $C_{13}H_{12}N_2O_8$: C, 48.16; H, 3.72; N, 8.64. Found: C, 48.14; H, 3.79; N, 8.57.
Crystallization of **5** from CH_2Cl_2/hexane gave suitable crystals for an X-ray crystal structure determination.

Ethyl 3-methyl-7-oxo-1,4-dioxa-6-azaspiro[4.4]non-2,8-diene-2-carboxyate (**6a**). In an argon atmosphere, $Rh_2(OAc)_4$ (30 mg, 0.067 mmol) was added to a mixture of **1** (1.5 g, 0.015 mol) and ethyl diazoacetoacetate (**2c**, 2.34 g, 0.015 mmol) in CH_2Cl_2 (10 mL). The reaction was complete after 3 h (TLC). The solvent was removed *in vacuo* to reach a volume of 4–5 mL. The product was precipitated by addition of Et_2O, and then it was filtered, washed with cold Et_2O, and dried *in vacuo*. Yield of **6a**: 1.4 g (42%). Colorless crystals; mp 85 °C (dec); R_f = 0.34 (CH_2Cl_2/hexane, 1:1). ^{1}H-NMR ($CDCl_3$): 1.29 (t, $J_{H,H}$ = 7.4 Hz, 3H, CH_3CH$_2$), 2.22 (s, 3H, CH_3–C=), 4.25 (q, $J_{H,H}$ = 7.4 Hz, 2H, CH$_3$CH_2), 6.10 (d, $J_{H,H}$ = 5.4 Hz, 1H, HC(8)), 6.79 (d, $J_{H,H}$ = 5.4 Hz, 1H, HC(9)), 7.35 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): 11.28 (*C*H$_3$–C=), 14.3 (*C*H$_3$CH$_2$), 61.1 (CH$_3$*C*H$_2$), 117.9 (C(5)), 127.0 (C(2)), 128.8 (C(8)), 141.7 (C(9)), 147.6 (C(3)), 159.8 (CO_2), 170.4 (CONH). IR (KBr): 1727 (93), 1685 (90), 1376 (74), 1336 (87), 1265 (75), 1143 (90), 1110 (93). EI-MS (70 eV): *m/z* 225 (24, $M^{+\cdot}$), 180 (8), 145 (17), 126 (33), 98 (37), 81 (67), 53 (48), 43 (100). Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.34; H, 4.92; N, 6.21. Found: C, 53.40; H, 5.17; N, 6.11.

2-Acetyl-3-methyl-1,4-dioxa-6-azaspiro[4.4]non-2,8-dien-7-one (**6b**). In an argon atmosphere, $Rh_2(OAc)_4$ (20 mg, 0.045 mmol) was added to a mixture of **1** (1.5 g, 0.015 mol) and diazoacetylacetone (**2d**, 1.89 g, 0.015 mmol) in CH_2Cl_2 (15 mL). The reaction was complete after 2 h (TLC). The solvent was evaporated *in vacuo* to reach a volume of 4–5 mL, and the residue was filtered through a small plug of silica gel to remove the catalyst. Then, the solvent of the mother liquor was removed *in vacuo* and the product was crystallized from Et_2O. Yield of **6b**: 1.3 g (44%). Colorless crystals; mp 80 °C (dec.); R_f = 0.4 (CH_2Cl_2/hexane, 1:1). ^{1}H-NMR ($CDCl_3$): 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.13 (d, $J_{H,H}$ = 5.7 Hz, 1H, HC(8)), 6.80 (d, $J_{H,H}$ = 5.7 Hz, 1H, HC(9)), 7.20 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): 11.6 (*C*H$_3$–C=), 27.5 (*C*H$_3$CO), 117.9 (C(5)), 128.9 (C(8)), 135.0 (C(2)), 141.7 (C(9)), 146.6 (C(3)), 170.6 (CONH), 189.0 (C=O). IR (KBr): 1733 (91), 1631 (89), 1425 (76), 1369 (79), 1263 (83), 1137 (90), 1083 (72). EI-MS (70 eV): *m/z* = 196 (100, [*M*+H]$^+$), 99 (53), 69 (37). Anal. Calcd for $C_9H_9NO_4$: C, 55.39; H, 4.64; N, 7.17.

Found: C, 55.57; H, 4.74; N, 7.05.

X-Ray Crystal-Structure Determination of **5** (*Figure 2*).[18] All measurements were made on a *Nonius KappaCCD diffractometer*[19] using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with *HKL Denzo and Scalepack*.[20] The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given below, and a view of the molecule is shown in *Figure 2*. The structure was solved by direct methods using SIR92,[21] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. The lactam and hydroxy H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the Me groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2–F_c^2)^2$. A correction for secondary extinction was applied. The space group permits the compound in the crystal to be enantiomerically pure, but the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was chosen arbitrarily. Neutral atom scattering factors for non-H-atoms were taken from ref.,[22] and the scattering factors for H-atoms were taken from ref.[23] Anomalous dispersion effects were included in F_C;[24] the values for f' and f'' were those of ref.[25] The values of the mass attenuation coefficients are those of ref.[26] All calculations were performed using the SHELXL97 program.[27] Crystal data for **5**: $C_{13}H_{12}N_2O_8$, M = 324.24, colorless, prism, crystal dimensions 0.08 × 0.15 × 0.15 mm, tetragonal, space group $P4_1$, Z = 4, a = 10.3321(2) Å, c = 12.6433(3) Å, V = 1349.70(5) Å^3, D_X = 1.596 g·cm^{-3}, μ(MoK_α) = 0.135 mm^{-1}, T = 160 K, ϕ and ω scans, $2\theta_{max}$ = 60°, total reflections measured 20255, symmetry independent reflections 2052, reflections with $I > 2\sigma(I)$ 1810, reflections used in refinement 2052, parameters refined 219, restraints 1, R (on F; $I > 2\sigma(I)$ reflections) = 0.0355, $wR(F^2)$ (all reflections) = 0.0820 ($w = (\sigma^2(F_o^2) + (0.0414P)^2 + 0.1564P)^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.052, secondary extinction coefficient 0.022(3), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.20; –0.19 e Å^{-3}.

ACKNOWLEDGEMENTS

We thank the analytical sections of our institutes for spectra and analyses, PD Dr. *Anthony Linden*, University of Zürich, for the crystal structure determination, and *F. Hoffmann-La Roche AG*, Basel, for

financial support.

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